Freeze casting
a new formulation for fast dissolving tablets or foods

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To my Dad

my Family

and my special beloved ONE

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Cám ơn **gia đình, bạn bè** đã luôn ủng hộ, quan tâm và lo lắng cho mình.

Cảm ơn **ông xã** thật nhiều, vì đã bên vợ mọi lúc mọi nơi.

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1. Introduction

In the modern pharmaceutical field tablets are the most common and convenient solid dosage form [Rit02]. Among various types of tablets, fast dissolving tablets are high of interest in pharmaceutical industries due to their excellent drug delivery [Goe08, Din11, Pet13, Ngu15a]. In food industry, fast dissolving (instant) products are preferable because of their convenience [Ngu13, Ngu14a,c]. They are being considered a replacing product for fine-powder forms to overcome the agglomeration problem [Ngu14a]. A lot of fine powdered-food substances such as cocoa, milk, etc. face the dissolving and dispersing problems which cause an uncomfortable mouth feeling when being used. The particles either float to the surface or sediment to the bottom of the container within a certain [Hla99].

The majority of pharmaceutical tablets are made by compression [Lie99, Nia09]. However, direct compression is only possible for a limited number of substances. Substances exhibiting elastic compression behavior or poor flowability properties, temperature (heat) or pressure sensitive substances (e.g. enzymes, proteins, ibuprofen, dimenhydrinate) or active agents tending to have polymorphism (e.g. barbiturates, hydrocortisone, phenylbutazone, carbamazepine) are difficult to be compressed [Sze07a]. Some substances even if they could be compressed into tablets, due to the high compact characteristic after the compression tend to have a slow dissolution rate, which is not effective for practical use. Consequently, these above mentioned substances are usually available in forms of capsules, the more expensive/less economic drug forms for industrial production than tablets [Pac07a]. Another possible way to delivery those drugs is through injections, however, this is not very comfortable and is not preferred by patients [Rit02]. Chemical processing of those substances into tablet forms without having trouble with slow dissolution rates or agglomeration is an interesting technical challenge and promises great economic values.

Freeze casting is a well-known cold compression technique which has been widely applied to produce porous materials, e.g. porous green bodies in the ceramic industry and the biomaterial field [Don05, Dev08, Dev10, Li12]. The process of freeze casting is briefly described as follows: First, an aqueous liquid suspension of the relevant substance is frozen. This is followed by a solvent removal step (an evaporation or sublimation). The negative image of the ice crystals are the pores. After this step, a porous solid body in the desired mold form is obtained without using any external pressure [Ngu14, Ngu15a].

The major interesting strength of the freeze casting technique is the ability to produce the high porous solid bodies (up to 60 % pore volume) with controllable microstructures of pores by means of controlling the ice crystal at a low temperature and free external pressure process.

With above presented advantages, freeze-casting is obviously to be considered a potential technique to produce the fast dissolving tablets of foods as well as the porous solid bodies in the development of solid drug delivery systems. Studies on the applications of the processing technique, especially, in producing fast dissolving products in pharmaceuticals and foods, however, have not quite yet reached its full extent for a complete understanding [Ngu15b]. In

the food industry, there is no application found, and in pharmaceutical production, there are only a few studies [Pac07a-c, Sze07a-b, Wit10a-b] carried out. A remaining limitation of this technique in pharmaceutical production is the low tensile strength of produced tablets, which hinders its applicability in industrial production and needs to be overcome [Ngu15b].

In order to develop practical uses for the freeze casting technique, this study is focused on its application in food and pharmaceutical production in terms of fast dissolving tablets. The work consists two parts corresponding to two case studies: foods (e.g. cocoa) and pharmaceuticals (e.g. paracetamol).

In the first part, the freeze casting technique is applied, the first time, to produce fast dissolving cocoa tablets based on aqueous suspensions using additives (e.g. sugar (sucrose) and sugar alcohols: isomalt, xylitol) as multifunctional agents. At first, the properties of suspensions (with and without additives) including thermodynamic and rheological properties are investigated and discussed. Secondly, the effect of freeze conditions including the freeze modes (one side and both side freezing), freezing temperature, and freezing time on the physical properties of produced tablets (including pore microstructure, porosity, tensile strength and dissolution time) are presented. In addition, the effect of the solid loading, additives will be carefully evaluated and considered. All critical factors are tested to find out the best parameters of the freeze casting process for fast dissolving cocoa tablets. Moreover, the working mechanism of additives (i.e. sugar and sugar alcohols) as multifunctional agent will be demonstrated. In the end, a successful production process for fast dissolving cocoa tablets by mean of a freeze casting process is proposed.

In the second part, the production of high tensile strength paracetamol tablets using modified starch as an additive is proposed. The properties of suspensions as well as freeze casted tablets in function of solid loading, additive contents are determined and discussed. The freeze casted paracetamol tablets are evaluated in comparison to the commercially compressed tablets and show the good improvement in both aspects of the tensile strength and dissolution/dispersal time. Furthermore, the discussion about the different working mechanisms of additives including modified starch and sucrose is presented.

It is noted that some results of this work are published by the authors in previous years, i.e. Nguyen and Ulrich [Ngu13, Ngu14a-c, Ngu15a,b]. Here, to get the whole package of the topic, the published results are reused and reorganized.

2. State of the art

2.1 Tablets

Tablets are considered to be formed by compaction of powders, crystals or granulations into small cakes. In literature, the definition of tablet has been extended to include other solid forms such as pills, pellets, dragees, lozenges and the like [Joh74].

The tablet is the most popular solid dosage form. This is due to the fact that tablets own many advantages, which for instance are high dose-precision/low content variability, low cost in oral dosage forms, suitable for large scale production, etc. [Rit02, Nia09].

In general, the ingredients of tablets fall into two main groups: active ingredients and additives. The additives can be: diluents (or fillers), binder and adhesive, disintegrants. In many cases some more ingredients such as lubricants and glidants, colouring, flavoring or sweetening agents are needed [Rit02].

There are many kinds of tablets. The classification of tablets can be based on the manufacturing methods, the application routes, or the characteristic of tablets. An example of the tablet classification is shown in Tab. 2-1. The definition and basis information about the tablets in pharmaceutical field can be found in the literatures [Joh74, Rit02].

Tab. 2-1: The example of tablet classificarion.

Tablet classification			

Tablets ingested orally:
- Compressed tablet
- Multicompressed tablet
- Chewable tablet
- Targeted tablet:
  o Gastro retentive tablet (floating tablet)
  o Colonic tablets
	Tablet used in oral cavity
	- Lozenges and troches
	- Sublingual tablet
		Tablet admitted by other routes
		- Vaginal tablet
		- Implant
			Tablets used to prepare solution
			- Effervescent tablet
			- Soluble tablet

2.2 Fast dissolving tablets

Today, many pharmaceutical tablet formations are directed toward the controlled release of the active material. Fast dissolving tablets are received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical [Din11] and food industry.

Fast dissolving tablets are tablets which are designed to have a quick dissolution/ disintegration time. The dissolution/disintegration time are varied from a few seconds upto 3 minutes [Eur02] depending on specific requirements of defined tablets. In general, the dissolving/disintegration time is suggested to be as short as possible. In most cases of fast

and mouth dissolving tablets, the dissolving/disintegration time is suggested to be less than 1 minute [Goe08]. With the instant food products, the excepted dissolving/disintegration time could be longer. However, there is non-specific or incomplete standard for other properties such as size, hardness and friability of tablets are not mentioned in the definition [Dob01, Cha09].

To achieve a fast dissolving/disintegration, for compressed tablets superdisintegrants are often used [Din11]. On the other hand, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are the fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability and the tablet structure should also have a highly porous network. However, high porous structure of tablets usually leads to a low mechanical strength. Therefore, a strategy to increase tablet mechanical strength without sacrificing its porosity or requiring a special packaging to handle fragile tablets should be provided [Din11].

The list of the production techniques for fast dissolving tablets is given by Tab. 2-2.

Tab. 2-2: The production techniques for fast dissolving tablets (after Dinesh et al. [Din11], Goel et al. [Goe08], Szepes et al. [Sze07a-c], Nguyen and Ulrich [Ngu13, Ngu14a-c, Ngu15a,b]).

Techniques	**References**	**Techniques**	**References**
Direct compression	[Boh09, Gup10]	OraSolv and DuraSolv technology	[Weh96, Amb01, Lag02,
Melt granulation	[Abd04, Yan07]	WOWTAB technology	[Dha13, Din11]
Freeze drying (Lyophilization)	[Bho09, Cha09]	Flashtab technology	[Cou95]
Freeze casting	[Sze07a-b, Ngu13, Ngu14a,c, Ngu15a]	AdvaTab technology	[Oht97]
Three-dimensional Printing (3GP)	[Yu08]	Dispersible tablet technology	[Kov91]
Mass extrusion	[Din11]	Pharmaburst technology	[Kau04]
Spray drying	[Bh09, Gup10]	OraQuick technology	[Seg98]
Tablet molding	[Bho09]	Quick-Dis technology	[Dob01]
Sublimation	[Hei75, Kni79, Mak98, Ros98]	Nanocrystal technology	[Kau04]
Phase transition process	[Kun05]	Zydis technology	[Seg98]
Frosta technology	[Gir10]		

Basis definitions and principles of these techniques are reviewed by Goel et al. [Goe08] and Dinesh et al. [Din11]. The simplicity of the process and cost effectiveness of the direct compression process makes this process preferible over other processes [Cha00]. However, this technique is not able to be applied for all substances. The heat or pressure sensitive or

low flowablity substances are not suitable to be compressed. In this case, an alternative technique with low temperature and a pressure free mode is required.

The first possible solution is freeze drying. Freeze drying (lyophilization) is a process in which the solvents are removed from a frozen drug/food solution or suspension containing structure forming excipients. In some recent years, freeze drying has been applied to produce fast dissolving tablets. The freeze-drying technique has demonstrated improved absorption and increased in bioavailability. Nevertheless, it is expensive and time consuming. In addition, fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions [Bho09]. Therefore, freeze drying even though it can solve the technical problem but is not the best choice. This leads to the second possible solution, freeze casting a less complicated and lower-cost method.

2.3 Freeze casting

Due to the demand for advanced material fabrication with enhanced properties and unique characteristics, different material shaping techniques have been developed. Compared to the dry processing routes, wet shaping techniques are more effective to produce materials with complex shapes, not only dense but also porous structures. Freezing techniques involving a colloidal suspension are desirable, among different wet shaping processes, as they are flexible, cost effective and have near net shaping capabilities. Freeze casting technique is a versatile forming technique in comparison to other wet shaping processes [Li12].

2.3.1 Process principles

In general freeze casting processes include four main steps: suspension preparation, mold filling, freezing and solvent removing [Pac07c], as shown in Fig. 2.3-1. The difference to the freeze drying which focuses more on the drying or removing of solvents, the freeze casting technique focuses more on the controlling of microstructures. The freezing is the most important stage in this process.

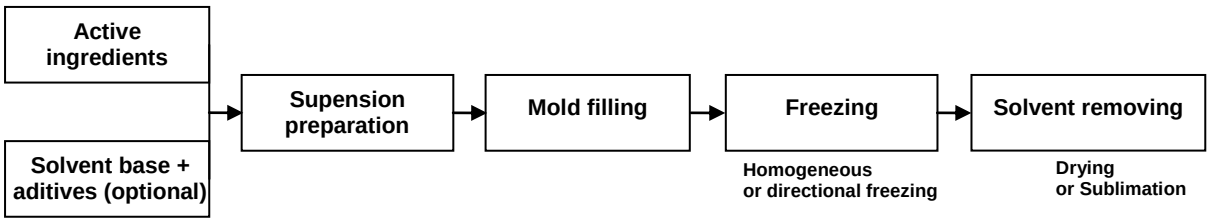


Fig. 2.3-1: General view of freeze casting process [Par07c].

The phase transition and the schematic diagram of the ice-templating principle are proposed in Fig. 2.3-2. At first the active ingredients (solid), additives and solvent base are mixed to obtain a stable and homogeneous suspension. The solvent base or the dispersing media should be liquids which a volume expansion upon freezing or have the suitable vapour

pressure and a adjustable crystal morphology as well. They can be water, camphene, naphthalene-camphor or tertiary butanol. Among these, water and camphene are the most commonly used [Li12]. Then the liquid suspension is filled in desired mold forms and frozen under homogeneous or directional freezing conditions. At last, solvent removing is carried out by conventional drying or sublimation of solidified solvent phase from the solid to the gas state under vacuum. Very desirably, freeze casting induces the solid formation by percolating the network of a dispersing medium such as waters and forms near net shape complex geometry parts with no external pressure and often environmental advantages [Li12]. A porous structure is obtained, where pores are replica of the solvent crystals [Dev08].

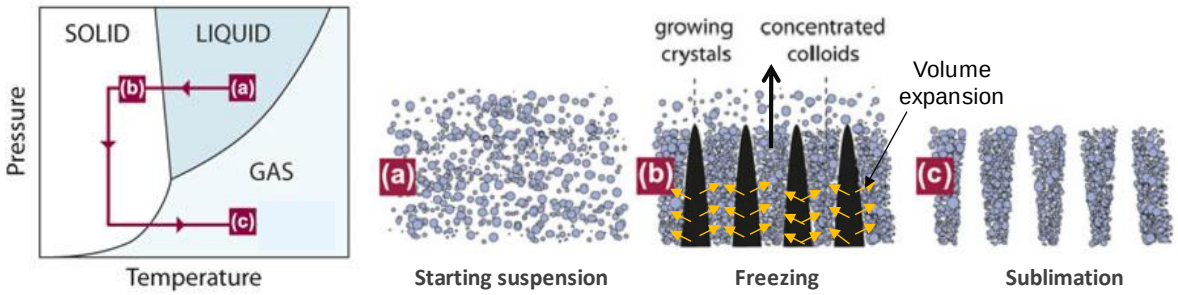


Fig. 2.3-2: Schematic diagram of the ice-templating principles (modified from Deville et al. [Dev08]). Left: phase diagram of liquid medium in the freeze casting process. Right: phenomena occur in freeze casted sample from initial suspension to the porous solid form.

2.3.2 Process control of the freeze casting

Process control is generated based on the target properties of the freeze casted solid body. Although the freeze casting technique can produce the solid form with dense or porous structure, the strongest point of this technique is able to create the adjustable porous structure. “How to regulate the microstructure of pores in produced solid bodies by the freeze casting process?” is the most regular question from the view of the process control.

There are many papers as well as reviews in literature studying the process control of freeze casting [Dev08, Was11, Li12]. In the year of 2012, the fundamental principles of porous microstructure evolution and critical factors that influence the fundamental physics involved in freeze casting of particulate suspensions was in detail elaborated by Li et al. [Li12].

In this review [Li12], it is stated that “*the most critical stage in the freeze casting process is the solidification of a prepared suspension. The formation of the porous microstructure is the result of the crystallization of the solvent and the rejection of the particles by the advancing solidification front*” and *“The additives, freeze casting conditions, suspension solids loading and particle size are critical factors influencing the resulting microstructures”.*

Tab. 2-3: Critical factors and their influences on the resulting microstructure and property of freeze casted solid body [Li12].

Factor	Effects (Influence on)	Result
Freezing condition	- Relatively independent of specific freeze casting system → possible to predict porous microstructure evolution when other factors are properly controlled	
Freezing mode	- Temperature gradient - Supercooling (supersaturation): the driving force of crystallization - Kinetic of nucleation and crystal growth	- Homogeneous freezing: result in homogeneous microstructure - Directional freezing: result in directional growth of crystal → directional microstructure
Freezing temperature	- Supercooling (supersaturation): the driving force of crystallization - Kinetic of nucleation and crystal growth	- High freezing temperature: the crystal growth control → big crystals (pores) - Low freezing temperature: nucleation is more favor → small crystals (pores)
Freezing rate		- High freezing rate: nucleation is faster than crystal growth → small crystals (pores), less organized structure - Slow freezing rate: crystal growth is kinetically more favorable than nucleation, well organized structure
Freezing time	- Crystal growth	- Crystal keep growing and small crystals can link to each other and form large crystals → bigger pores
Solid loading of suspensions	- Water content - Homogeneity of the resulting microstructure - Provide heterogeneous nucleation side	- High solid loading → dense structure, less homogeneity of resulting microstructure and vice versa - Change the morphology of crystals (pores)
Particle size	- Number of nucleation site of heterogeneous nucleation process - Interforce between particles	- Small particle: fine pore microstructure, compromised structural homogeneity - Large particle: lost detailed features in microstructure, weak solid compactivity, bigger pore size - Upper limit in particle size → a particle sedimentation and suspension instability can occur
Additive	- Thermodynamic properties of liquid phase and suspensions - Create gelation or bond to solvent molecules/solid particles	- Modify the freezing condition - Change pore microstructure - Enhance the solid connection between particle - Binding effect

The detail effects of these critical factors are clearly summarized and discussed based on the example studies of aqueous or non-aqueous systems in homogeneous or directional

microstructure. For a brief overview, a short summary for effects of the critical factors is shown in Tab. 2-3.

Based on the knowledge of the critical factors, the freeze casting procedure is operated and controlled to achieve wanted properties of solid bodies. For a fast dissolving tablet, a high dissolution/dispersal rate is the first order of requirements, however, the tensile strength of tablets is also required to be high enough to be stable under the procedure of processing, packaging, storage, transportation and in use. To achieve this target, it requires a combination adjustment of critical factors, especial, freezing conditions and additives.

2.3.3 Freezing condition effect

The freezing modes (homogeneous or directional freezing) mainly determine the type of microstructure (homogeneous or directional) in the solid bodies. Freezing temperature, freezing rate and freezing time are significant factors affecting nucleation and crystal growth and subsequently the morphology of porous microstructures. For a fine microstructure with numerous small pores, a low freezing temperature and high freezing rate is necessary. Short freezing time and low heat transfer efficiency promote the homogeneity of microstructure. It is good that the effect of freezing conditions are dependent dominately on the properties of the liquid media, they are relatively independent of the solid phase of the specific freeze casting systems. Therefore, it is possible to predict porous microstructure evolution when other factors are properly controlled.

The example studies on the effect of freezing conditions in the freeze casting process can be found in literatures, i.e. Szepes et al. [Sze07a-b].

For fast dissolving tablets, the high porous microstructure with large size pores is highly remcomended. However, the produced tablets also need to be hard enough to be stable in the manufacturing and deliver processes. Therefore, an optimized microstructure needs to be found.

The freezing conditions should be controlled to get the optimized microstructure, and hence, desired properties of freeze casted tablets. However, the energy cost need to be considered to guarantee the economic efficiency of processes.

2.3.4 Use of additives in the freeze casting

Additives are used to improve the properties of the freeze casted solid body such as tensile strength [Pac07a-c, Sze07a-b], dissolution behavior [Wit10a-b, Ngu13, Ngu14a-c, Ngu15a,b]. They can also be used to modify the freeze casting parameters. Since the additives are able to dissolve in the liquid phase, hence, they are able to change the solvent phase diagram [Ngu14a, Ngu15a], the anisotropy of the solid/liquid interfacial energy, the interparticle forces, the degree of undercooling, the solvent viscosity, the suspension freezing point and the volume expansion of the system [Li12]. Thus, additives are able to modify a nucleation rate as well as a growth behavior of the liquid phases in suspensions which leads to change in the morphologies and structures of the pores inside solid bodies.

Moreover, some additives are able to create a gelation or bonds to solvent molecules [Mun09, Li12]. The additives can be dissolved in the liquid media, improve the interaction between solid particles or liquid-solid phase. Upon freezing, they also can crystallize and solidify and thus remain as binding agents in the matrix of solid particles (see Fig. 2.3-3). Therefore, it leads to an increase of the suspension and solid stability.

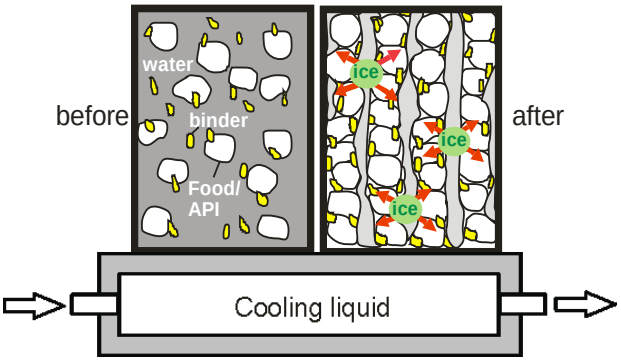


Fig. 2.3-3: Binding function of additives (binder) in the freeze casting process.

Furthermore, if soluble-additives are used as binding agents, they also enhance the dispersal/dissolution behavior of solid bodies.

In the production of porous solid materials, glycerol [Sof01, Lu07, Fu08], polyacrylic acid (PAA) [Lu07], gelatin [Zha09], silica and clay [Bli09, McK09, Li11] are the common additives for aqueous systems. In the pharmaceutical and food field, sugar and sugar alcohols including saccharose [Sze07a-b], lactose [Wit10a-b], sucrose and isomalt [Ngu14a,c, Ngu15a] or food proof acids such as citric acid [Sze07a-b] and ascorbic acid [Pac07a-c] and starch [Sze07a-b] or modified starch [Ngu15b] are often chosen as additive.

2.3.5 Application sides and its potential in pharmaceuticals and foods

Freeze casting is able to be used in plenty of industrial and research fields. It has been successfully applied as a near net shape forming technique for producing porous materials in ceramics [Lau92, Koc03, Jon00], metals [Lu06] or even polymers [Nav15]. In recent years, it has focused on producing tailored porous materials for bioapplication [Dev06, Dev08 Dev10, Fuk01a-b, Fuk02] such as cell growth template [Kim05, Gon08, Min11, Port07]; bionics, e.g. tooth and bone [Tan13]. Besides bioapplications, freeze casted porous materials are also excellent insulators, separation filters and gas distributors, since the high pore connectivity and the dense walls provide high specific strength, surface area and adsorption ability [Li12]. The high permeability as well as high chemical and thermal resistance allows these materials to be used as catalyst supports and thermal and acoustic barriers [Lu06', Mor07', Ye11].

The power of the freeze casting technique in above mentioned fields is clearly demonstrated in literature, thus, it will not be repeated here. Following in this chapter, the potential application of the freeze casting in the field of pharmaceuticals and foods will be considered and discussed.

In the year of 2007, the freeze casting was used for the first time in pharmaceutical production. The application is focused on the formulation of drug carrier in tablet form to improve the drug dissolution rate, bioavalability, theraepeutic effect as well as shelf life of active ingredients. This research branch has been carried out by Ulrich's group [Pac07a-c, Sze07a-b, Wit10a-b].

The low temperature process facilitates the formulation of drug carrier, and the designable microstructure can promote matrix-solvent interaction and therefore improve the drug dissolution, bioavailability, the therapeutic effect of the active ingredients as well as capability to prolong the life time of bio product [Li12]. The freeze casting process could avoid problems of standard tableting techniques, i.e., high temperature, high pressure and high amounts of excipients, and to bring about an improvement in the bioavailability of active ingredient in the produced tablets.

As a cheap, harmless and environmental friendly liquid, water is the most frequent dispersing medium commonly used, especially applied in the pharmaceutical and food fields. The ice crystals in the frozen suspension are the negative images of the pores in the tablet bodies after sublimating the ice. A solid form with very high porosities and adjustable structures is achievable by the freeze casting process. Therefore, the dissolution behavior is also controllable [Wit10a]. So, freeze casting is a promising technique to make a fast dissolving tablet.

Almost all previous studies in pharmaceutical fields found out that a drug containing tablet produced by freeze casting meets well the required dissolution rates. However, the mechanical stability is still too low compared to the standard value of normal drug tablets. Szepes [Sze07a-b] had investigated the freeze casting technique to develop a fast-dissolving solid dosage form containing theophylline as an active pharmaceutical ingredient, potato starch as filler, and saccharose and citric acid as binder. The result was a tablet having a rapid dissolution rate, a high porosity (up to 50%), but a lower mechanical strength of 0.32 MPa compared to that of compressed tablets with an eccentric tableting machine of ~ 2-4 MPa.

In the year 2007, Pachulski [Pac07a-c] had obtained paracetamol tablets with a good tensile strength of 2 Pa which met the tensile strength standard of normal tablets (1.5-2.5 Pa, [Wit10a, Mar02]) by using the combination of a sol-gel and a freeze casting technique. The process is based on the colloidal silica suspensions. With the advantage related to the irreversibility of a sol-gel transforming process, the water can sufficiently be removed from the sample by a simple drying. Here, a following sublimation process is not necessary. However, this process requires the use of silica colloidal as the liquid dispersal medium and SiO_2 particles are remaining in the final product.

Another solution for the low tensile strength problem is an addition of additives. Using additives often named as binder could improve the mechanical strength of produced tablets. Using saccharose and citric acid as binders could gently enhance the tensile strength of tablets from a very fragile and difficult to handle to a handled one [Sze07a]. However, the

further improvement in the tensile strength of tablets was not able to be achieved in this case study.

In 2010, Witte [Wit10b] investigated on a fast dissolving tablet of ibuprofen using the sol-gel freeze casting with sublimation. Witte also found that the target value of the dissolution behavior was always more than necessary. The tensile strength of produced tablets is in range of 0.13 - 0.65 $N*m^{-2}$ and is dependent by the composition of initial suspensions. The tensile strengths are still lower than the standard requirement of normal tablet, but nevertheless, the tablets are stable and do not break or crumble while being handled [Wit10b]. Witte also found that using lactose as binder can increase the tensile strength of tablets and also improve the dispersal rate.

Pachulski [Pac07a-c] find out ascorbic acid used as binder can improve the mechanical strength of paracetamol tablets, but they also slow down the dispersal/dissolution rate of products as well.

Until now, the balance between the mechanical strength and the dissolution/dispersal behavior of freeze casted tablets has not been reached to get the desired properties. The application of the freeze casting processes in drug production is still not widely well-known. Further studies need to be carried out.

In addition, although the freeze casting process has a potential for the production of porous solid bodies, studies of its application in foods is not to be found in literature.

2.4 Crystallization of water

In the freeze casting process of the aqueous suspensions or solutions, ice formation is the most critical and important process. The general theory and practical knowledge related to the crystallization are well-known and introduced in detail in the literatures [Mul01, Ulr03]. Here, the crystallization of water is in the focus.

The p-T phase diagram of water is shown in Fig. 2.4-1. Under normal conditions, water is the only substance which exists in all liquid, solid and gas phases. At triple point (p = 611.655 Pa, T = 273.16 K), all three phases (solid, gas and liquid) are in equilibrium and co-exist. At the end of liquid-gas equilibrium curve, the critical point (p = 22.06 MPa, T = 647.096 K) is determined. From this point, the properties of liquid and gas (vapor) are identical and impossible to be separated. At normal pressure (1.01 bar) and ambient temperature (0<T<100 °C), water stays in liquid phase, when it is cooled down lower the freezing point of 273.15 K (0 °C), it is frozen and called ice. It is transferred to gas when it is heated up to boiling temperature of 373.15 K (100 °C).

Depending on the phase transition conditions (pressure and temperature) the formed ice could exist in various polymorphs. In crystalline phases of ice, the water molecules linked to four neighboring water molecules by hydrogen bonds [Zhe06] (see Fig. 2.4-2).

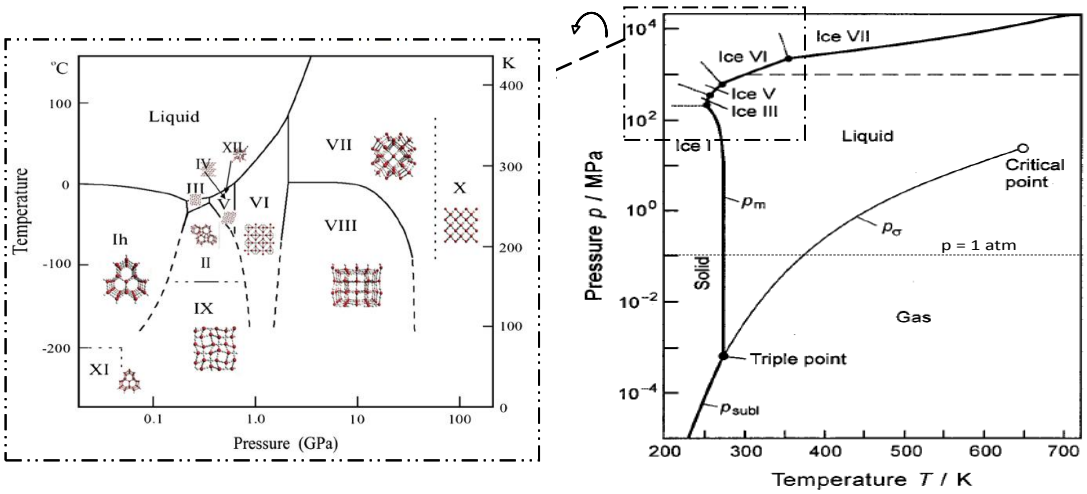


Fig. 2.4-1: Right: The p-T diagram of water [Wag02]. Left: The solid-liquid phase diagram of ice (the solid-liquid-gas triple point and liquid-gas coexistence line lie off the diagram to the left) [Bar12].

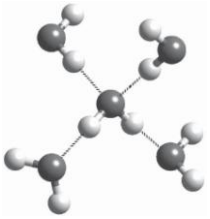


Fig. 2.4-2: A four-coordinated water molecule showing the classic tetrahedral arrangement of the first neighbor environment, of hydrogen bonds to four neighbors: The central molecule 'donates' two hydrogen bonds to its two lower neighbors and 'accepts' a hydrogen bond from each of its two upper neighbors [Fin04].

The oxygen atoms are fixed positions relative to each other, however, hydrogen atoms may or may not disordered but obeying the 'ice rules' [Ber33]. The flexible of the position of hydrogen atoms enrich the structure arrangement of ice crystals in crystal lattice and create the polymorphism phenomena. There are 18 or so crystalline phases and three amorphous phases of ice [Mar15]. Some of them are marked in a phase diagram in left side of Fig. 2.4-1. It is lucky that the polymorphism phenomena of ice do not occur at normal condition. Virtually all the ice on Earth's surface and in its atmosphere (such as, ice from freezer, snowflake and icebergs) is of a hexagonal crystalline structure denoted as ice "Ih" (see Fig. 2.4-3). However, changing pressure and temperature can cause changes of phase into other forms, as indicated in the phase diagram of Fig. 2.4-1. These structures can be simply rationalized in terms of fully connected tetrahedral networks of water molecules, with each molecule donating hydrogen bonds to two neighbors and accepting two hydrogen bonds from two others (see Fig. 2.4-2). In the low-pressure ice "Ih", the O–O–O angles are close to the ideal tetrahedral angle of 109.47°. As pressure is increased, the molecules have to rearrange themselves to occupy less volume and this is done initially by both changes to the network structure (but still retaining four coordination) and increased distortion of the O–O–O angles: for example, in ice II these angles vary between 80° and 129°. As the pressure is increased, the system comes to a point at which the reduced volume available cannot be filled by

merely increasing hydrogen-bond distortion: The water molecules then form interpenetrating networks, as in ice VII which consists essentially of two interpenetrating diamond-type lattices. But each network remains four coordinated [Bar12]. By rearrange the structure to occupy less volume, ice polymorphs are formed at high pressure conditions owning a significantly higher density in comparison to the density of water. Only the ordinary ice “I” has the lower density than water.

Morphology of ice

As be seen in Fig. 2.4-3, a schematic picture of a simple ice prism is shown.

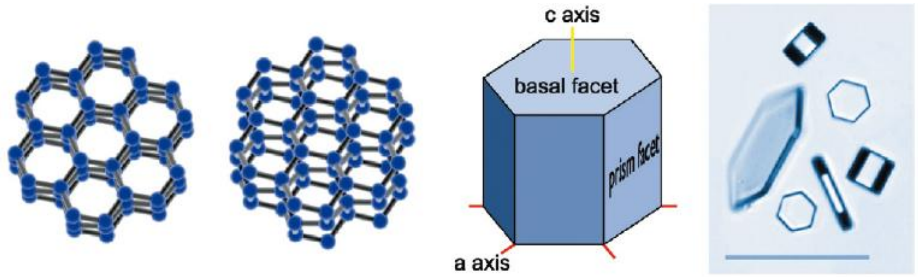


Fig. 2.4-3: Left: two views of the crystal structure of ice “Ih”, showing a lattice of ‘puckered’ hexagons. Here balls represent oxygen atoms and bars represent hydrogen atoms. Middle: A schematic picture of a simple ice prism, defining the principal crystal axes and facet planes. Right: A mosaic image of some typical small ice prisms grown in the lab, showing different aspect ratios. The scale bar is 100 μm long [Lib05].

The basic crystal unit is the hexagon structure. However, depending on the nucleation and growth mechanism, morphologies of ice crystals at the end of crystallization processes are much different. An interesting example of the diversity of the ice morphology is snow. Snow is consisting of ice crystals which are formed from vapor in atmosphere. The atmosphere conditions are different at almost every certain position, therefore the morphological behavior of snowflakes seem to be endless variability. The snow morphology diagram Fig. 2.4-4) presented by Libbrecht [Lib05] shows different types of snow crystals that grow in air at atmosphere pressure, as a function of temperature and water vapour supersaturation relative to ice. In this figure, it is noted that the morphology of ice switches from the plates (T~-2°C) to columns (T~-5°C) to bigger plates (T~-15°C) to predominantly columns (T<-30°C) as temperature is decreased. Temperature mainly determines whether snow crystals will grow in to plates or columns, while higher superstaturations produce more complex structures.

In the crystallization of ice form liquid, the ice morphology is various based on the thermodynamic and kinetic factors. While the nucleation mainly depends on thermodynamic properties, crystal growth is more dependent on the kinetic mechanisms. In normal ice freezers, the morphology of ice is mainly controlled by controlling the freezing temperature, the freezing surfaces and the temperature gradient. By fast directional freezing, the ice grows

in a needle-like structure. While, by slow and homogeneous freezing, the ice obtains a small prism structure, which is preferred as planar layer or plannar lamellar structure.

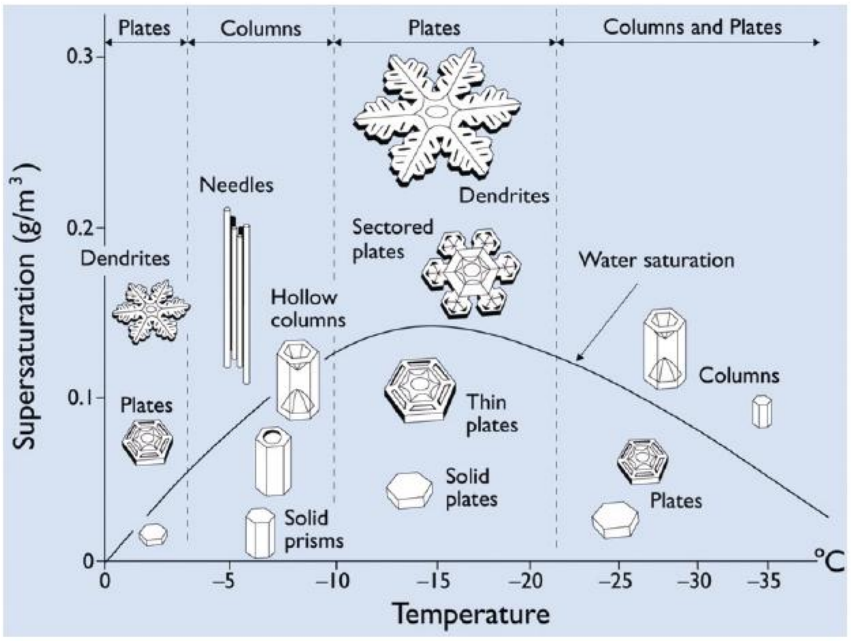


Fig. 2.4-4: The snow crystal morphology diagram [Lib05].

3. Aims of the work

Fast dissolving products are of high interest in pharmaceutical industries due to their excellent drug delivery. Such tablets are being interested in food industries for instant products, too. Since tablets may be considered a alternative product for fine-powder forms which can prevent the agglomeration problem.

Conventional compression is the most common technique to produce tablets. However, not all of drug ingredients are suitable to be compressed. The substances which are sensitive to heat and pressure are not stable under the conventional compressing. In addition, the active pharmaceutical ingredients which own a good enough solubility but have a slow dissolution rate are not effective for practical use as compressed tablets. Hence, new tableting techniques which can overcome the above-mentioned problems of the conventional compression and enhance the dissolution/disintegration of such above-mentioned substances are of high interest.

A high dissolution rate of tablets can be achieved by the addition of disintegrants or by controlling the porosity and thus the surface area of tablets. Using cold compression of aqueous liquid suspensions and followed by a sublimation process, the so called freeze casting techniques is able to produce high porous solid bodies with a controllable microstructure by means of low temperature and free external pressure.

It opens a new challenge for the freeze casting technique in new fields of application: Tablet production of pharmaceuticals and foods. However, as mentioned in the previous chapter, the application of the freeze casting process in the food industry is not to be found in literature yet. Although a few studies in tablet production have been presented [Pac07a-c, Sze07a-b, Wit10a-b], freeze casted tablets of drugs are still hindered in pharmaceuticals due to their poor tensile strength. The hardness of produced tablets was demonstrated to be improved by a combination of the freeze casting and sol-gel technique [Pac07a-c]. However, the silica particles are remaining in the final products and a very fast dissolution/ disintegration behavior is difficult to be achieved in such a production so far.

Due to the current status of the freeze casting process in pharmaceutical and food fields, the following questions need to be addressed:

1. How to overcome the low tensile strength problems without slowing down the dissolution/disintegration behavior of produced tablets in aqueous suspensions of foods and pharmaceuticals?
2. Is it possible to produce a new dosage form as a fast dissolving tablet replacing fine-powder forms of foods by means of a freeze casting process?

This work aims to demonstrate the application ability of the freeze casting process in new fields, foods and pharmaceuticals. The work is focused on the use of multifunctional

additives to improve both the tensile strength and dissolution/disintegration behavior of freeze casted tablets. The experiments of the freeze casting process are investigated based on the aqueous suspensions with and without additives. Here, the kinetics of the nucleation and the growth of crystals in the freezing step are not focused. The optimization of sublimation parameters is not investigated.

The first objective is to produce a fast dissolving/dispersal tablet of foods from a fine-powder form. The following aspects must be clarified in detail:

- Determination of the metastable zone width to choose the proper range of processing temperatures. Here the prior tests of the thermodynamic properties of suspensions should be done.
- The influence of the freeze conditions on ice morphology and consequently the quality of produced tablets.
- The influence and the working mechanism of additives on the modification of pore microstructures and consequently the quality of products.
- The effect of solid loadings on the quality of freeze casted tablets.
- A brief understanding on the physical properties of suspensions, especially, the rheological properties for the further processing design.

As result, a freeze casting process in lab scale to produce fast dissolving tablets of foods should be proposed. The freeze casted products should fulfill the necessary requirements in terms of the tensile strength and dissolution time of instant products in food uses.

The second objective of this work is to prove the ability of the freeze casting process in drug productions regarding improvements in both the hardness and the dissolution rate of freeze casted tablets. Here, in this case study the focus is:

- The modifying of the defined freeze casting process of the previous studied food system for the application of the drug system.
- Creation of high tensile strength freeze casted tablets of drugs with a good improvement of the dissolution rate.
- Explanation regarding the role of additives in the control of the product quality.
- The investigation on the physical properties of suspensions to get a brief understanding.

The experimental results in this case study should show a significant improvement of the product quality. Freeze casted drug tablets with competitive characteristics related to the hardness and the dissolution rate in comparison to compressed tablets should be achieved.

In both case studies, a proof of concept should be presented.

4. Materials and Methods

4.1 Materials

4.1.1 System 1 – food: cocoa tablet

4.1.1.1 Cocoa powder

Cocoa is a food ingredient that is not only important for the contribution of flavor to foods and beverages but is also associated with potential health benefit [Mil08]. Chocolate liquor, cocoa butter, chocolate paste, and cocoa powder are main products produced from the cocoa bean which is botanically the seed of the fruit of the cacao tree, Theobroma cacao L.

The handling routine of cocoa products is well known and simple. After harvesting, the cacao seeds are separated and typically fermented for 4-5 days, dried, deshelled and roasted at 100-150 °C. The roasted cocoa beans are then usually ground into a suspension. Cocoa powder, also named cocoa solid, cocoa and cacao is usually made by mechanically pressing the liquor of this suspension to expel most of the cocoa butter, leaving a solid cake, which is then ground into the product.

Typical cocoa powders contain 10-12 % residual cocoa butter, with the remainder being nonfat cocoa solids, the brown particulate matter of seed. It is a mixture of many substances, containing several minerals including calcium, copper, magnesium, phosphorus, potassium, sodium and zinc. All of these minerals are found in greater quantities in cocoa powder than either cocoa butter or cocoa liquor. In particular, cocoa solid are one of the richest sources of flavanol antioxidanes [Mil08]. It is also well known as substance that can reduce the number of free radicals involved in cardiovascular and cancerous diseases [Jal08]. Cocoa powder can contain up to 10% its weight in falvonoids. This amount can be reduced depending on how long and how many amounts of processing and manufacturing the cocoa powder undergoes. With the healthy properties, fantastic taste and flavor, cocoa, especial cocoa powder, become a worldwide essential food ingredient for people in daily life. While chocolate liquor and cocoa butter are used for the manufacturing of chocolate candy, significant quantities of cocoa powder are used to manufacture chocolate syrups and coatings as well as other nonconfectionery food applications such as baking, flavorings in ice cream, icings, and beverages. Hot chocolate simply prepared from cocoa powder and hot milk or water, became a favorite drink for human in cold weather.

Natural cocoa powder has a light brown color and a pH level of 5.1 to 5.4. The processed (alkalized) cocoa powder is darker in color, ranging from brownish red to nearly black, with a pH from 6.8 to 8.1. The alkalization process reduces bitterness and improves solubility, which is important for beverage product applications. All of these pH values are considered safe for food use. Natural cocoa solid is commonly used in powder form. Most grades of

cocoa powder have an average bulk density of 0.56 g*cm^{-3}. However, the cocoa powder in fine particles can have some inconvenient behaviors, i.e. sticking on wetting spoons, easily being agglomerated when they are wet or poured into liquids, the powder just floats on the surface and is difficult to disperse or dissolve. Furthermore, cocoa powder is aeratable, meaning air movement may cause the cocoa powder to take flight and settle as dust, if not properly contained. To overcome these inconveniences in use, the instant cocoa products should be produced in granular forms which are heavy enough to sink down and dissolve in liquid.
In this work, cocoa powder (Gepa The Fair Trade Co., Germany) with particle sizes smaller than 160 µm was chosen as a food candidate. The cocoa powder is the highly defatted cocoa with a cocoa butter content of 10–12 wt% and K_2CO_3 as impurity. The components and nutrition data of cocoa powder are listed in Tab. 4-1.

Tab. 4-1: Composition of cocoa powder [GEP14].

Components	wt%	Nutrition	Per 100g
Highly defatted cocoa	97	Energy	310 kcal
(Cocoa butter content: 10 - 12%)		Protein	23.5 g
Others	3	Carbohydrate	14 g
		Fat	11 g

4.1.1.2 Water and Ice

There is no doubt about the significant role of water in life cycles. Almost all living objects need water to maintain their life, their growth and development. In technical and production fields, water is the most widely used excipient in all industrial sizes, especial in food industry, pharmaceutical production operations, and plays the most importance role in biological processes [Zhe06]. However, it is an unusual liquid. Owning a dipolar molecule, water molecules easily form the hydrogen bondings between each other as well as with other partners. Therefore, it has a very high boiling point and high heat of vaporization, a very high surface tension, the greatest dielectric coefficient of any liquid, and become an excellent solvent for salts and polar molecules. The important properties of water and ordinary ice are listed in Tabs. 4-2 and 4-3.

Ice has a very high melting point (0°C at atmosphere pressure). The interesting point is that water expands its volume upon freezing. For almost all liquids substance, a density of a liquid decrease when temperature increase, and further increase when a liquid transfer to a solid form, because of the more compactive structure of solid phase in comparison to liquid phase. Apart from that, the density of water reaches a maximum value at a temperature of 3.98 °C, not at the freezing point. When water freezes it expands rapidly adding about 9 % by volume. As ice is lighter than water at ambient conditions, it floats. A full picture of the

density of water and ice as a function of temperatures in atmosphere pressure is shown in Fig. 4.1-1.

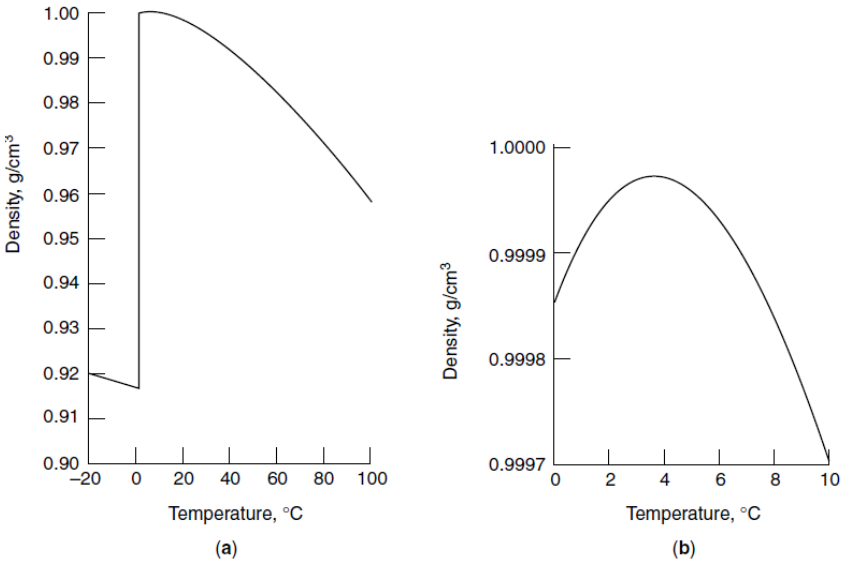


Fig. 4.1-1: (a) The density of ice and liquid water at 1.01 bar as a function of temperature, and (b) the density in the domain of its maximum [Mor07].

Tab. 4-2: Properties of water liquid at 1.01 bar [Mor07].

Property	Unit	Value
formula		H_2O
molecular weight	$g*mol^{-1}$	18
heat of formation at 25 °C	$kJ*mol^{-1}$	285.890
apparent dipole moment	C*m	6.24×10^{-30}
viscosity at 25 °C	mPa*s	0.8949
density, at 25 °C	$g*cm^{-3}$	0.9979751
at 0 °C		0.99987
surface tension	$mN*m^{-1}$	72.8
freezing point	°C	0.0
boiling point	°C	100.0
isothermal compressibility, over the range of 0.1-1 mPa, at 25 °C	nPa^{-1}	0.45
specific heat at constant volume at 25 °C	$J*g^{-1}*K^{-1}$	4.17856
thermal conductivity 20 °C	$W*cm^{-1}*K^{-1}$	0.00598
temperature of maximum density	°C	3.98
electrical conductivity at 25 °C	$S*cm^{-1}$	$<10^{-8}$
heat of fusion	$J*g^{-1}$	334.774

Due to the volume expansion upon freezing, water is selected as a liquid medium for the freeze casting process. In this study, distilled water was used as the solution base or dispersing medium.

Tab. 4-3: Properties of ice at 1.01 bar [Mor07].

Property	Unit	Value
heat of formation at 0 °C	$kJ*mol^{-1}$	292.72
Young's modulus of elasticity at -10 °C	MPa	967
density at 0 °C	$g*cm^{-3}$	0.9168
coefficient of cubical thermal expansion at 0 °C	$cm^3*g^{-1}*°C^{-1}$	120×10^{-6}
coefficient of linear thermal expansion at 0°C	$°C^{-1}$	52.7×10^{-6}
isothermal compressibility at 0 °C	nPa^{-1}	0.12
specific heat at 0 °C	$J* g^{-1}*K^{-1}$	2.06
thermal conductivity	$W*cm^{-1}*K^{-1}$	210

4.1.1.3 Sugar (sucrose)

Sucrose is a sugar obtained from sugar cane, sugar beet and other sources. It is a popular food product named sugar or saccharose. The other synonyms are refined sugar, beet sugar, cane sugar and a-D-glucopyranosyl-b-D-fructofuranoside. Sucrose can exhibits as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder. It is odorless and has a sweet taste. The structural formula of sucrose is shown in Fig. 4.1-2, and its typical properties are listed in Tab. 4-4. At room temperature and moderate relative humidity, sucrose has good stability. The moisture can absorbed up to 1% of sucrose, and is released upon heating at 90 °C. When heated to temperatures above 160 °C, sucrose caramelizes and decomposed.

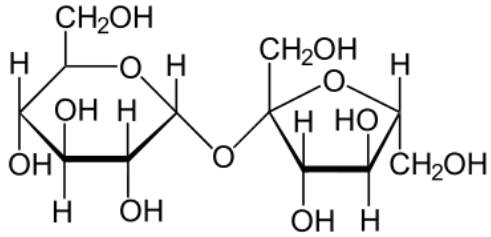


Fig. 4.1-2: Structural formula of sucrose molecule.

With sweet and pleasant taste, sucrose is known as a must-have ingredient for daily meals, a popular ingredient in food field (i.e., candy, drinks, cake, etc.). Besides that, it is widely used in oral pharmaceutical formulation in various functional categories, namely: base for medicated confectionery, coating agent, sweetening agent, sugar coating adjunct, suspending agent, sweetening agent, viscosity-increasing agent [Row09]. Particularly, in tablet production it can be applied as binder, tablet and capsule diluents and filler as well, tablet-coating agents.

In this work, sucrose is dissolved in aqueous phase and used as a binder to improve the tensile strength of tablets.

Tab. 4-4: Typical properties of sucrose [Row06].

Property	Unit	Value
formula		$C_{12}H_{22}O_{11}$
molecule weight, M		342.3
color		Colorless or white crystals
density (bulk)	$g*cm^{-3}$	0.93 (crystalline)
		0.60 (powder)
density (tapped)	$g*cm^{-3}$	1.03 (crystalline)
		0.82 (powder)
density (true, or apparent)	$g*cm^{-3}$	1.6
melting point	°C	160-186
		(with decomposition)
solubility in water		1 in 0.5 at 20 °C
		1 in 0.2 at 100 °C

4.1.1.4 Isomalt

Isomalt is a sugar alcohol which has a pleasant sugarlike taste with a mild sweetness approximately 50-60% of that of sucrose. It is a mixture of two stereoisomers 6-O-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) and 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (1,1-GPM) (see Fig. 4.1-3). 1,6-GPS is more soluble than 1,1-GPM, therefore, by changing the ratio of two components, the solubility and water crystal contents can be adjusted. In general, isomalt occurs as a white or almost white powder, granular or crystalline substance. Because of the lower sweetness tastes and noncariogenic properties, isomalt is used in a variety of pharmaceutical preparations including tablets or capsules, coatings, sachets, suspension and in efferverscent tablets. It is also used widely in lozenges, sugar-free chewing gum, hard-boiled candies and as a sweetening agent in confectionery for diabetics. Negligible negative heat of solution, mild sweetness and 'mouth feeling' properties make it be commonly used in chewable tablets. Furthermore, it can also be used in direct compression and wet granulation [Row06]. The selected properties of isomalt are list in Tab. 4-5.

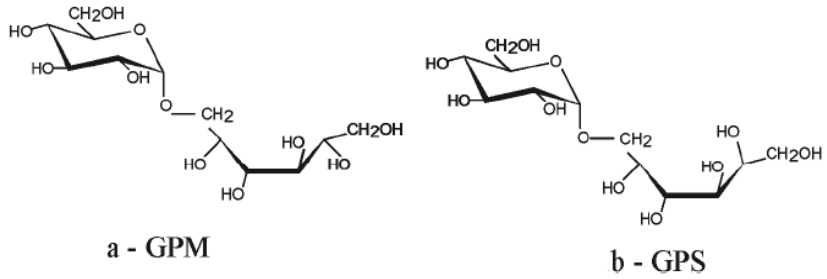


Fig. 4.1-3: Structure of the two isomeric components of isomalt [Bor01].

Tab. 4-5: Typical properties of isomalt [Row06].

Property	Unit	Value
Fomular/Molecule weight, M		1,6-GPS: $C_{12}H_{24}O_{11}$/344.32
		1,1-GPM: $C_{12}H_{24}O_{11}.2H_2O$/380.32
Color		white
Density (bulk)	$g*cm^{-3}$	0.43-0.85
Density (tapped)	$g*cm^{-3}$	0.48-0.70
Density (true, or apparent)	$g*cm^{-3}$	1.52 for 1,6-GPS
		1.47 for 1,1-GPM
Melting point	°C	166-168 for 1,6-GPS
		168-171 for 1,1-GPM
		141-161 for a 1:3 mixture of 1,1-GPM
		and 1,6-GPS
Heat of solution	$kJ*mol^{-1}$	+14.6 for an equimolar mixture
		of 1,1-GPM and 1,6-GPS
Solubility in water		GalenIQ 720, GPM/GPS=1/1
		(with decomposition)
		~ 23 % at 20 °C
		~ 80 % at 100 °C

Isomalt also has very good thermal and chemical stability. There are no changes in molecular structure, when it is melted. It exhibits considerable resistance to moisture (up to humidity of 85 %), acids and microbial influences. If stored under normal ambient condition, isomalt is chemical stable for many years.

In this work, isomalt (C*Isomaltidex^{TM}, Cargill GmbH, Germany) is dissolved in aqueous phase and used as an additives to improve the tensile strength of tablets. It is the white powder with melting point of 145 °C and solubility in water of 245 $g*L^{-1}$.

4.1.1.5 Xylitol

Xylitol also named as xylit is a small molecule sugar alcohol which occurs as a white, granular solid comprising crystalline particle. It is odorless with a sweet taste and cooling sensation. It is used as a noncariogenic sweetening agent in variety of pharmaceutical dosage forms, including tablets, syrups and coating. With equal sweetness intensity to sucrose, combined with a distinct cooling effect upon dissolution of the crystals (due to a negative heat of solution of -157.1 kJ*mol^{-1} [Row06]), xylitol is significantly effective in enhancing the flavor of tablets and syrups. It can be used to mask the unpleasant or bitter flavor associated with some pharmaceutical actives and excipients. It is also widely applied as an alternative to sucrose in food and confectionery. Unlike sucrose, xylitol is not fermented in cariogenic acid end products and by inhibiting the growth of cariogenic bacteria, it has been shown to reduce dental caries. Therefore, it is to be found more and more in its application in dental care product such as chewing gum, mouthrinses and toothpastes. It is also found to be used in cosmetic and toiletry application [Row06]. The structural formula of xylitol is shown in Fig. 4.1-4, and its typical properties are listed in Tab. 4-6.

In this study, xylitol (≥ 98.5 %, Carl Roth GmbH & Co. KG) is used.

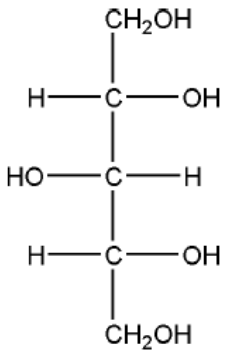


Fig. 4.1-4: Structural formula of xylitol [Row09].

Tab. 4-6: Typical properties of xylitol [Row06].

Property	Unit	Value
Fomular/Molecule weight, M		$C_5H_{12}O_5$/152.15
Color		white
Density (bulk)	g*cm^{-3}	0.8-0.85 (crystalline)
		0.5-0.7 (granulated grade)
Density (true, or apparent)	g*cm^{-3}	1.52
Melting point	°C	92.0-96.0
Heat of solution	kJ*mol^{-1}	-157.1
Solubility in water		1 in 1.6 at 20°C

4.1.2 System 2 – drug: paracetamol tablet

4.1.2.1 Paracetamol

Paracetamol, N-acetyl-p-amino phenol (also known as acetaminophen), is a readily available, nonprescription antipyretic and analgesic compound. It is the most often prescribed drug to treat mild-to-moderate pain or fever in infants, including neonates, and can be administered by different routes (i.e., oral, rectal, or intravenous). It has analgesic and antipyretic activity, but has only very modest peripheral anti-inflammatory properties. It is also the only compound recommended to treat fever in neonates [Pac15]. The formula structure of paracetamol molecule is shown in Fig. 4.1-5 and its typical physical properties is listed in Tab. 4-7. Paracetamol often exists in an odorless, white solid form and has slightly bitter taste. It has the melting point in range of 169 and 170.5 °C. Paracetamol dissolves well in alcohol, dissolves moderately in water at room temperature (20 °C) (c = 14 g*L^{-1}) [O'Ne01]. It is sensitive to light, should be stored at a temperature less than 40 °C, preferably between 15-30 °C [Sun69]. Paracetamol reacts as a derivative phenol, the saturated aqueous solution has pH value in range of 5.5-6.5 [Lew01]. It is easily synthesized in laboratory as well as in industry from phenol. In market paracetamol is available in a tablet, capsule, liquid suspension, suppository, intravenous, intramuscular and effervescent form. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose, for adults, is 4000 mg.

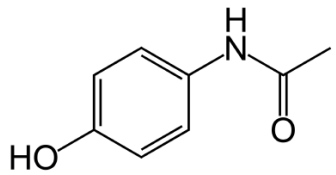


Fig. 4.1-5: Molecular structure of paracetamol [O'Ne01].

Tab. 4-7: Typical properties of paracetamol [O'Ne01].

Property	Unit	Value
Fomular/Molecule weight, M		$C_8H_9NO_2$/154.17
Color		white
Density	g*cm^{-3}	1.293
Melting point	°C	169-170.5
Solubility in water at 20°C	g*L^{-1}	14

In this work, the paracetamol purchased from Caelo, Germany. It is the white solid powder, melting point of 169-171 °C, density at 20°C of 1.293 g*cm^{-3}, solubility in water at 20 °C of 14 g*L^{-1} [Cae13]. The distribution of particle size paracetamol determined by Mastersizer 2000

(Malvern, UK) particle size analyzer, is in range of 1.26-224.40 μm with the mean value around 50 μm.

4.1.2.2 Modified starch

Starch is a nature biopolymer which has been widely applied in the manufacturing of textiles, paper, adhesives and food because of its thickening, gelling, adhesive and film-forming abilities. It consists of linear amylose and branched amylopectin, two polysaccharides based on a (D)-glucose (see Fig. 4.1-6).

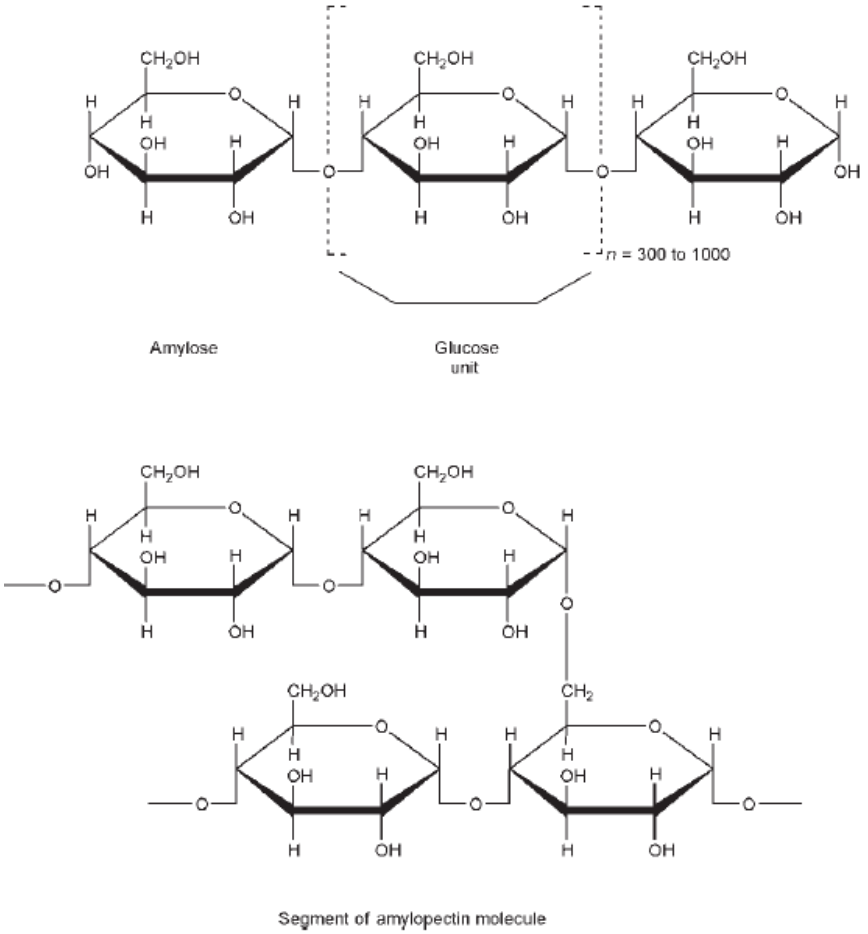


Fig. 4.1-6: Structural formula of amylose and amylopectin [Row09].

Both polymers are organized in a semicrystalline structure, and in the starch granule, amylopectin forms the crystalline portion. The exact structure of starch is still not yet fully understood. The molecules of polymers are organized in similar structure as clusters. The different configurations of these molecules result in different behavior in cold aqueous solutions. Amylose (only 1,4 bonds) tend to crystallize in insoluble adducts, whereas amylopectin slowly jellify and form opaque and highly viscous preparations after some days. Starch can be found in different food sources, such as maize, potato, rice, tapioca, wheat,

pea, etc. Depend on the origin and the nature of the starch, the molecular weight can range between 50 and 500 million Da.

Starch is a versatile excipient. It has an odorless and tasteless, occurs in fine, white to off-white powder and can be naturally degraded in human body. In addition, it has inert properties and do not often react with active drug substance. Therefore, it has a wide application in pharmaceutical field. In pharmaceutical formulation and technology, especial, in oral solid-dosage formulations, it is often used as a binder, diluents and disintegrant [Row09]. Depend on the needs of specific applications, starch can be modified to be soluble, partly soluble or good flow properties.

In this work, a water-soluble modified starch, namely, CAPSUL® (Ingredion Inc., Germany) is used as additive in production of paracetamol tablets. It is a modified food starch derived from waxy maize, appears as an off-white powder [Ing12]. The typical properties of modified starch are listed in Tab. 4-8.

Tab. 4-8: Typical properties of the modified starch - CAPSUL® [Ing14].

Property	Unit	Value
Molecular weight		>10000
Color		Off-white powder
Odor		Starch
Moisture	%	~ 10
pH (1% solution)		~ 3.5
Solubility in water		Soluble
Density (true, or apparent)	$g*cm^{-3}$	1.500

4.1.3 Summary of used materials

Additionally to the chemicals named in two previous chapters, lactose, citric acid and potato starch are also used as additives in the experiments. Diluted hydrochloric acid is used as the liquid medium for dissolution tests in the case study of paracetamol tablets. A summary of all used chemicals is given in Tab. 4-9.

Tab. 4-9: Summary of chemicals used in experiments.

Chemical	**Product name**	**Supplier**	**Use**
Cocoa powder	Kakao Amaribe	Gepa The Fair Trade Co.	Food substance
Water (distilled)	-	-	Liquid medium
Sucrose	Zucker	Sudzucker AG	Additive: binder and enhanced solubility agent
Isomalt	C*Isomaltidex^{TM}	Cargill GmbH	Additive: binder and enhanced solubility agent
Xylitol	Xylit	Carl Roth GmbH & Co. KG	Additive: binder and enhanced solubility agent
Lactose	Lactose monohydrate	Carl Roth GmbH & Co. KG	Additive: binder and enhanced solubility agent
Citric acid	Citic acid	Sigma – Aldrich Co. LLC	Additive: binder and enhanced solubility agent
Paracetamol	Paracetamol plv., API	Caesar & Loretz GmbH	Drug substance
Modified starch	CAPSUL ®	Ingredion Inc.	Binder and disintegrant
Maize starch	Starch 1500® Partially Pregelatinized Maize Starch	Coloron	Binder and disintegrant
HCl	Hydrochloric acid 37 %	Sigma – Aldrich Co. LLC	Create the liquid medium for dissolution tests.

4.2 Methodologies and instruments

4.2.1 Freeze casting process – tablet production

The experimental flow design of the freeze casting process, based on the general process of freeze-casting (as seen in Fig. 2.3-1), is shown in Fig. 4.2-1. This process includes four main steps: (1) suspension preparation by mixing, (2) casting in the preferred form mold, (3) solidification by freezing at low temperature and ambient pressure, (4) and solvent removal by sublimation under reduced vacuum. And the experimental set up is shown in Fig. 4.2-2.

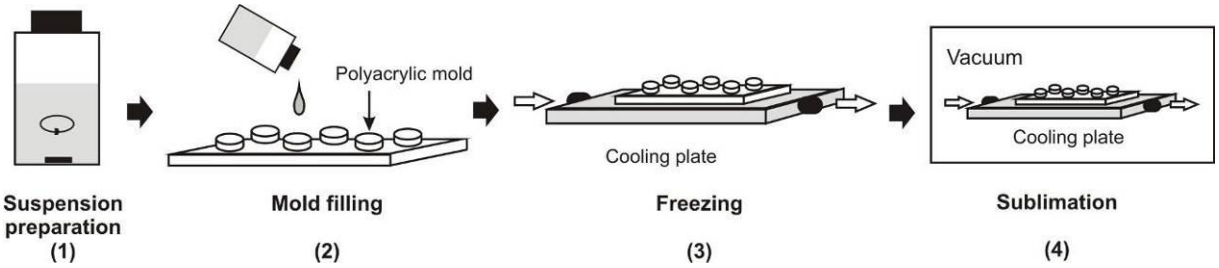


Fig. 4.2-1: The freeze casting process [Ngu14a].

In first step, the suspensions were prepared by mixing a solid ingredient (cocoa or paracetamol) in a dispersal medium at room temperature at a defined solid loading. Depending on the experiment series, the solid can be paracetamol or cocoa, the dispersal medium can be water or an aqueous solution of additives. Here additives were modified starch or sugar and sugar alcohols, i.e., sucrose, isomalt and xylitol. After being mixed, the well prepared suspensions were filled into the molds. Cylindrical polyacrylic molds in different sizes (16 and 6 mm inner diameter, 10 mm in height for cocoa, or 16 and 10 mm inner diameter, 5 mm in height for paracetamol) were used to achieve the tablet forms. Then the suspensions in mold forms were frozen on a cooling plate at ambient pressure and low temperature exactly controlled by a super-low temperature circulator thermal bath.

The freezing process can be generated in two modes: one-side cooling (only from the bottom) and two-side cooling (from both the bottom and the top of the polyacrylic mold with two cooling plates). In case of freezing from two sides, the upper cooling plate was positioned by “spring units” (see Fig. 4.2-2) at a distance guaranteeing contact with the suspension surface, however, without any extra pressure on the samples resulting from the plate’s own weight. This upper cooling plate was removed after the freezing step by releasing the valve of the spring units, to obtain a free surface for the sublimation step. After the freezing step, to switch from the freezing temperature to the drying temperature, a heating step was performed at a heating rate of 1 $K*min^{-1}$. Then, the ice crystals were removed by sublimation at a constant drying temperature of -8.1 °C under reduced pressure. The vacuum was generated by a vacuum pump (Leybold Trivac, D4B) until no water remained. In general,

the drying process was generated overnight. The produced tablets obtained after the drying step were stored in the sealed bottles to be ready for further quality evaluation processes.

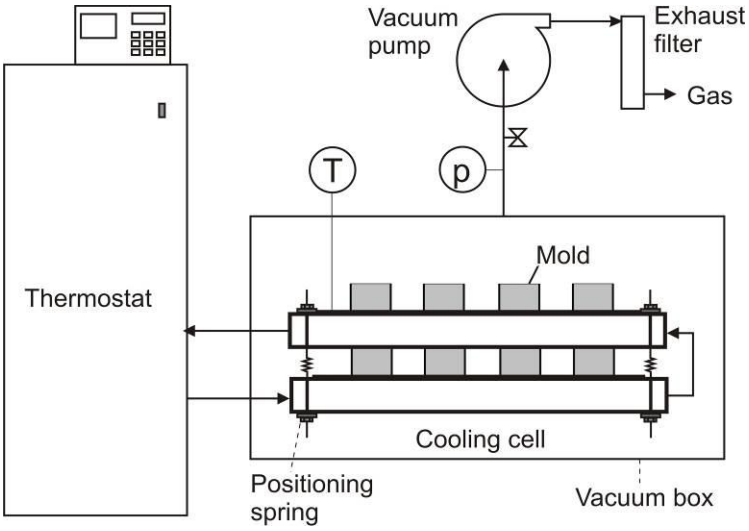


Fig. 4.2-2: The experimental setup.

4.2.2 Characterization properties of suspensions

In order to understand the system and design the operating parameter of processing, the properties of suspension such as basic physical and thermodynamic properties need to be determined. Here, the density, viscosity, surface tension, melting and freezing point of suspensions were determined by following analysis techniques. All sampling procedures and measurements for analysis were carried out in triplicate.

4.2.2.1 Density measurement

Density ρ, is defined as the amount of substance in an volume unit. The most common density is mass density which is calculated as:

$$\rho = \frac{m}{V} \qquad \text{(Eq.4-1)}$$

where m is mass of substance [g], V is the volume of substance [cm^3].

The relative density (RD) is the ratio of the density ρ of a substance to the reference density ρ_0 of a reference substance under conditions which must be specified separately for both substances. In general, the density of water at 4°C, or at measurement temperature is used as the reference density.

With assumption that the air is degassed from suspension, the density suspension of one solid in liquid can be calculated as:

$$\rho = \frac{100}{\frac{c_w}{\rho_s} + \frac{100 - c_w}{\rho_l}} \quad \text{(Eq. 4-2)}$$

where c_w is the weight concentration of solid in suspensions [wt%], ρ_s is the apparent density of the solid [g*cm^{-3}], ρ_l is the density of liquid [g*cm^{-3}].

In this presented work the densities of solutions and suspensions were measured by D40 Density Meter from Mettler Toledo. The principle of this method is based on the electromagnetically induced oscillation of a U-shaped glass tube as the variation of its mass. The U-shaped glass has a defined volume capacity. When a measured substance is filled, the oscillation is determined and the density of filled substance is estimated. The measured density will be compared with the calculated value as well.

4.2.2.2 Rheology and viscosity measurement

Rheology describes the deformation of a body under the influences of stresses. The body here can be solids, liquids or gases. The ideal solids deform elastically and fully energy recovered when the stresses are removed, while the ideal fluids (liquids and gases) deform irreversibly and flow when the stresses are applied. However, the real bodies behave neither as ideal solids nor as ideal fluids. Real solids can also deform irreversibly under the influence of forces of sufficient magnitude, they creep or flow. Only a few liquids of technical or practical importance come close to ideal liquids in their behavior, the vast majority of liquids show a rheological behavior in between the liquids and the solids. They are in varying extents both elastic and viscous named “visco-elastic”. Solid can be subjected to both tensile and shear stresses while liquid such as water can only be sheared [Schr00].

In industrial processing, the rheology properties of substances are considered as a must-known factor to control processes, especially, in the production where the substance need to be flowed, pumped or moved, for example: the process of mixing, pumping, drying, feeding, etc. Therefore, the rheological property of the fluid becomes more important. In field of fluid, rheology property is considered in term of viscosity. It is defined as the resistance of a fluid against any irreversible positional change of its volume elements. To maintain flow in a fluid, energy must be added continuously.

The basic law of viscometry describing the flow behavior of an ideal liquid was generated by Issac Newton:

$$\tau = \frac{F}{A} = \eta * D \quad \text{(Eq. 4-3)}$$

where τ is shear stress [mPa], F is the applied force [N], A is the area where the force F applied to, η is the dynamic viscosity [mPa*s] and D is share rate [s^{-1}].

The liquid has flow behavior as described in Newton's basic law is called Newtonian liquid. However, many real liquids do not follow this behavior and are named Non-Newtonian liquids. Most types of common flow behaviors of liquids are shown in Fig. 4.2-3.

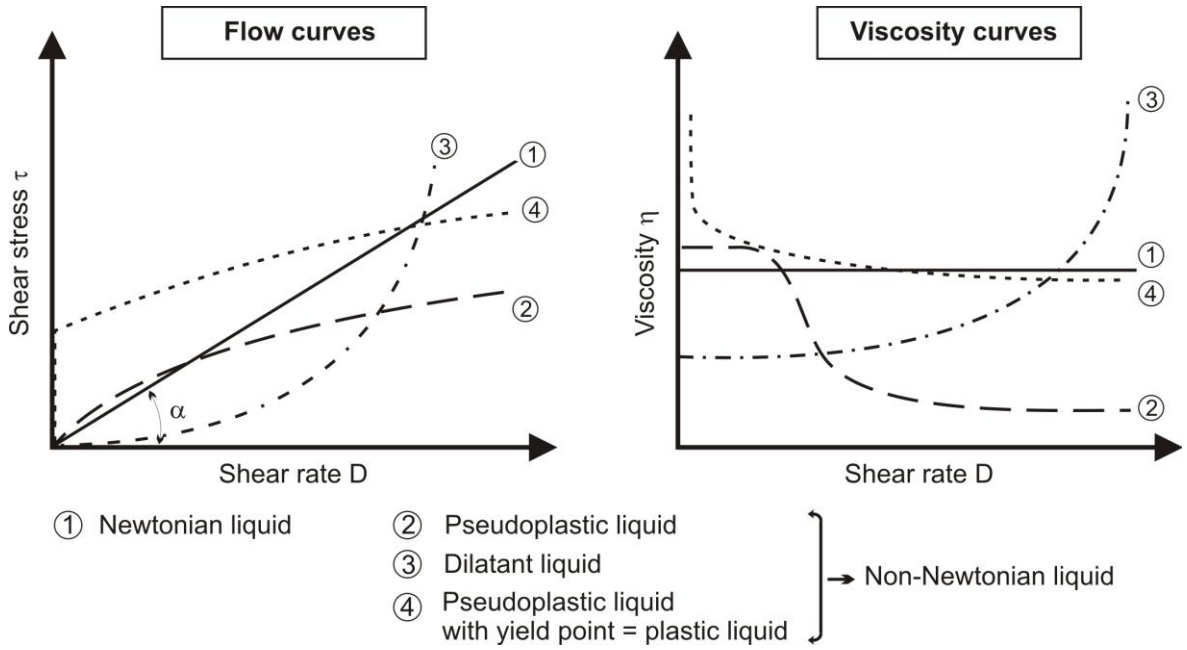


Fig. 4.2-3: Various types of common flow behavior [Schr00].

For Newtonian liquids (line 1), the viscosity stays constant and independent with shear rate. Pseusdoplastic liquids (curve 2) show a similar behavior of Newtonian liquids in the first stage, the viscosity stays constant as the shear rate rises, after that viscosity decreased with increasing shear rate and reaches the second Newtonian range where the viscosity stays constant, independent of any further increase of the shear rate. The pseusdoplastic flow behavior is the most common flow which is found in a big range substance such as emulsions or suspensions. The dilatant liquid (curve 3) has a shear rate dependent viscosity. When the shear rate higher the viscosity is increased, too. Dilatancy in liquids is rare, this flow behavior is found for example in highly concentrated suspension, i.e. plastisols which is formed from mixing emulsion-PVC with plasticizers liquid. The plastic liquid (curve 4) describes pseudoplastic liquids which additionally feature a yield point at beginning. This group can be classified in both liquids and solids groups. The bodies of this group are mostly the dispersions which have the intermolecular or interparticle network, i.e. polar forces, van der Waals forces, etc. These forces restrict the position change of volume elements and give the substance a solid character with an infinitely high viscosity at beginning [Sch00]. Only when the outside forces are strong enough to overcome the network forces the substances flow as a liquid. The point where the share stress surpasses the threshold is called the yield point. The typical substances for this group are oil well drilling muds, greases, lipstick masses, toothpastes and natural rubber polymers.

As be known as an importance factor for the process operation, rheological characterization of the aqueous suspensions in this work was carried out by using a rotational viscosimeter ViscoTester 550 (VT550 DIN/ISO Cylinder Package, HAAKE) with a stainless steel coaxial cylinder measuring system. The rotational viscometer is designed with a rotational speed preset and measures the flow resistance of a sample. The principle set up of a rotational viscosimeter cell is shown in Fig. 4.2-4. The substance to be measured is located in the measuring gap of the sensor system. The rotor is rotated at a preset speed (n). The measured substance exerts resistance to this rotational movement (due to its viscosity) which becomes apparent as a (braking) torque value. The built-in computer calculates the relevant measuring values such as: viscosity η [mPa*s], shear rate D [s^{-1}], shear stress τ [Pa]. A thermostat is connected to the viscometer to control the temperature of substances. The temperature T is also determined by an attached sensor. Three parallel measurements were carried out for every single sample.

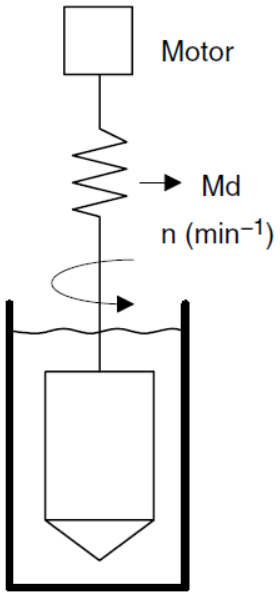


Fig. 4.2-4. Principle setup of a rotational viscosimeter cell in the Searle sensor system [Haa96].

4.2.2.3 Surface tension measurement

Krüss K10T was used to determine the surface tension of the suspension at the room temperature of 25 ± 1°C.

4.2.2.4 Differential Scanning Calorimetry (DSC)

To design the cooling profile for the freeze-casting process, the thermodynamic parameters of the suspensions should be known. Differential scanning calorimetry (DSC) measurements were carried out by a Mettler Toledo DSC 12E instrument in order to determine the freezing and melting points of the suspensions. Approximately 17 mg of suspension sample was weighed out in a 25 µL aluminum crucible. One cooling and one heating period in the temperature range from 20 to -30 °C was carried out, at a cooling/heating rate of 1 K*min^{-1} under a nitrogen flow of 30 mL*min^{-1}.

4.2.3 Characterization properties of produced tablets

The quality of the produced tablets was evaluated by their porosity, pore morphology, dissolution/dispersal behavior and their tensile strength. Apart from tensile strength

measurement which are reproduced six times, all sampling procedures and measurements for other analysis were carried out in triplicate.

4.2.3.1 Porosity measurement

The porosity is an important property of produced tablets, which can directly determine the contacting surface area, the dissolution behavior as well as mechanical strengths of tablets. Among the possible techniques of porosity measurement, mercury intrusion and gas adsorption/desorption are the most widely used. In this presented work, the Mercury Porosimetry technique was applied. This method was developed in 1945 by Ritter and Drake allows the measuring of volume and size of macropores and mesopores in solid porous substances. The principle of this technique is based on the non-wetting liquid behavior of mercury with a lot of solid materials. Mercury can penetrate through the open pores of a solid sample under the effect of increasing pressure. The pore radius is inversely proportional to the applied pressure. By measuring the quantity of mercury penetrated into the sample pores and the equilibrium pressure at which intrusion occurs, experimental data are obtained to calculate the pore volume distribution as a function of their radius [Ther07].

The Pascal 140/440 porosimeter combination (Porotec GmbH, Germany) based on the mercury porosimetry method was used to determine the porosity of the tablets. Low-pressure measurements were performed between 0.01 and 400 kPa. The high pressure range was from 0.01 to 400 MPa. A surface tension of 480 $mM*m^{-1}$ and a contact angle value of 140° were used in the calculations for mercury. Because of the limitation of the dilatometer size, the small size of the cylinder tablet (Ø 6 mm x 10 mm or Ø 10 mm x 5 mm) was chosen for this measurement.

4.2.3.2 Morphology measurement

A digital microscopic system (VH-Z100, Keyence) was used to record the morphology of the pores and tablets.

The structures of freeze casted bodies were studied using a scanning electron microscope (Philips XL 30 ESEM). To get better SEM images, the particles for scanning microscopy examination were mounted and coated with platinum in a sputter coater before the SEM measurement.

4.2.3.3 Tensile strength measurement

The crushing strengths of produced tablets were measured by a crushing force tester (TBH 30, Erweka). Then tensile strength was calculated from these data and the geometrical parameters of the tablets (Mitutoyo, Japan) via the equation of Fell and Newton [Fel70] for round-cylindrical tablets:

$$\sigma_t = \frac{2P}{\pi Dh} \qquad \text{(Eq. 4-4)}$$

where σ_t [N*mm^{-2}] is the maximum diametral tensile strength, P [N] is the applied crushing force, D [mm] is the tablet diameter and h [mm] is the tablet thickness.

To get the representative data, the measurements are reproduced six times for every sample.

4.2.3.4 Dissolution/Dispersal behavior measurement

Cocoa system

A simple visible method was applied to observe the dispersion behavior of the tablets. For one tablet (Ø 16 mm x 10 mm), a calculated dosage of 50 mL hot distilled water was added into a 100 mL double jacketed vessel, which was maintained at a constant temperature by a thermostatic bath. The amount of hot distilled water was calculated to fit the recommended concentration of hot drinking chocolate (one teaspoon of cocoa powder for one cup of milk or water) [GEP14]. A temperature of 90 °C, corresponding to the temperature of boiled water, was chosen for the dissolution/dispersal behavior test. A low mixing speed of 100 rpm was generated by a mechanical mixer (RW16B, IKA, Staufen Germany) with a paddle of 28 mm in diameter. The dispersal time was defined as the period from the moment when the tablets were added until the time when the tablets were totally dispersed (dissolved) in water.

Paracetamol system

The dissolution profiles of tablets were investigated according to the European Pharmacopoea with a paddle method (paddle dissolution tester, Erweka DT6, Erweka) [Pac07c]. The produced tablets (Ø: 15.5 – 16.0 mm, h: 4.4 – 5.3 mm) contained about 500 mg paracetamol were dissolved in 900 mL HCl (0.1 N) stored in 1 L vessel at temperature of 37 ± 0.5 °C with a paddle speed of 100 rpm. At the time t = 0 s, a tablet with a defined mass is naturally droped to the HCl 0.1 N solution which is considered the same as the acidic medium in the human's stomach. During dissolving measurement, the solutions were sampled with the certain time schedule and offline analyzed the dissolved paracetamol concentration by using a UV-vis spectrophotometer (SPEKOL® 1200, Analytik Jena). The sampling was done manually by a 2 mL syringe connected to a mini filter tube to be sure that only 0.5 mL clear solution was taken out per each sampling time. The interval for sampling was set minimum at 30 s and maximum at 10 min depending on how fast behavior of the dissolution process of measured tablets take place.

In previous study [Pac07c] the wavelength (λ) was chosen at 240 nm. However, in this work, the result of wavelength scanning of the standard paracetamol solution in HCl 0.1 N solution shows the maximum absorption at λ = 242 nm. Therefore the fixed wavelength of 242 nm

was chosen for UV measurement. Using HCl 0.1 N as reference solution, the calibration curve of paracetamol concentrations vs their absorbance value was generated in Fig. 4.2-5. Based on this calibration, the relationship of absorbencies and concentrations of paracetamol in HCl 0.1 N solution at λ = 242 nm was determined:

$$A_{Paracetamd,242nm} = 0.0682 \cdot c \ \ [\mu g \cdot mL^{-1}] \qquad \text{(Eq. 4-5)}$$

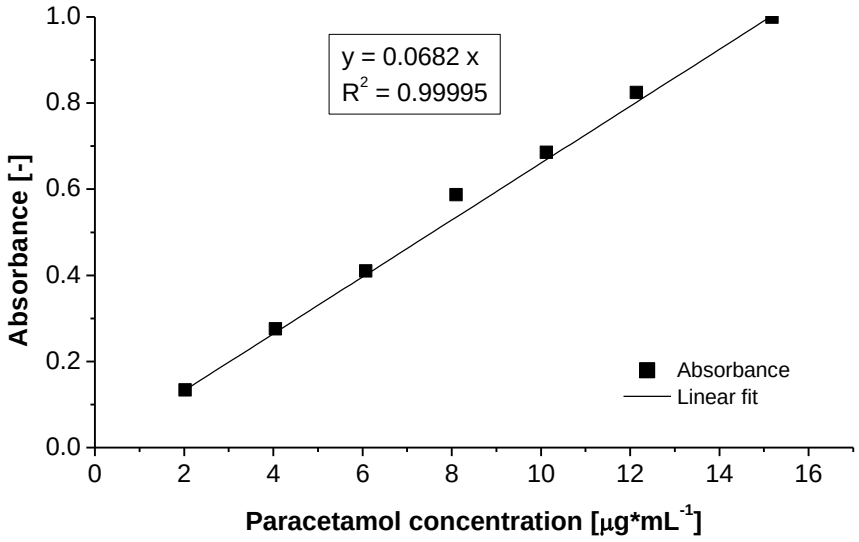


Fig. 4.2-5: Calibration curve of paracetamol in HCl 0.1 N.

Based on the calibration curve, if the absorbance of paracetamol in HCl 01 N solution is determined in the absorbance range of calibration measurement, the paracetamol concentration (c) of solution is estimated through Eq. 4-5. Using this method, the absorption value should be in range of 0 to 1, therefore, the sampled solution need to be diluted before being measured by UV test. Then the mass dissolved paracetamol in solution was calculated as:

$$m_{p,n} = m_{pv,n} + \sum_{i=0}^{n} m_{ps,i} \qquad \text{(Eq. 4-6)}$$

where $m_{p,n}$ is the mass of total dissolved paracetamol in solution at the sampling step n, $m_{pv,n}$ is the mass of dissolved paracetamol in solution remaining in vessel after n sampling steps, $m_{ps,i}$ is the mass of paracetamol in the taken-out sampled solution at the sampling step i.

Because the volume of sampled solution in every sampling step is really small in comparison to the volume of solution in vessel (0.5 mL vs. 900 mL), the number of sampling steps (n) is

not so high (n_{max} = 15), the mass of paracetamol in taken-out sampled solutions $\sum_{i=0}^{n-1} m_{ps,i}$ can be neglected. Equation 4.6 can be rewritten as:

$$m_{p,n} \approx m_{pv,n} = \frac{A_n}{0.682} \cdot \frac{V_s + V_d}{V_d} \cdot V_{v,n} \cdot 10^{-6} \quad [g] \qquad \text{(Eq. 4-7)}$$

where A_n is the absorbance value of the sampled solution at the sampling step n. V_s is the volume of taken-out sampled solution used for dilution step, here V_s = 0.015 mL. V_d is the volume of HCl 0.1 N solution added to dilute the sampled solution, here V_d = 1.220 mL. $V_{v,n}$ is the volume of solution in the vessel after n sampling steps, $V_{v,n} = 900 - 0.5 \cdot n$ mL.

Then the dissolution rate can be calculated as:

$$D_n[\%] = \frac{m_{p,n}}{m_0} \cdot 100 \qquad \text{(Eq. 4-8)}$$

where D_n is the dissolution rate at sampling step n [%], m_0 is total mass of paracetamol in initial tablet [g].

5. Results

5.1 System 1 – food: cocoa tablet

5.1.1 Properties of suspensions

Physical and thermal dynamic properties of suspensions are informative data which are not only significantly useful to get a good understanding of processes but are also very important to design and to operate a process. In case of suspensions, density, surface tension, and rheological properties are extremely important for processing. These properties are in close relation to profiles of solute concentrations, solid loadings and temperatures. In this chapter, the results of the density, surface tension and rheological measurements of suspensions will be presented. Furthermore, the thermodynamic properties of the suspensions are also investigated through DSC measurements.

It is noted that here, in this work, additives are dissolved in the liquid phase, therefore to be sure that the ratios of solid/water were not changed by mass increasing of aqueous solutions due to addition of additives, solid contents and additive contents were calculated based on water quantity only. Here, the solid content (in wt%) was calculated as the weight percent of the solid in the slurry of itself and the water:

$$solid\ \ content\ \ [wt\%] = \frac{m_{sokid}[g]}{m_{solid}[g] + m_{water}[g]} x100 \qquad \text{(Eq. 5-1)}$$

The additive content (in g*mL^{-1}) was calculated as ratio of the mass of the additive ($m_{additive}$) and the volume of water (V_{water}) used to dissolve the binder:

$$additive\ \ content\ \ [g * mL^{-1}] = \frac{m_{additive}[g]}{V_{water}[mL]} \qquad \text{(Eq. 5-2)}$$

5.1.1.1 Density

The density measurements were carried out based on the method presented in chapter 4.2.2.1. The list of the density measurements shown in Tab. 5-1 were designed to focus on the effects of the type of additives, solid contents as well as temperatures on the densities of the suspensions. The density measurements have been investigated in a temperature range of 5 to 35 °C with an increment of 5 °C. Because of the potential freezing of water, thereby the ice crystals can be stuck in U-tube of the device or the volume expansion might damage the device, the temperature below 0 °C has not been examined. In this work, temperatures above 35 °C were not used or not necessary for the process of the freeze casting where the slurries go through a normal or low temperature process. Therefore, the density measurements at temperatures higher than 35 °C were not carried out.

Tab. 5-1: The experimental summary of the density measurements.

Effect of temperatures and solid contents T = 5, 10, 15, 20, 25, 30, 35 °C					Effect of additives T = 20 °C		
Cocoa content, wt%	w/o additive (water)	0.20 g*mL^{-1} additive solution			Additive	solution	28 wt% cocoa suspension
		xylitol	isomalt	sucrose			
0	X	X	X	X	w/o additive (water)	X	X
25			X		0.20 g*mL^{-1} xylitol	X	X
28			X		0.20 g*mL^{-1} isomalt	X	X
30			X		0.20 g*mL^{-1} sucrose	X	X

The density is temperature dependent, it needs to be presented at a specified temperature. To get a general overview on the density changes during suspension preparations, the densities of water, various aqueous sugar (sucrose) and sugar alcohol solutions (xylitol, isomalt) at the same concentration of 0.20 g*mL^{-1} and the densities of aqueous cocoa suspensions containing various cocoa contents (from 25 to 33 wt%) dispersed in 0.20 g*mL^{-1} isomalt solution were plotted in Fig. 5.1-1.

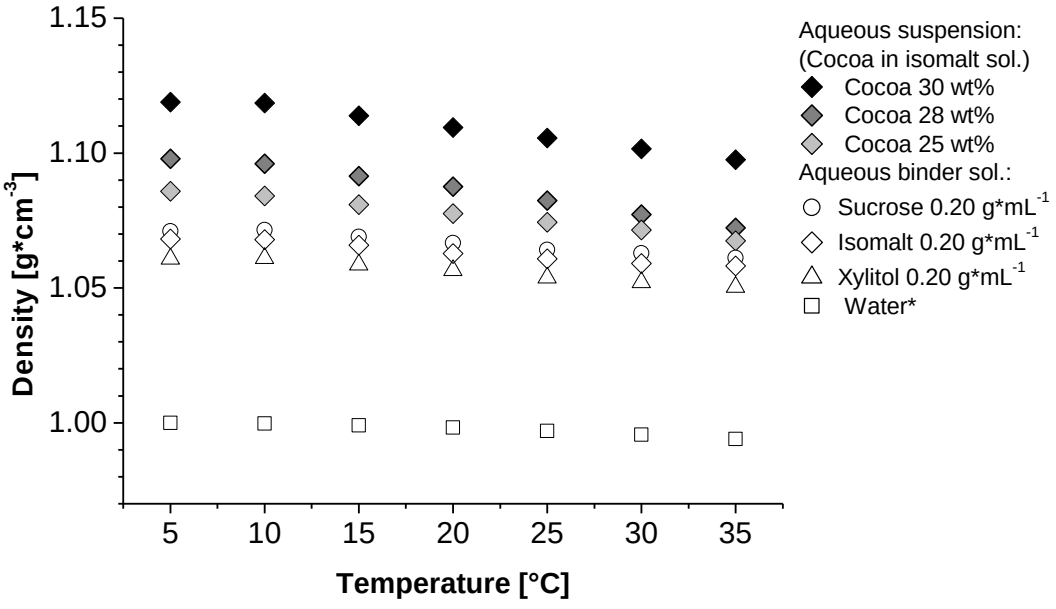


Fig. 5.1-1. Densities of the sugar alcohol solutions and the aqueous cocoa suspensions. * - the water densities were collected from Weast, 1988 [Wea88].

It is seen that, as the temperature increases from 5 to 35 °C, the densities of all aqueous samples slightly decrease. In general, the densities of samples increase in the following order: water < additive solutions (xylitol < isomalt < sucrose solution) < aqueous

suspensions. It means the density of aqueous solutions rises when the sugar and sugar alcohols were added to the water, and were further higher as the cocoa was added. Xylitol affected the density of the additive solution less than isomalt, and even lesser than sugar. Furthermore, the densities of the cocoa suspensions of various solid contents in a 0.20 g*mL^{-1} isomalt solution shows that higher solid contents results in higher density values.

The summary of the density profiles of the liquid phases and the 28 wt% cocoa suspensions in water as well as in additive solutions at 25 °C are shown in Tab. 5-2. These results again confirm the order of the increase in density in both the liquid and the suspension phase: water < xylitol < isomalt < sucrose. The relative density (RD) was calculated as the density ratio of the suspension and the aqueous solution.

Tab. 5-2: The densities of aqueous solutions and suspensions of the cocoa system at 25 °C, 1.01 bar.

Additive	0.20 g*mL^{-1} solution	28 wt% cocoa suspension	Relative density (RD)
Water	0.9971*	1.0552	1.0583
Xylitol	1.0538	1.0700	1.0154
Isomalt	1.0608	1.0824	1.0204
Sucrose	1.0641	1.0946	1.0287

* - the water densities were collected from from Weast, 1988 [Wea88].

5.1.1.2 Rheology measurements

Viscosity describes the physical property of a liquid to resist shear induced flow. It may depend on the independent properties such as the physical – chemical nature of substances, the temperature, pressure, share rate and time. In this chapter, the results of rheology measurements will be presented following the experimental plan shown in Tab. 5-3.

Flow behavior

As a first example the flow behavior of the liquid phases, i.e. the sucrose and isomalt solutions, and the cocoa suspensions were investigated. Viscosities and shear stresses of the suspensions and solutions were measured with continuously increasing (up) and decreasing (down) shear rates in range of 10-1000 s^{-1}. A changing rate of the shear rates was kept constant at 33.3 s^{-1} per second. Figs. 5.1-2 and 5.1-3 show flow and viscosity curves of the sucrose and isomalt solutions. Both liquid phases have a Newtonian flow behavior in low shear rate range of 10 – 180 s^{-1}. A non-Newtonian flow behavior is found when the shear rate is increased further. The viscosities and the shear stresses slightly rise with the increasing share rate.

In full shear rate range of 10 - 1000 s^{-1}, the viscosity and shear stress values of the up and down circles of three rounds are identical.

Tab. 5-3: The experimental plan of the rheology measurements of cocoa system at p = 1.01 bar.

	Flow behavior *T = 20°C*			Additive effect - time dependence *T = 20°C* *D = 200 s^{-1}*				Temperature effect *T = 5, 10, 15, 20, 25, 30, 35°C*			Effect of additive contents and solid contents *T = 20°C, D = 50, 200, 400 s^{-1}*			
cocoa content, wt%	sucrose 0.2 g*mL^{-1}	isomalt 0.2 g*mL^{-1}	water	water	isomalt 0.2 g*mL^{-1}	xylitol 0.2 g*mL^{-1}	sucrose 0.2 g*mL^{-1}	sucrose 0.2 g*mL^{-1}	isomalt 0.2 g*mL^{-1}	water	cocoa content, wt%	Isomalt solution, g*mL^{-1}		
												0.00	0.10	0.20
0.00	X	X		X	X	X	X	X	X		20.0	X	X	X
20.0				X	X						21.9	X	X	X
24.8				X	X						23.1	X	X	X
28.0	X	X	X	X	X	X	X	X	X	X	24.8	X	X	X
30.0	X													

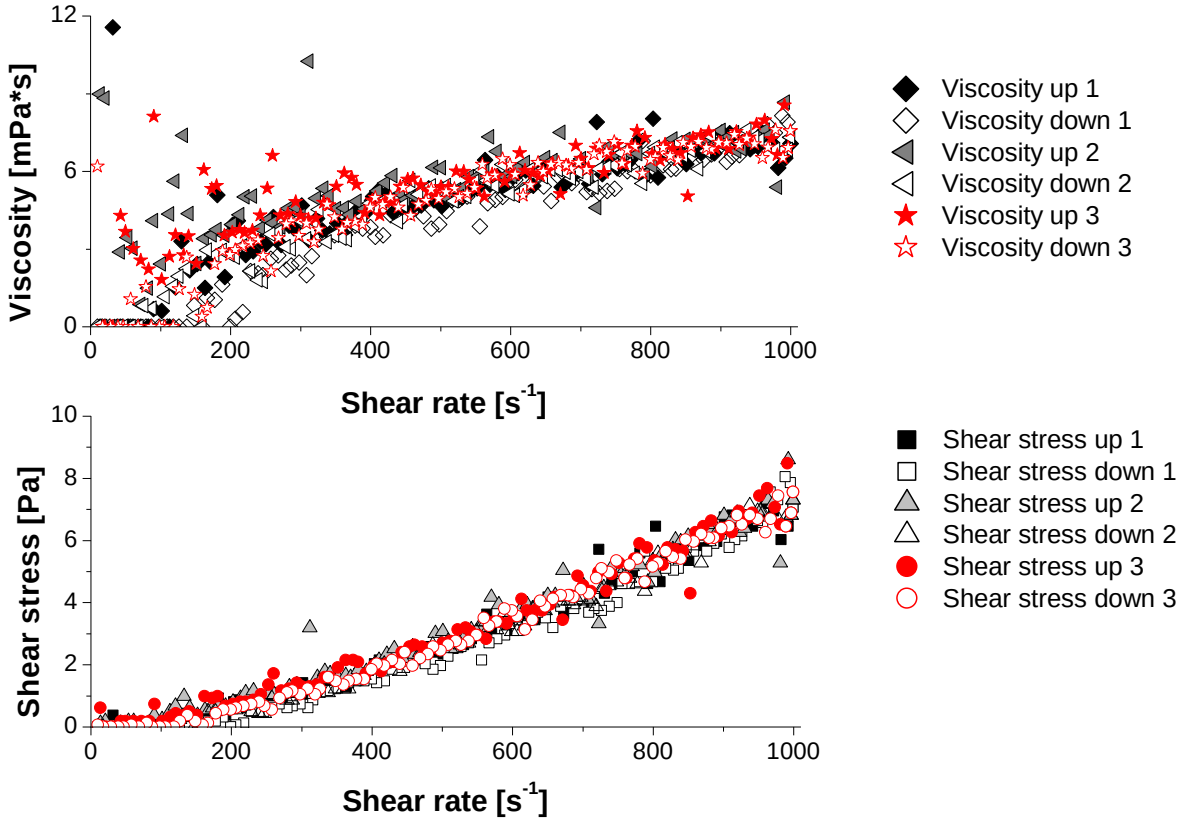


Fig. 5.1-2: The flow behavior of the 0.20 g*mL^{-1} sucrose solution.

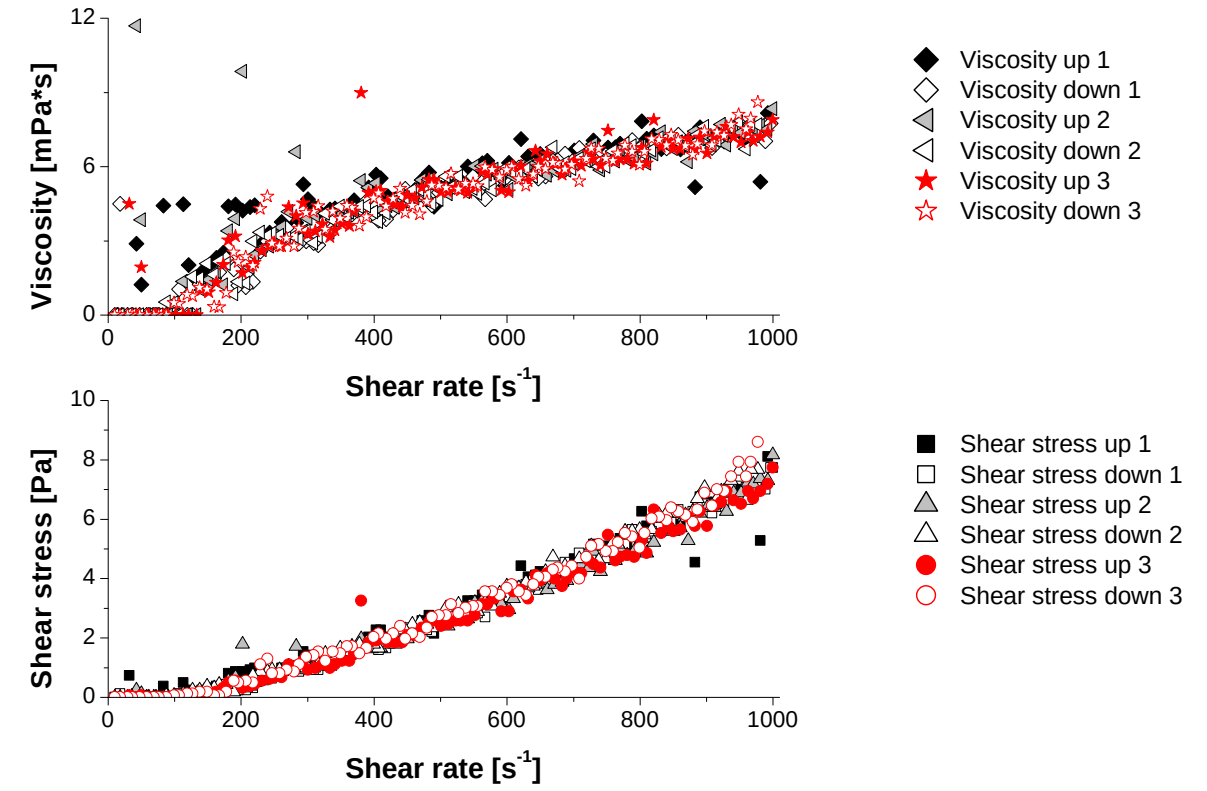


Fig. 5.1-3: The flow behavior of the 0.20 g*mL^{-1} isomalt solution.

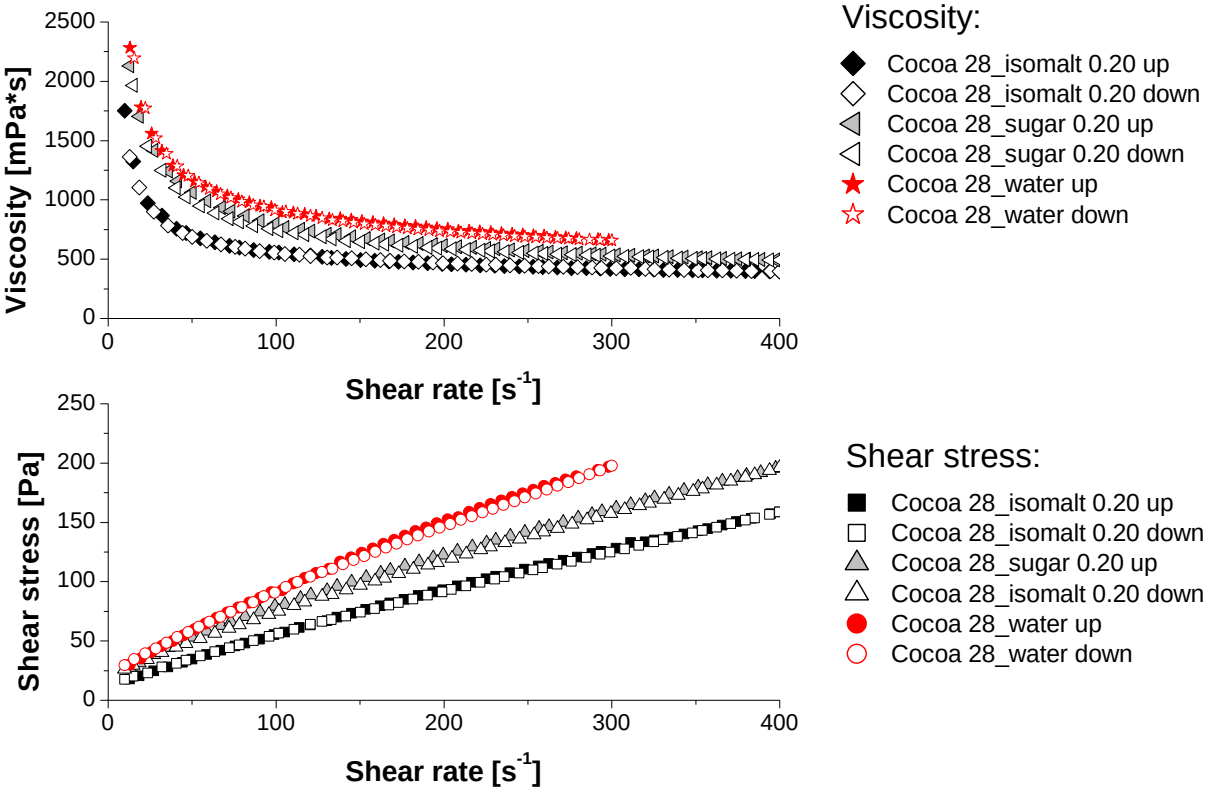


Fig. 5.1-4: Effect of additives on the flow behavior of the cocoa suspensions.

The viscosity and flow curves of 28 wt% cocoa suspensions in water, in 0.2 g*mL^{-1} sugar and isomalt solutions are plotted in Fig. 5.1-4. All cases of these suspensions show the similar flow behavior. The up and down curves are identical. The shear stresses increase with the rising shear rates, while the viscosities significantly decrease at beginning and seem to be stable thereafter as the shear rate is rising up. Due to a limitation of the rotation speed occurring in high viscosity samples, the maximum applicable shear rate was 400 s^{-1} in the cases of 28 wt% cocoa suspensions in 0.2 g*mL^{-1} sugar and isomalt solutions. In the case of 28 wt% cocoa suspension in water, the maximum shear rate was 300 s^{-1}.

Time dependence

Table 5-4 summarizes time dependences of the suspension and solution viscosities. An example of the viscosity curves with shearing times at the 200 s^{-1} shear rate is shown in Fig. 5.1-5. According to this figure, the viscosities of the liquid phases were time independent. Whereas, the viscosities of 28 wt% cocoa suspensions, at first, were significantly decreased, then were gradually stable with elapsed times. More examples of the viscosities curves vs. the elapsed time of the suspensions at various shear rates are shown in Fig. 5.1-6.

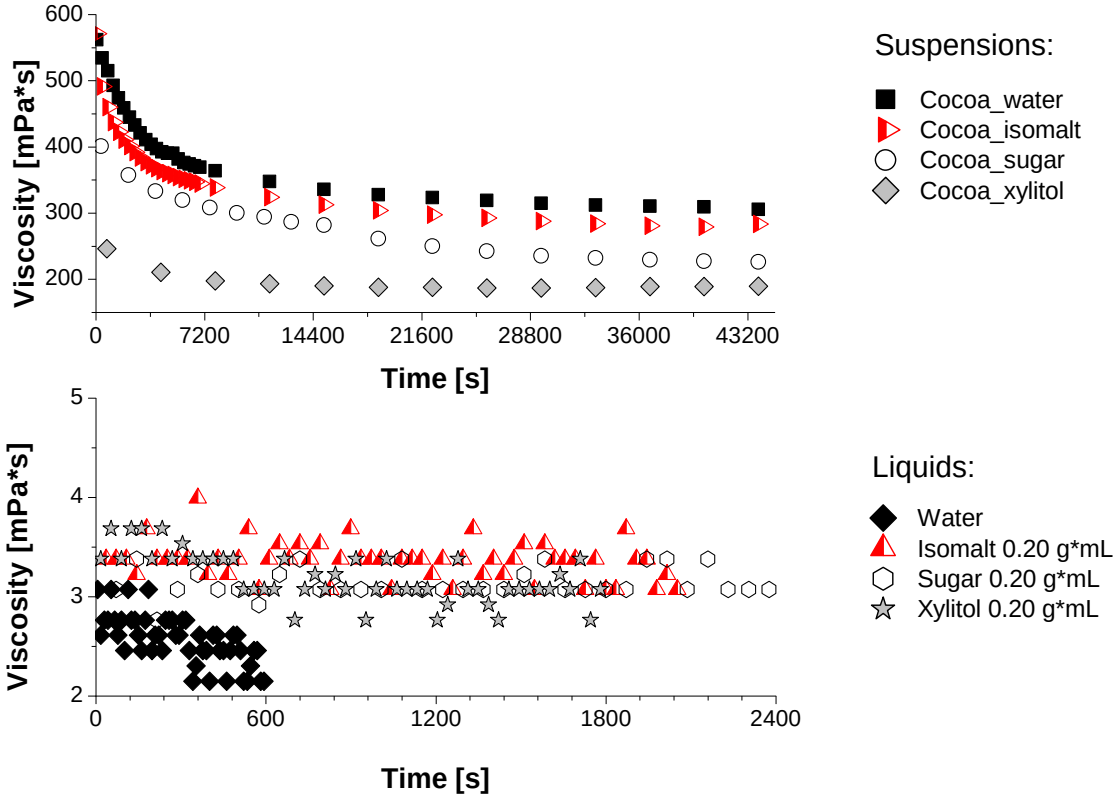


Fig. 5.1-5: Time dependent viscosity curves of the additive solutions and the 28 wt % cocoa suspensions with and without additives.

Tab. 5-4: The time dependences of the viscosities.

T = 20 °C, D = 200 s^{-1}				T = 20 °C									
		liquid phase	28 wt% cocoa suspen-sions	cocoa content, wt%	w/o isomalt			0.10 g*mL^{-1} isomalt			0.20 g*mL^{-1} isomalt		
					shear rate, s^{-1}			shear rate, s^{-1}			shear rate, s^{-1}		
					50	200	400	50	200	400	50	200	400
water		X	√	0.0	X	X	X	X	X	X	X	X	X
0.20 g*mL^{-1}	sugar	X	√	20.0	X	√	√	√	√	√	√	√	√
	xylitol	X	√	21.9	√	√	√	√	√	√	√	√	√
	isomalt	X	√	23.1	√	√	√	√	√	√	√	√	√
				24.8	√	√	√	√	√	√	√	√	√

X: independent , √: dependent

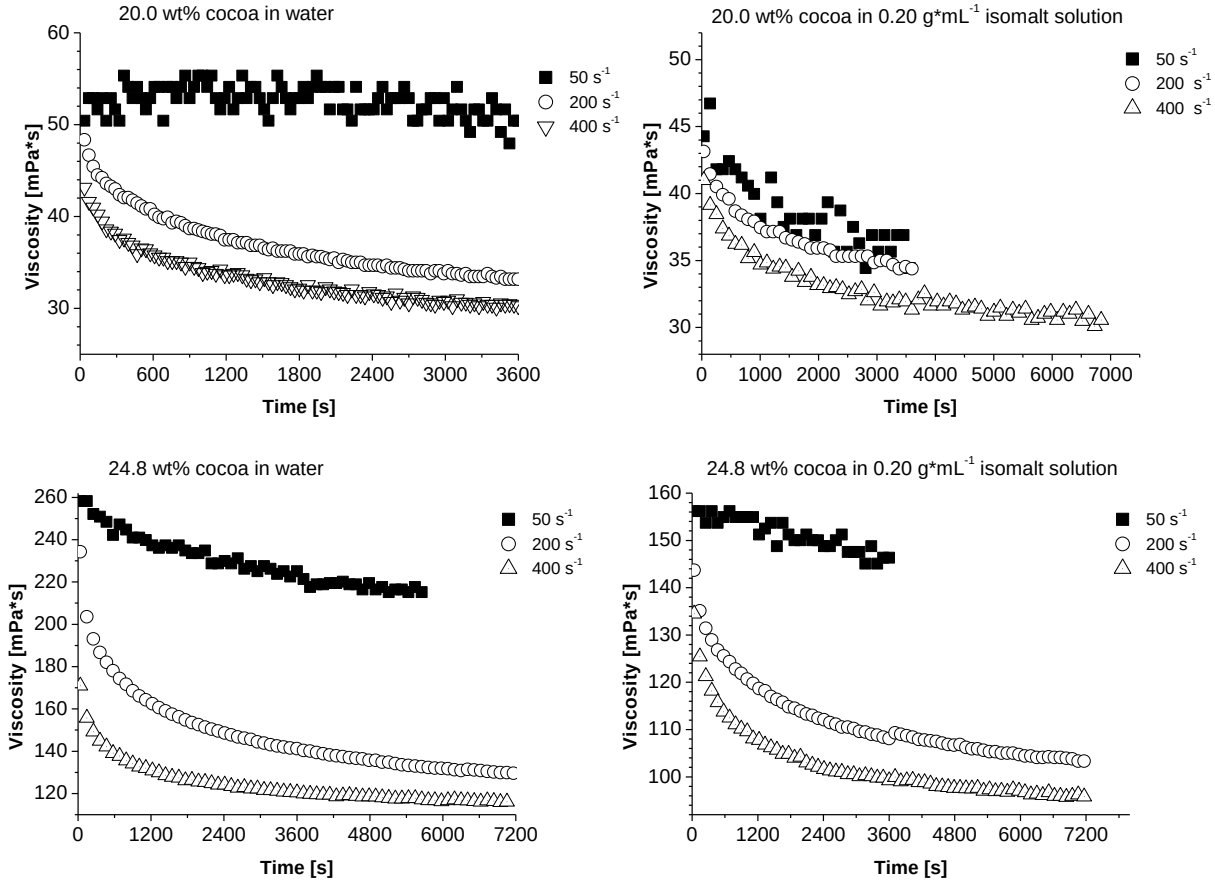


Fig. 5.1-6: The viscosities vs. the elapsed times of the suspensions at various shear rates.

Solid loading and additive effect

Effects of solid loadings and additive contents on the viscosities of suspensions at the shear rate of 200 s^{-1} are shown in Fig. 5.1-7. Because the viscosity decreases with the shearing time, in this work the viscosities values are calculated by the average values in a time range of first measuring hour. In almost all cases, the viscosities seem to be stable or decrease extremely slow after one hour. The error bars show maximum and minimum values of the viscosities. As to be seen in Fig. 5.1-7, an increasing of the solid loadings dramatically rises the viscosities of the suspensions. Adding sugar and sugar alcohols, i.e. isomalt as additive generally decreases the viscosity of suspensions. The higher the isomalt contents the lower values have the suspension viscosities.

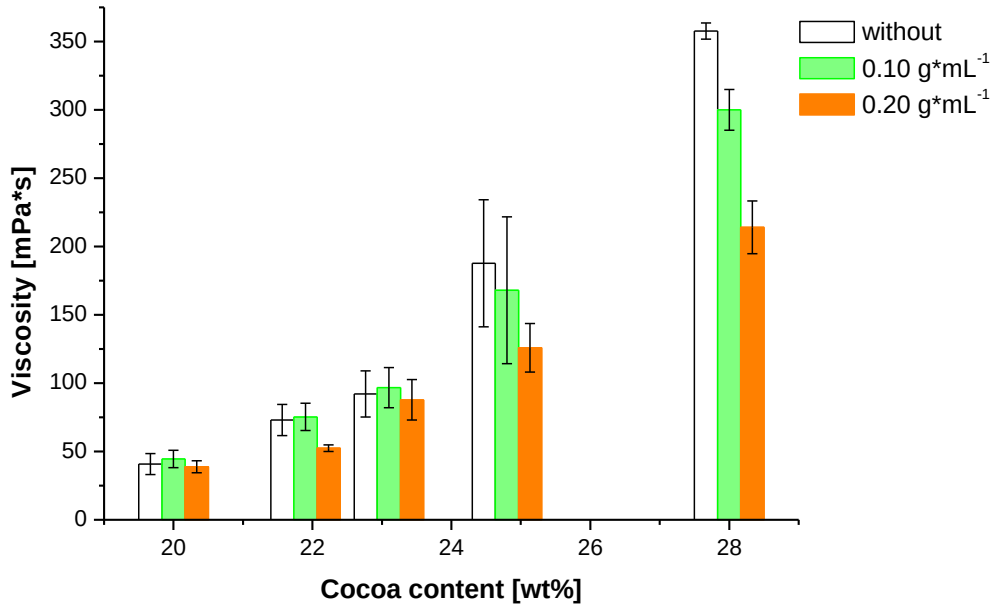


Fig. 5.1-7: Effect of the additive and the solid contents on the viscosities of the cocoa suspensions using isomalt as the additive.

Temperature effect

To check effects of temperatures on viscosities, the viscosities of suspensions were measured with decreased temperatures from 35 to 5 °C and plotted in Fig. 5.1-8. It is clear that the viscosity rises with the decreased temperature. This behavior was found in all 28 wt% cocoa suspensions in water, in sugar as well as in isomalt solutions.

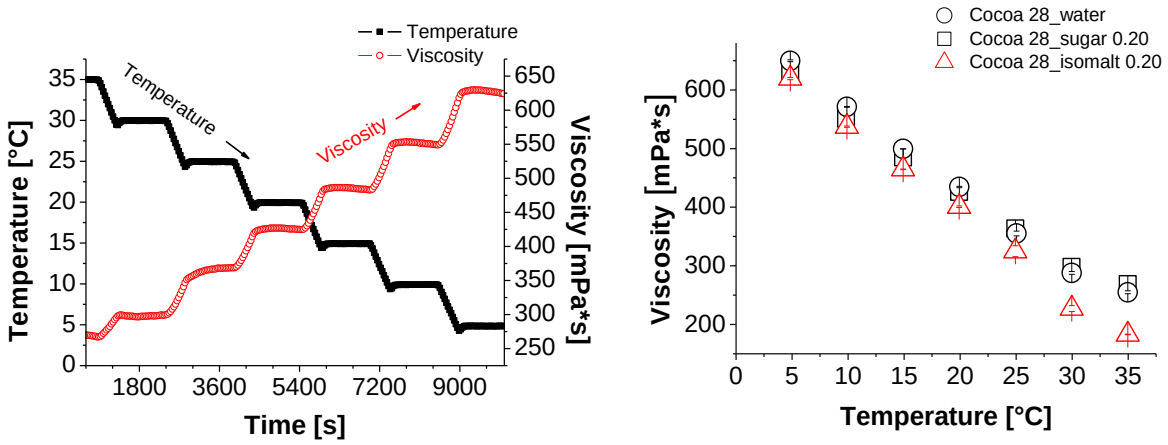


Fig. 5.1-8: Left: The temperature and viscosity profiles of the 28 wt% cocoa suspension in 0.20 g*mL^{-1} sugar solution with the elapsed time. Right: The effects of temperatures on the viscosities of the 28 wt% cocoa suspensions in water, in 0.2 g*mL^{-1} sugar and isomalt solutions.

5.1.1.3 Surface tension measurements

To check the effect of additives and solid loadings on the surface tensions of suspensions, the measurements listed in Tab. 5-5 were carried out.

Tab. 5-5: The experimental list of the surface tension measurements.

Cocoa content, wt%	Effect of additives T = 20 °C, p = 1.01 bar				Cocoa content, wt%	Effect of additive contents T = 20 °C, p = 1.01 bar		
	w/o additive (water)	0.2 g*mL^{-1} solution of				Isomalt content, g*mL^{-1}		
		xylitol	isomalt	sucrose		0.00	0.10	0.20
28.0	X	X	X	X	20.0	X	X	X
					21.9	X	X	X
					23.1	X	X	X
					24.8	X	X	X

The surface tensions of suspensions measured at the temperature of 20 °C are shown in Tab. 5-6. It is clear that the sugar and sugar alcohols show a negligible change in the surface tension of aqueous solutions and suspensions. In addition, Fig. 5.1-9 demonstrates that the surface tension of suspensions rise corresponding to the increase of solid contents. A higher content of isomalt in the suspensions tends to increase the surface tensions. However, the influence of the isomalt content on the surface tension of suspensions was gradually reduced as the solid loadings increased in the studied concentration range. With the cocoa content of

25 wt%, the differences in the surface tensions of suspensions containing varvious isomalt contents from 0.00 to 0.20 g*mL^{-1} are negligible.

Tab. 5-6: The surface tensions of 28 wt% cocoa suspensions at T = 20°C, p = 1.01 bar.

Aqueous phase	Water	Sucrose solution 0.20 g*mL^{-1}	Isomalt solution 0.20 g*mL^{-1}	Xylitol solution 0.20 g*mL^{-1}
Surface tension, mN*m^{-1}	45.7 ± 0.4	45.4 ± 1.6	42.8 ± 1.2	45.4 ± 0.1

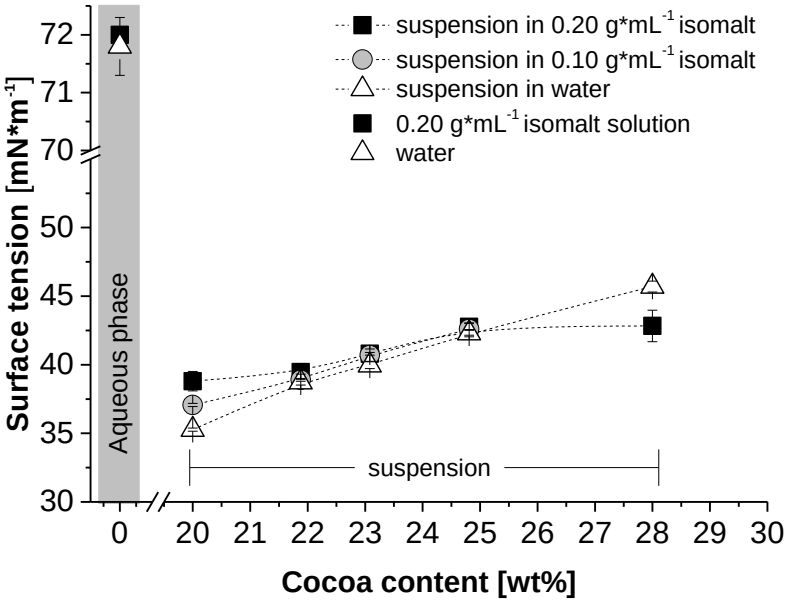


Fig. 5.1-9: The effect of solid and additive contents on the surface tension of the cocoa suspensions.

5.1.1.4 Thermodynamic properties of cocoa suspensions

To set up the parameters for two major stages namely freezing and drying of the freeze casting process, the thermodynamic properties of the suspensions need to be determined. As introduced in chapter 4.2.2.4, the DSC analysis was applied for all suspensions. The list of prepared suspensions for DSC measurements is shown in Tab. 5-7.

An example DSC curve of 28 wt% aqueous cocoa suspension without additive is shown in Fig. 5.1-10. It is clear that by generating a continuous freezing and heating profile in the temperature range of -30°C to 20°C, there were two clear freezing and melting peaks corresponding to the heat flow (DSC) curve in temperature ranges of about -18 °C and -3°C, respectively.

Tab. 5-7: The list of prepared suspensions for DSC measurements.

Cocoa content, wt%	Liquid phases					Additive	28 wt% cocoa suspensions				
	Water	Sucrose solution, g*mL^{-1}					Additive contents, g*mL^{-1}				
		0.05	0.10	0.15	0.20		0.00	0.05	0.10	0.15	0.20
25	X	X				Sucrose	X	X	X	X	X
28	X	X	X	X	X	Isomalt	X	X	X	X	X
30	X	X	X	X	X	Xylitol	X	X	X	X	X
33	X										

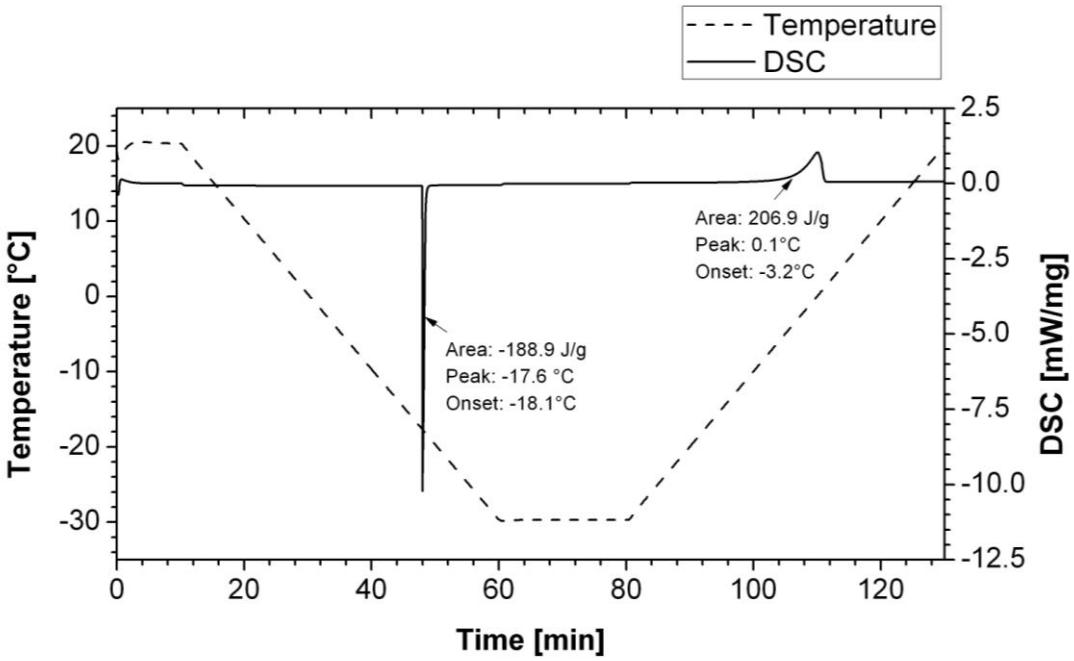


Fig. 5.1-10: The example of DSC curve of the 28 wt% aqueous cocoa suspension without additive.

Solid loading effect

To check the effect of the solid loadings on the thermodynamic properties of the aqueous suspensions, the thermodynamic properties of melting and crystallization of the aqueous suspensions with the cocoa contents of 25, 28, 30, and 33 wt% without containing additives are shown in Fig. 5.1-11.

To get a comparison, the example melting and freezing peaks in each suspension sample are plotted together in Fig. 5.1-11a. With increasing cocoa contents from 25 to 33 wt%, the peaks corresponding to the thermodynamic changes of both crystallization and melting processes are shifted to the left in the graphs. To ensure that the freezing and sublimation conditions were sufficient to guarantee that the aqueous suspensions were completely solidified and perfectly sublimated without destruction of the remaining structure in the solid

body, the onset values of the DSC curves were determined to obtain the representative minimum freezing and melting points. These results are plotted in Fig. 5.1-11b. It was found that the melting points of aqueous suspensions were slightly decreased from -2.6 to -4.2°C as the cocoa content was increased from 25 to 33 wt%. At the same time the freezing points are lowered from -13.5 to -19°C.

The absolute value of the latent heat of fusions in both freezing and melting processes of the suspension decreases as the cocoa content is increased (see Fig. 5.1-12).

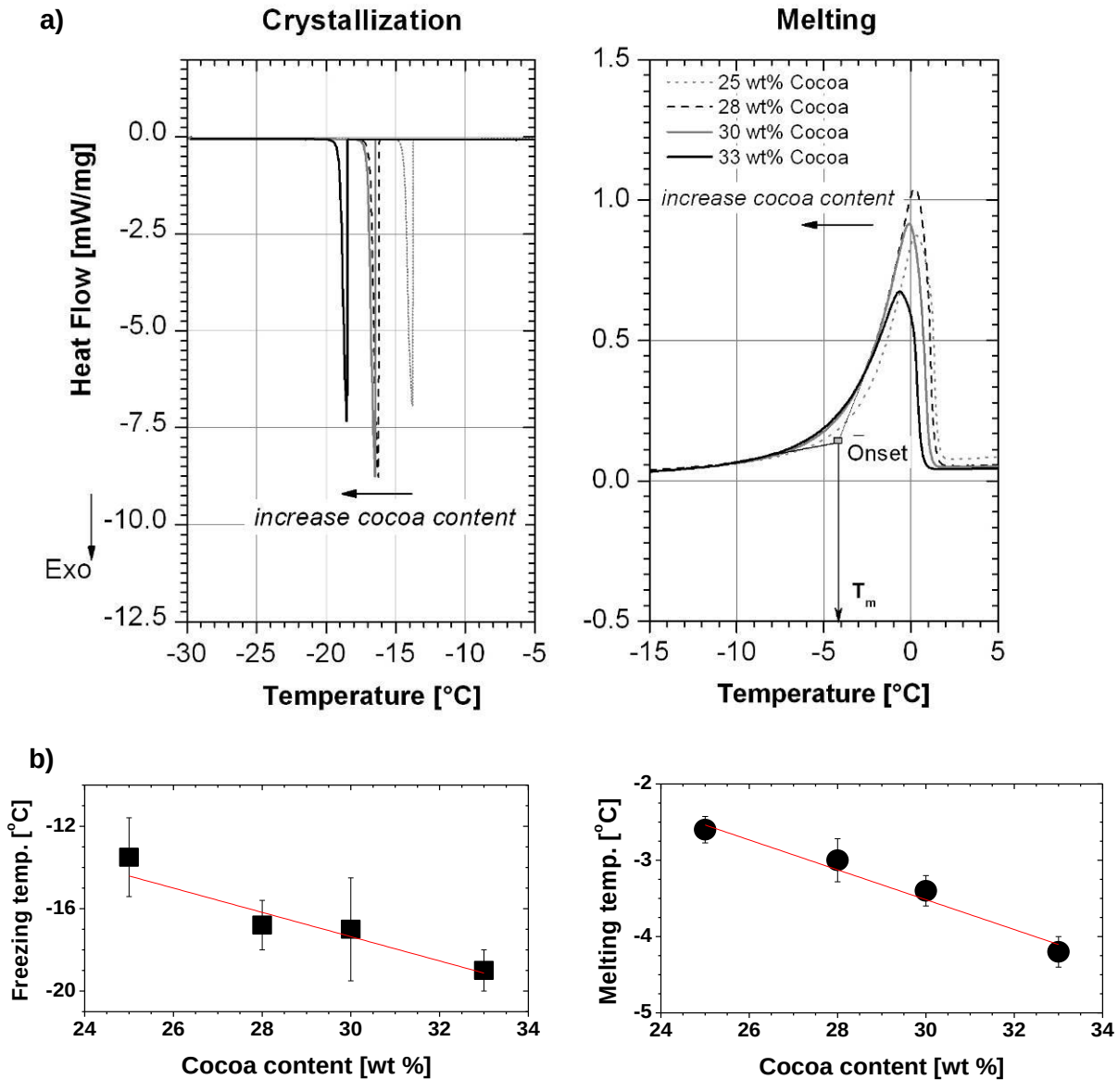


Fig. 5.1-11: DSC curves and thermodynamic parameters of the cocoa suspensions at various cocoa contents from 25 to 33 wt% without containing additives [Ngu13].

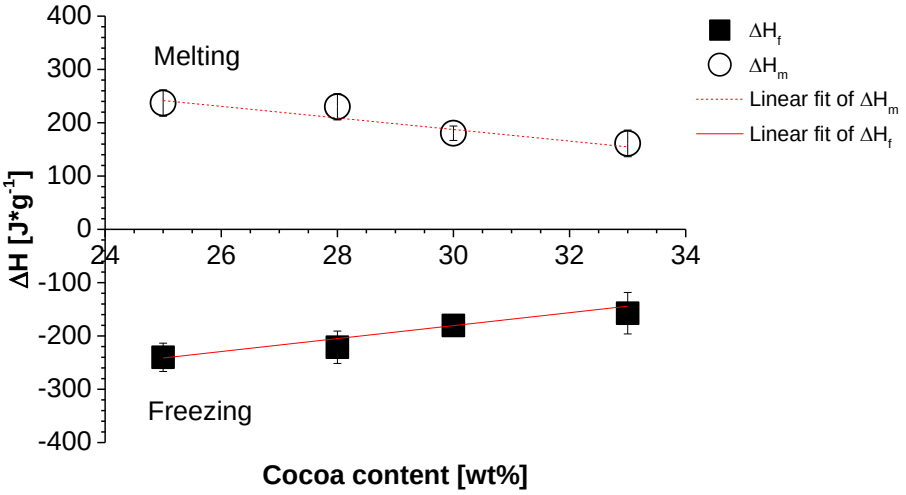


Fig. 5.1-12: The latent heat of fusions of the cocoa suspensions in function of the cocoa contents without containing additives.

Effect of additives

Fig. 5.1-13 shows the freezing and melting points of suspensions containing various sucrose contents from 0.00 to 0.20 g*mL^{-1}. It is clear that the higher the soluble sucrose contents in the suspension the lower were the freezing and melting points of the suspensions. This phenomenon was also found in other sugar alcohols: xylitol and isomalt (see Fig. 5.1-14). The decrease level in the freezing and melting points of sucrose and isomalt is almost equal, while those of xylitol are much more pronounced. Furthermore, the higher solid contents in suspensions also resulted in lower freezing and melting points.

In addition, as be shown in Fig. 5.1-15, the lantent heat of fusions of the suspensions decreases when the additive content is increases.

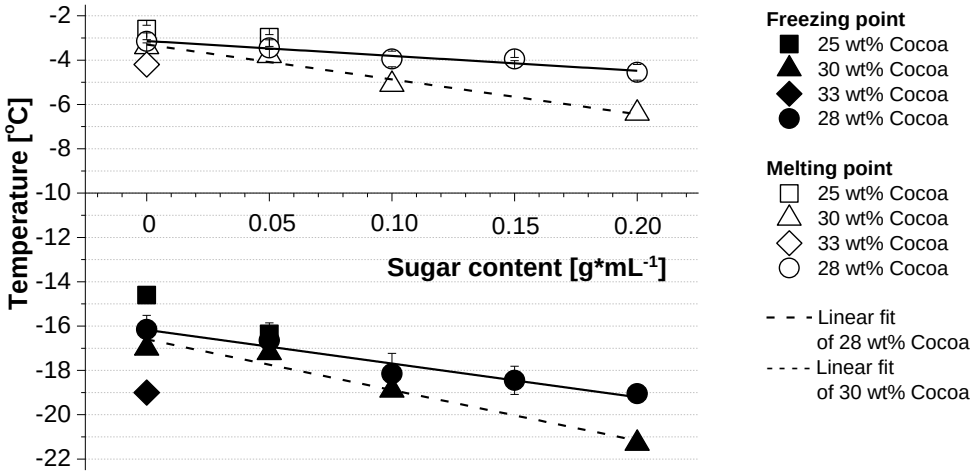


Fig. 5.1-13: The phase diagram of the aqueous cocoa suspensions containing sucrose as additive.

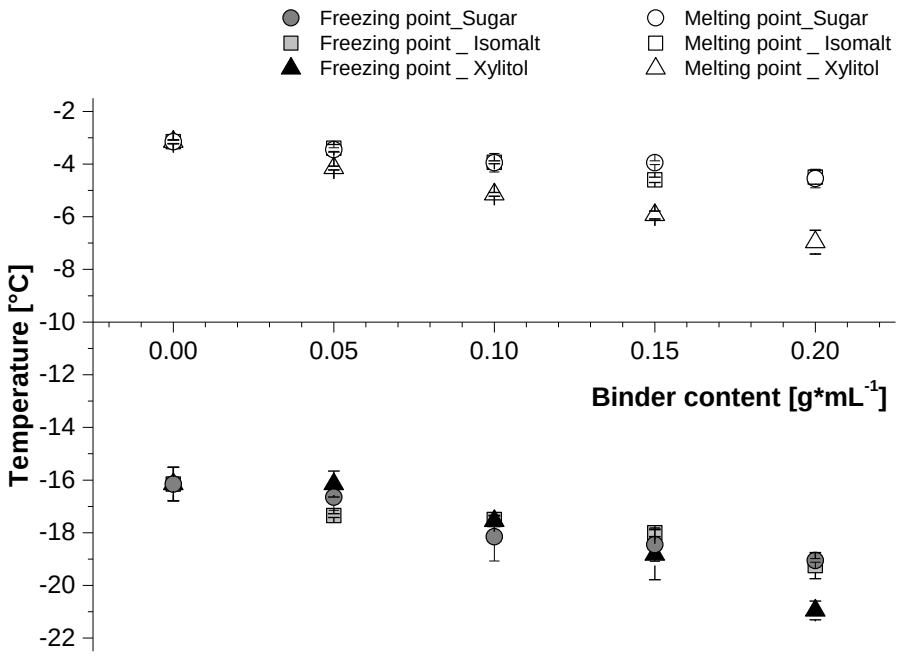


Fig. 5.1-14: The phase diagram of the 28 wt% aqueous cocoa suspensions containing sugar, isomalt and xylitol in various contents.

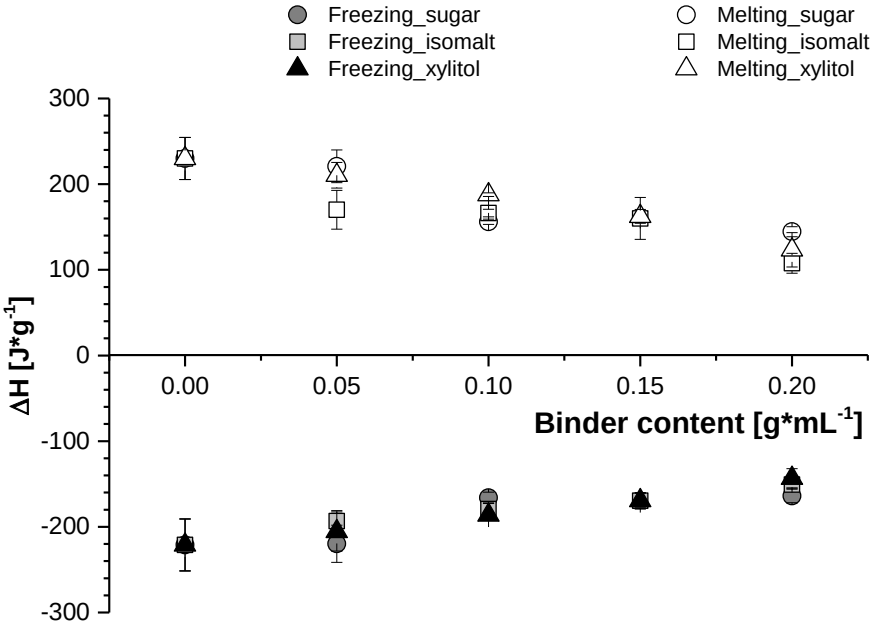


Fig. 5.1-15: The latent heat of fusions of the 28 wt% aqueous cocoa suspensions containing sugar, isomalt and xylitol in various contents.

With the additive concentration in range of 0 - 0.20 g*mL^{-1}, the minimum melting point was about -6.5 °C and minimum freezing point was a little beyond -21 °C. Based on these results,

the minimum freezing temperature (the temperature of cooling plate surface) of -24 °C and fixed drying temperature of -8.1 °C were set for further tablet producing experiments.

5.1.2 Effect of freezing temperatures

Based on the result of the thermal dynamic properties of the suspensions presented in chapter 5.1.1.4, an instant freezing process at various freezing temperatures of -24, -30 and -34 °C were applied to check the effect of the freezing temperature. The morphologies of tablets produced in the one-side and two-side freezing mode at various freezing temperatures and solid contents are shown in Fig. 5.1-16. It was found that the tablets in the one-side freezing mode were well produced at all studied-freezing temperatures. The tablets had similar looks with the needle-like pattern of pores. They were able to keep the tablet form and can be handled. However, in the case of the both-side freezing mode the tablets were not successfully produced. There were always disruptions in the middle of all tablets.

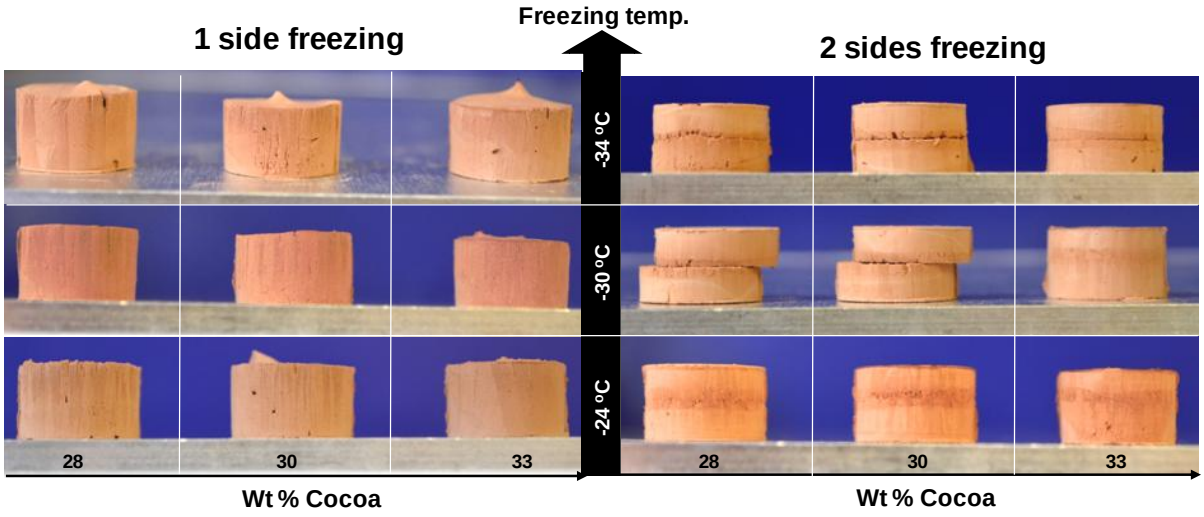


Fig. 5.1-16: The effect of instant freezing temperatures and freezing modes on the morphologies of tablets.

The crushing forces (in the horizontal and vertical direction) and the dispersal times of tablets produced by the one-side freezing mode are shown in Fig. 5.1-17. Due to the breaking behavior of tablets, the mechanical strength measurement was not carried out for the tablets produced by the two-side freezing mode. The porosity values and pore sizes of the tablets are listed in Tab. 5-8.

It is found that a decreasing of the freezing temperature proposed a faster freezing behavior. As result, slightly higher porosities in form of needle-like channels in the tablets were found. Pore sizes are estimated to be smaller according to a deeper freezing temperature. Faster dispersal behaviors were obtained as the freezing temperatures were decreasing, however, lower mechanical strengths were created in parallel.

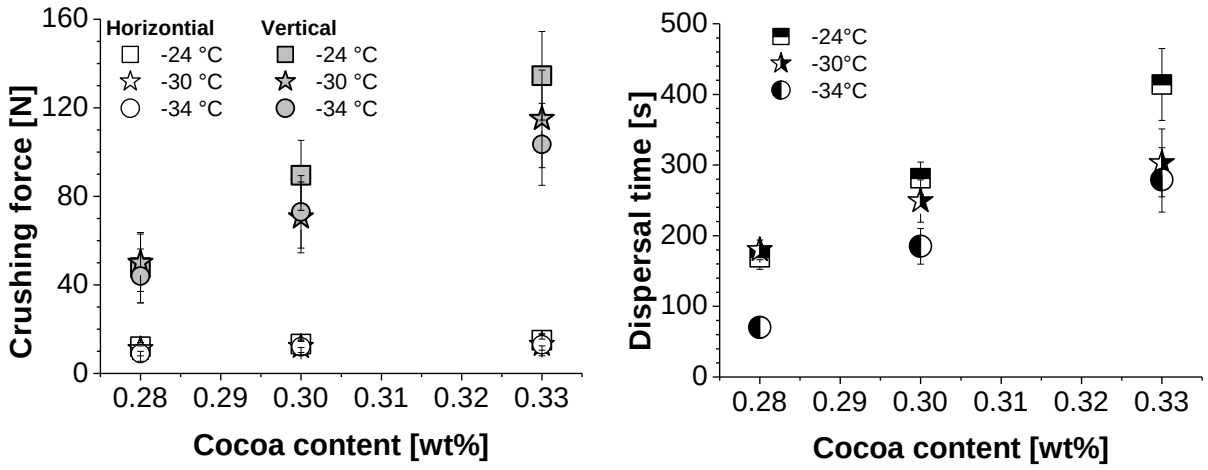


Fig. 5.1-17: The effect of the instant freezing temperatures on the mechanical strengths (crushing force) and the dispersal behaviors (dispersal times) of tablets produced by the freeze casting process with the one side instant freezing mode at various solid loadings.

In general, tensile strengths of tablets in vertical direction were in the range of 45-130 N and were more than five times higher than the tensile strengths in the horizontal direction (about 10 to 15 N). The influence of the freezing temperatures on the mechanical strength of tablets can clearly be seen in the change of the tensile strength in the vertical direction. However, the change in the tensile strength in the horizontal direction is negligible. The dispersal times of the produced tablets were in the range of >1 to 7 min.

Tab. 5-8: The porosity and the pore size of tablets produced by the one-side instant freeze casting process at various freezing temperatures and solid contents.

Freezing temperature, °C		Porosity, %			Pore size, µm		
		-24	-30	-34	-24	-30	-34
Cocoa contentt, wt%	28	75.37 ± 1.67	-	76.60 ± 0.89	6.28 ± 0.16	-	5.23 ± 0.06
	30	71.48 ± 3.39	-	71.91 ± 0.64	4.82 ± 0.19	-	4.37 ± 0.64
	33	66.03 ± 1.73	68.82 ± 0.73	69.45 ± 0.21	4.00 ± 0.03	3.35 ± 0.20	3.36 ± 0.01

5.1.3 Effect of the freezing modes and the cooling profiles

To check the effect of the freezing modes and the cooling profiles on the properties of freeze casted tablets, two freezing modes were investigated: Freezing from one side and two sides at two freezing profiles – instant cooling and cooling at 1 K*min^{-1}. Instant cooling means that the suspension was directly positioned on the cooling plate at -24 °C for 4 h. Cooling at 1 K*min^{-1} means that the suspension was positioned on the cooling plate and then cooled from

1 to -24 °C at a cooling rate of 1 K*min^{-1}, and thereafter maintained at a constant temperature of -24 °C for 4 h.

The morphologies of produced tablets and pores are shown in Fig. 5.1-18.

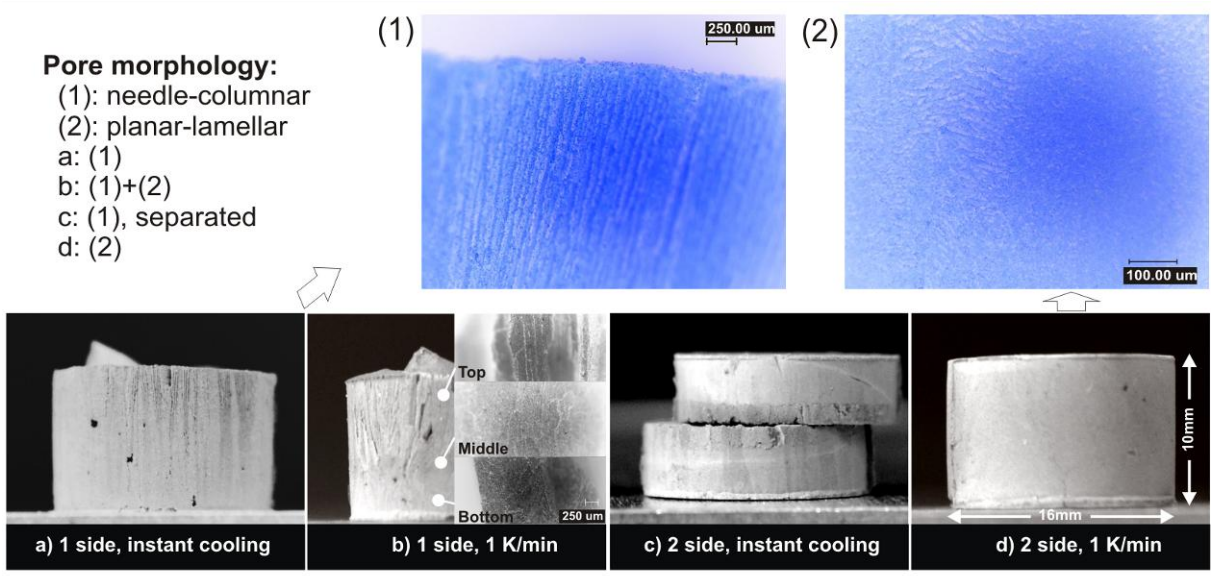


Fig. 5.1-18: Effects of freezing modes and cooling profiles on the morphologies of tablets produced by the freeze-casting process. (a) One-side freezing mode with instant cooling, (b) one-side freezing mode with the cooling rate of 1 K*min^{-1}, (c) two-side freezing mode with instant cooling, (d) two-side freezing mode with the cooling rate of 1 K*min^{-1} [Ngu14a].

As can be seen in the above figure, there are two types of pore morphologies obtained as the freezing profile is changed. At the very fast freezing profile (instant cooling), a needle-columnar-like structure was found (see Figs. 5.1-18a and 5.1-18(1)). At the slower freezing rate of 1 K*min^{-1}, a planar-lamellar structure was built (see Figs. 5.1-18d and 5.1-18(2)). Furthermore, a combination of these morphologies of pores and tablets was found in Fig. 5.1-18b, there the tablet was produced by one-side freezing at the cooling rate of 1 K*min^{-1}. In Fig. 5.1-18b, there are three different parts to clearly be seen when looking at the tablet from the bottom to the top. At the bottom region where the tablets were contacted with the cooling surface, a dense layer of particles which have the same looks as in Fig. 5.1-18d was formed. In the middle area, a mediating area from a dense layer structure to a columnar microstructure was found. In the top area, a clearly needle columnar microstructure, which is similar with the pore pattern in the case of Fig. 5.1-18a, is found. In particular, in the case of the two-side freezing mode at the instant cooling profile there is a horizontal splitting in the middle area of the tablets (see Fig. 5.1-18c).

The views of the bottom (the contacting surface with the cooling plate) and the top-open surface of tablets are shown in Fig. 5.1-19 and the views of middle-splitted surfaces of the splitted tablets are shown in Fig. 5.1-20.

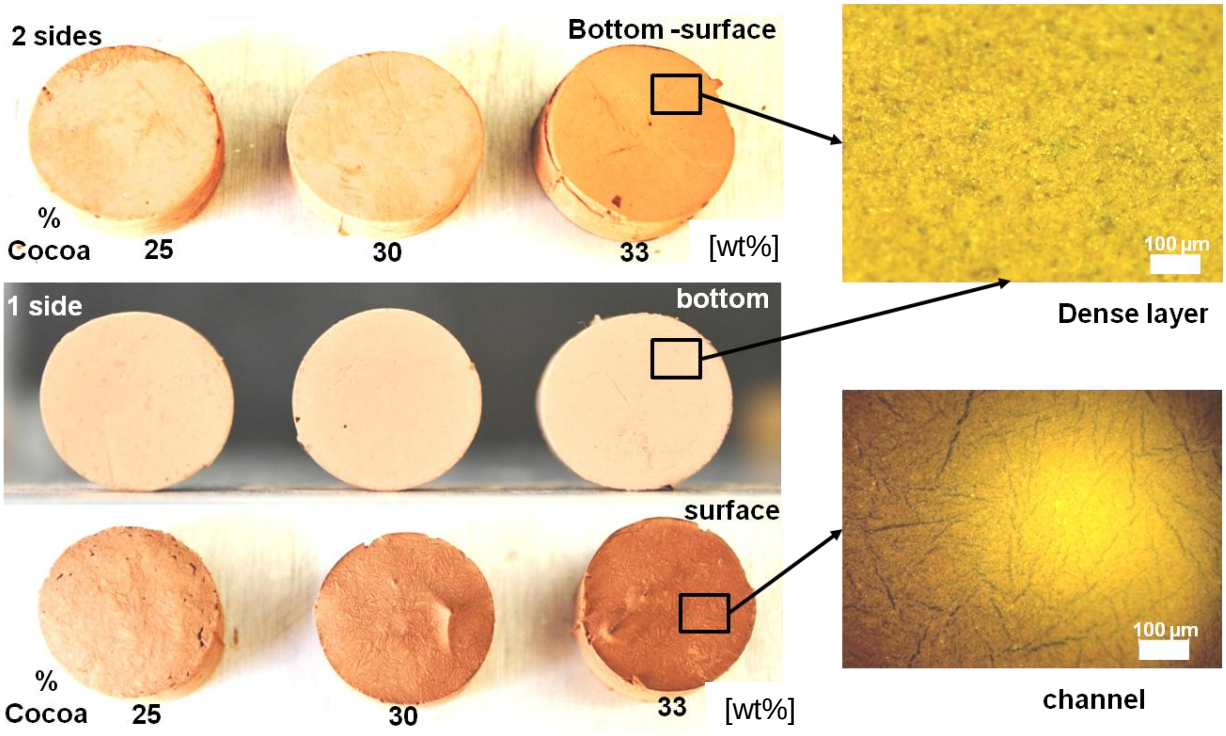


Fig. 5.1-19: The view on surfaces of tablets.

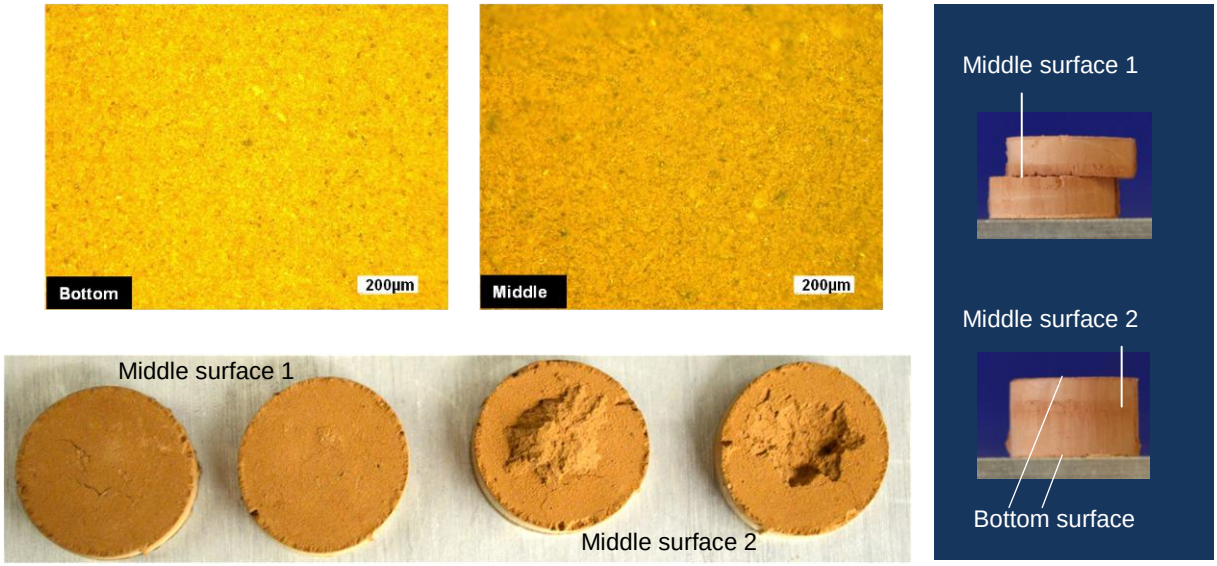


Fig. 5.1-20: The view of the bottom surfaces and the middle surfaces of middle-broken tablets.

It is seen that a flat and dense layer surface were always found at the surface of the bottom where the cocoa suspensions were in direct contact with the cooling plate. A dark crossed network which represents the image of the open-pore channels in the view from the top of the tablets was found on the top-open surface of tablets (see Fig. 5.1-19). This crossed network could not be seen in the open middle surfaces of the splitted tablets in Fig. 5.1-20, here, a dense but not smooth surface and covered by thin layers of powders was found. At

the cocoa loading of 33 wt% as be seen in middle surface 2 in Fig. 5.1-20, sometimes, the two parts of the produced tablets were not totally separated, they were still linked in the central point, but, the surround areas are totally separated.

The porosity and pore size of the tablets produced by different freezing modes and cooling profiles are summarized in Tab. 5-9. It is noticeable that the pore sizes in the case of the two-side freezing are considerably smaller than the one side freezing (see Tab. 5-9). The porosities of the tablets were in the range of 66–75%.

The good looking, non splitted and handable tablets were further evaluated by the mechanical strength, porosity and dispersal/dissolution tests.

Tab. 5-9: The porosity and pore sizes of the produced tablets.

Cocoa content, wt%	Porosity, %			Pore size, µm		
	1-side cooling		2-side cooling	1-side cooling		2-side cooling
	Instant cooling	1 K*min^{-1}	1 K*min^{-1}	Instant cooling	1 K*min^{-1}	1 K*min^{-1}
28	75.37 ± 1.67	75.56 ± 0.25	75.58 ± 1.57	6.28 ± 0.16	8.65 ± 0.64	3.07 ± 0.97
30	71.48 ± 3.39	71.21 ± 1.27	72.89 ± 1.48	4.58 ± 0.19	4.88 ± 1.48	2.82 ± 0.78
33	66.03 ± 1.73	69.19 ± 1.51	69.49 ± 1.64	4.00 ± 0.03	5.12 ± 0.52	2.99 ± 0.55

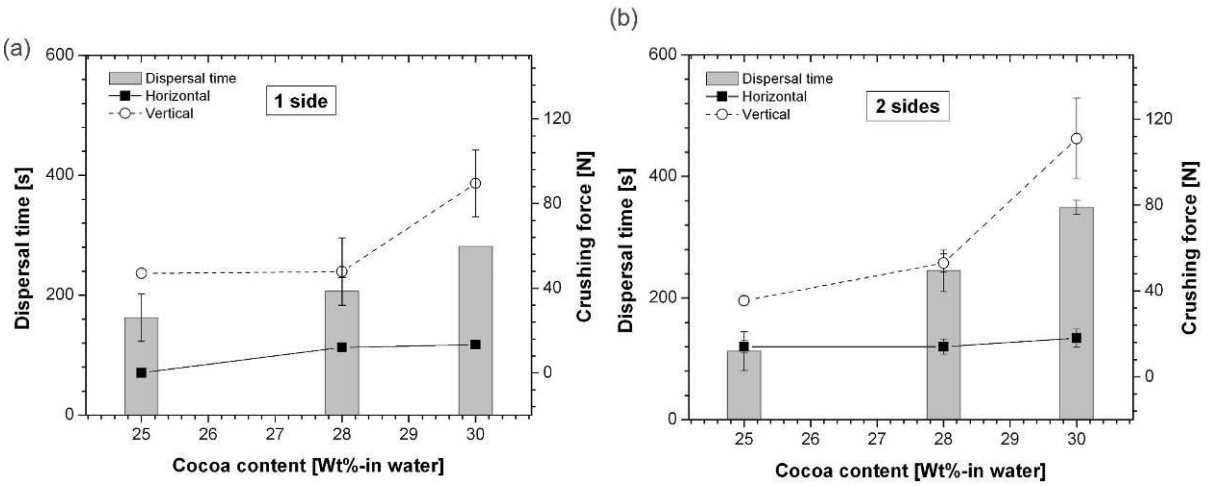


Fig. 5.1-21: Dispersion behavior and mechanical stability of cocoa tablets produced by the freeze-casting process as a function of the cocoa content. (a) One-side instant freezing mode, (b) two-side freezing mode at a cooling rate of 1 K*min^{-1}. The symbols termed ‘‘horizontal’’ and ‘‘vertical’’ indicate the crushing forces applied on the tablets in the horizontal and the vertical direction, respectively, [Ngu14a].

Figure 5.1-21 displays the effects of the solid contents on the tensile strengths and the dispersal behaviors of the tablets produced in two freezing modes: One-side instant freezing (Fig. 5.1-21a) and two-side freezing with a cooling rate of 1 $K*min^{-1}$ (Fig. 5.1-21b). The tensile strengths were in range of 0-20 N and 40-105 N in the horizontal and the vertical direction, respectively. The dispersal times were about 2-6 min.

It was also found that the mechanical strengths in the vertical direction are much higher than the ones in the horizontal direction. It seems that freezing from two sides improves the mechanical strength of the tablets. However, it also requires a longer dispersal time in the case of cocoa contents of 28 and 33 wt %. The opposite behavior was found in the case of 25 wt% cocoa.

In addition, in both freezing modes the solid contents have a strong effect on the properties of the tablets. A lower porosity, smaller pore size (see Tab. 5-9), longer dispersal time, and a higher applied crushing force (Fig. 5.1-21) were found as the cocoa content is increased, corresponding to a decreasing water content.

5.1.4 Effect of additives

For the fast dissolving tablets, in order to get an improvement in both the tensile strength and dispersal behavior, additives which are highly and fast soluble in the dispersal medium are strongly recommended [Sze07a,b, Pac07a,b, Wit10, Ngu14a,c, Ngu15a]. In addition, the additives also need to interact well with the main active ingredients in both solid and liquid states to successfully get a “stable” suspension during the sample preparation step as well as to form bonds to reinforce the tablet body during the freeze casting process. In order to classify the potential additive groups, a simple screening of additives (i.e., sugar, sugar alcohols and acidic food additives) based on their solubility and dissolution rate in water, and the stability of the suspensions were investigated. The summary results of the screening of additive are listed in Tab. 5-10. As results three promising substances: Sugar (sucrose), isomalt and xylitol were chosen as additives for further studies.

Tab. 5-10: Results of additive screening.

	sucrose	isomalt	xylitol	lactose	Citric acid
Solubility	+	+	+	+	+
Dissolution rate	+	+	+	-	+
Miscibility	+	+	+	+	+
Tablet form	+	+	+	+	+
Taste	+	+	+	+	-

(+): good, (-): not good

The tablets produced by the freeze casting process with a one side and a two-side freezing mode of the aqueous suspensions resulting by mixing of cocoa powder (at a cocoa content

ratio of 28 wt%) in aqueous solutions of a sugar alcohol, e.g. sugar, isomalt, xylitol with various contents of 0.00-0.20 g*mL^{-1} were investigated.

Figure 5.1-22 shows the effect of additives on the tensile strength of the produced tablets. Because of the tensile strengths in the vertical direction are much higher than the one in the horizontal direction, therefore the horizontal tensile strength is needed to be more considered and improved. From here until the end of this present work, the tensile strength is always represented to the tensile strength in the horizontal direction.

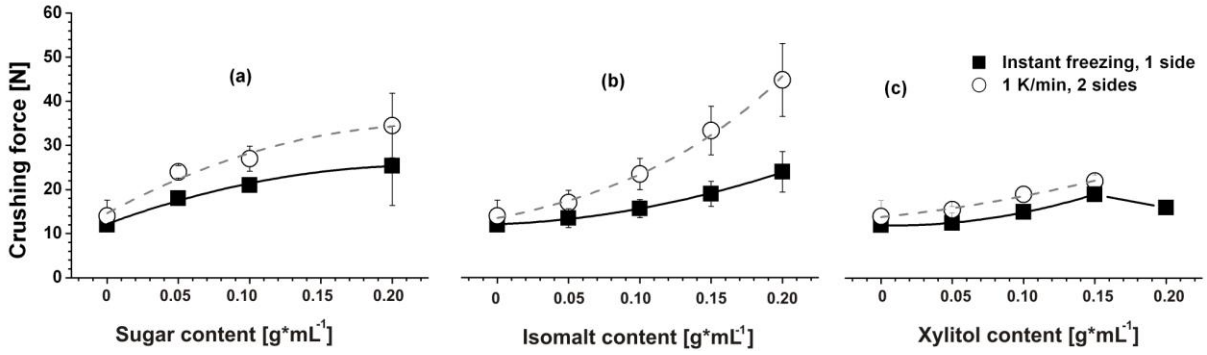


Fig. 5.1-22: The effect of additive contents on the tensile strength (the applied crushing force) of produced tablets by freeze casting with the one side and the two-side freezing mode at constant cocoa content of 28 wt%: (a) sugar, (b) isomalt, (c) xylitol [Ngu15a].

It can clearly be seen that all three sugar- or sugar alcohol additives dramatically improved the mechanical stability of produced tablets. The two-side freezing mode significantly enhances the hardness of produced tablets. Using isomalt as a additive with a content of 0.20 g*mL^{-1} could result in more than 3.5 times an increase of the applied crushing forces of tablets produced by the freeze casting process with the two-side freezing mode. A twofold increase could be in case of the one side freezing mode (see Fig. 5.1-22(b)). The maximum crushing force value of 44.8 N (i.e. 0.18 N/mm^2 diametral tensile strength, calculated by Eq. 4-4) could be reached in case of isomalt, which is higher than the maximum crushing force value of 34.5 N of the produced tablets using sugar as an additive (see Fig. 5.1-22(a)). In case of xylitol (Fig. 5.1-22 (c)), there is a different behavior. The difference in the effect of the freezing modes in the increase of the applied crushing forces was not as pronounced as with sugar or isomalt. The mechanical strength of the produced tablets slightly increases when the xylitol content increases from 0.00 to 0.15 g*mL^{-1}, thereafter the tensile strength decreases as the xylitol content reaches 0.20 g*mL^{-1}.

The morphologies of produced tablets with various additives were shown in Fig. 5.1-23. It is obviously to be seen that the looks and the porous structures of the produced tablet bodies are different when the additives were added. At the same additive content of 0.20 g*mL^{-1}, the looks of produced tablet body in case of isomalt are denser than the ones of the produced tablet in case of sugar and xylitol.

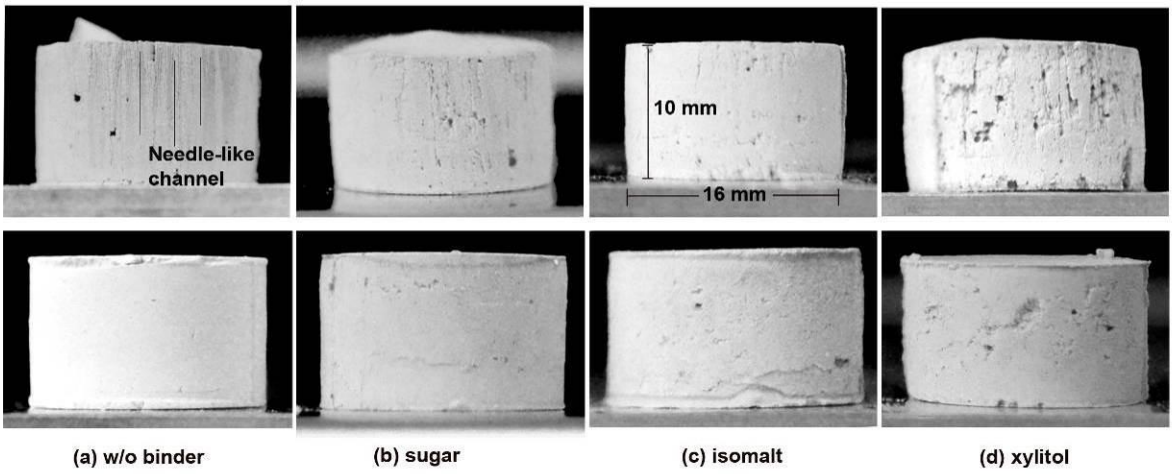


Fig. 5.1-23: The morphology of tablets produced by the freeze casting process using one side freezing (upper images) and two-side freezing mode (below images) at constant cocoa content ratio of 28 wt% containing various sugar and sugar alcohols (from left to right side): (a) without additive, (b) sugar content of 0.20 g*mL^{-1}, (c) isomalt content of 0.20 g*mL^{-1} and (d) xylitol content of 0.20 g*mL^{-1} [Ngu15a].

To see more details of the morphology of the pores in solid tablet bodies, the microscopic images of the vertical-cut surface of produced tablets by the one side freezing mode were presented in Fig. 5.1-24.

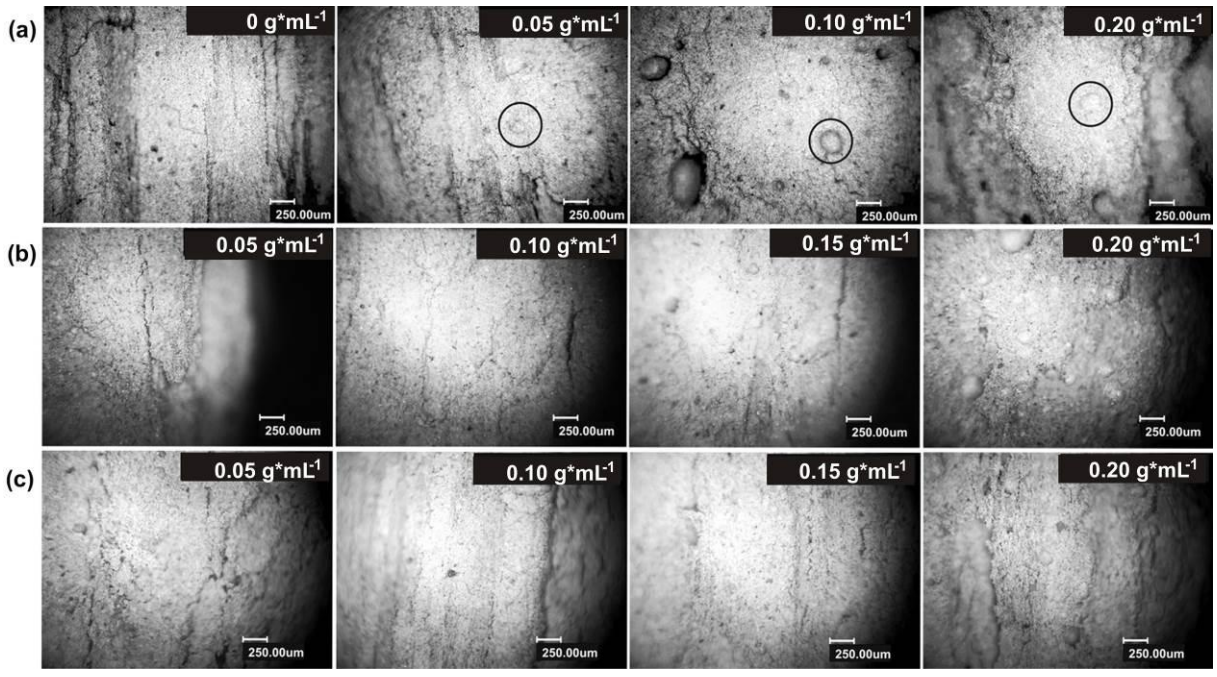


Fig. 5.1-24: Microscopic images of the vertical-cut surface of produced tablets containing different additive contents: (a) sugar; (b) isomalt; (c) xylitol [Ngu15a].

The needle-like structure channels of the pores (see the first left image of Fig. 5.1-24(a)) was gradually substituted by a porous and size increasing sphere-like pore structure since the

additive contents were increased. This porous morphology was found in all cases of sucrose, isomalt and xylitol in both the freezing modes, which made these solid bodies look more porous.

The closed up SEM images of vertical-cut surfaces of the tablet bodies are displayed in Figs. 5.1-25 and 5.1-26. Here again the needle channels of pores were clearly observed in case of the one side freezing mode from the suspensions not containing additives. The additives create the binding effect in which they linked solid particles into a network growing in various directions. As result, undefined shape holes were formed and distributed in the middle of surrounding solid chains connected by the additives. The matrix binding connections were also found in the SEM images of tablets produced by both size freezing (see Fig. 5.1-26).

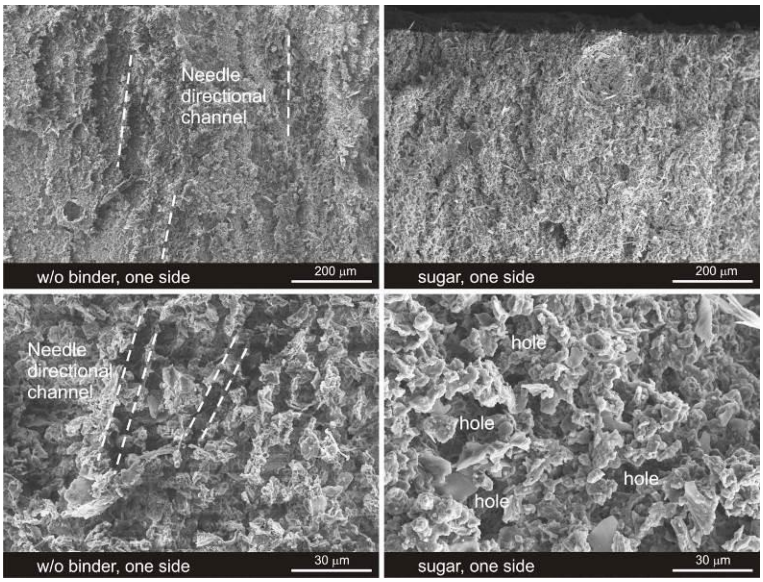


Fig. 5.1-25: SEM images of the vertical-cut surfaces of tablets produced by the one side freezing mode [Ngu15a].

The porosity data of the produced tablets are listed in Tabs. 5-11 and 5-12. Table 5-11 demonstrates that the produced tablets had an about 5-10 % lower porosity, but, larger pore sizes compared to the case where the additives were added. The one side freezing also produces the tablets with a bigger pore size in comparison to the two-side freezing.

The porosity and pore size of produced tablets in function of sugar contents as well as freezing mode is summarized in Tab. 5-12. It is found that for all freezing modes and cooling profiles, the increase of the sugar contents results in a decrease of porosity and a raise of the pore size.

Tab. 5-11: Porosity data of produced tablets with different additives at the additive content of 0.20 g*mL^{-1} and cocoa content ratio of 28 wt%.

	Porosity, %			
	w/o additive	sugar	isomalt	xylitol
1 side, instant cooling	75.37 ± 1.67	64.14 ± 2.08	69.61 ± 0.92	65.26 ± 4.52
2 sides, 1 K*min^{-1} cooling	75.58 ± 1.57	66.24 ± 1.48	69.70 ± 1.05	-
	Pore size, µm			
	w/o additive	sugar	isomalt	xylitol
1 side, instant cooling	6.28 ± 0.16	4.84 ± 0.30	4.53 ± 0.55	3.80 ± 0.63
2 sides, 1 K*min^{-1} cooling	3.07 ± 0.97	3.92 ± 0.79	3.68 ± 0.67	-

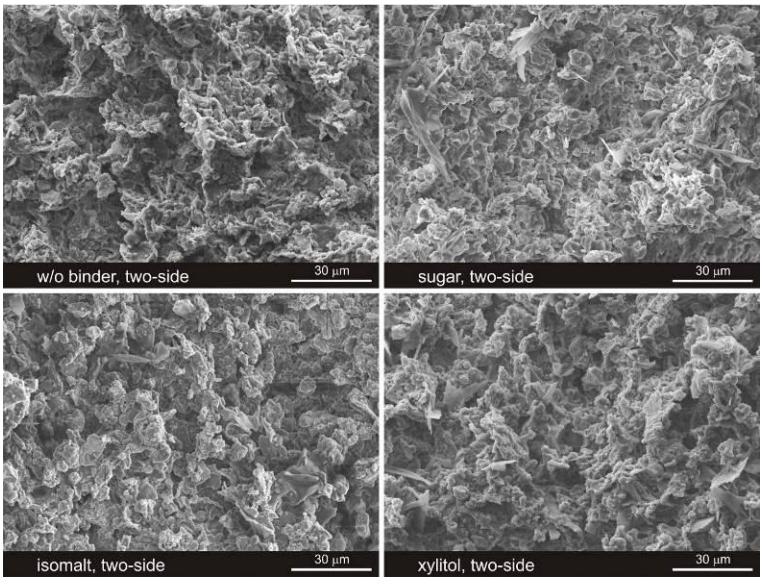


Fig. 5.1-26: SEM images of the vertical-cut surfaces of tablets produced by the two-side freezing mode [Ngu15a].

Tab. 5-12: The porosity and pore sizes of the produced tablets from 30 wt% cocoa suspensions at the various sugar contents.

Sugar content, g*mL^{-1}	Porosity, %			Pore size, µm		
	1-side cooling		2-side cooling	1-side cooling		2-side cooling
	Instant cooling	1 K*min^{-1}	1 K*min^{-1}	Instant cooling	1 K*min^{-1}	1 K*min^{-1}
0.00	71.48 ± 3.39	71.21 ± 1.27	72.89 ± 1.48	4.58 ± 0.41	4.88 ± 1.48	2.82 ± 0.78
0.05	68.91 ± 3.35	68.29 ± 0.08	68.21 ± 1.12	4.86 ± 0.98	4.55 ± 1.25	2.90 ± 0.86
0.10	70.21 ± 1.53	62.81 ± 1.02	65.93 ± 4.07	5.15 ± 0.32	4.23 ± 0.78	2.89 ± 0.13
0.20	61.87 ± 2.08	62.79 ± 2.15	64.97 ± 2.31	5.00 ± 0.45	6.42 ± 0.30	3.27 ± 0.69

The dispersal/dissolution behaviors of produced tablets are displayed in Fig. 5.1-27. All samples result in a reduced dispersal time of produced tablets as additives were added. The produced tablets using isomalt as additive show a slightly better dispersal behavior. At the additive content of 0.20 g*mL^{-1}, the dispersal times of 45.5 and 51.5 s in case of isomalt, 58.5 and 60 s in case of sugar (sucrose) were achieved corresponding to the results from the freeze casting process at one side freezing and two-side freezing mode. In summary, by means of adding additives, i.e. isomalt and sucrose, always a dispersal time lower than 1 min was achieved.

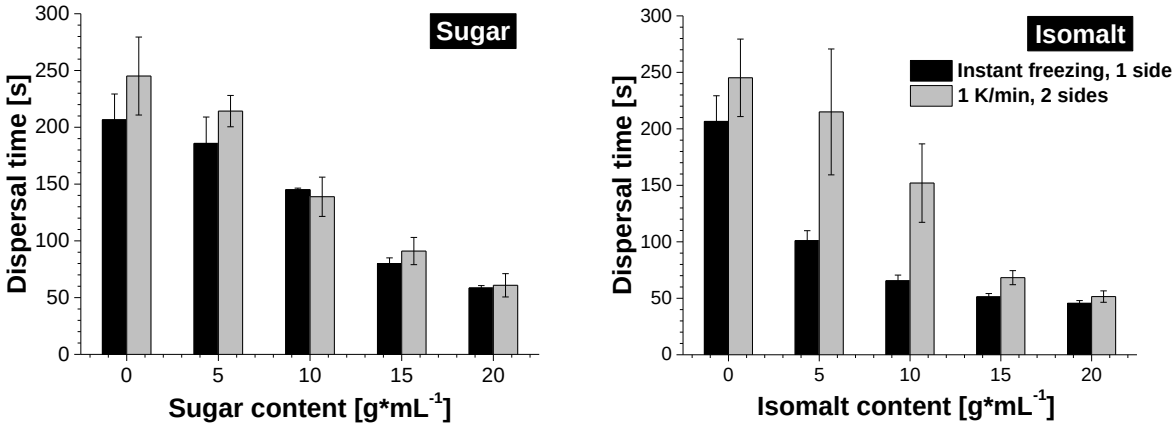


Fig. 5.1-27: The effect of additive contents (left: Sugar, right: Isomalt) on the dispersal/dissolution behavior of produced tablets by freeze casting with an one side and a two-side freezing mode at constant cocoa content ratio of 28 wt% [Ngu15].

5.1.5 Effect of solid loadings or water contents

As mentioned in chapter 5.1.4, despite of the reduction of porosities, the remarkable improvements in both the dispersal behavior and the hardness of tablets were found when the sugar and the sugar alcohols were added to the aqueous phase of suspensions. This leads to the question: Whether the additive content is the key factor controlling the physical properties of tablets especial the dispersal time? To understand the role of the hardness, the porosity and the tablet compositions on the dispersal time of tablet, the experiments focusing on the effect of solid loadings of suspensions were investigated. The weight ratio of additives and cocoa was kept constant of 1:2 which is the same ratio of the optimized produced tablets in chapter 5.1.4. The different solid loadings of suspensions were generated by increasing the water content in suspensions from minimum values of 57.2 to 66.46 wt%. The minimum value of the water content is the minimum amount of the water phase added to obtain a homogenous and mixable suspension. The changes of the dispersal time and the crushing force of the produced tablets from suspensions containing various water contents were presented in Fig. 5.1-28. It is clear that increasing the water contents led to a raise of the porosities (see Tab. 5-13), a considerable decrease of the applied crushing forces and resulted in a marked reduction of the dispersal time.

Tab. 5-13: Porosity data of produced tablets by the one side, instant freezing process of suspensions containing different water contents.

Water content, wt%	Porosity, %		Pore size, µm	
	sugar	isomalt	sugar	isomalt
57.20	58.52 ± 0.90	59.18 ± 1.21	3.72 ± 0.26	2.96 ± 0.01
62.94	64.14 ± 2.08	69.61 ± 0.92	4.84 ± 0.30	4.53 ± 0.55
66.46	72.75 ± 1.51	74.57 ± 1.51	6.51 ± 0.27	5.58 ± 0.13

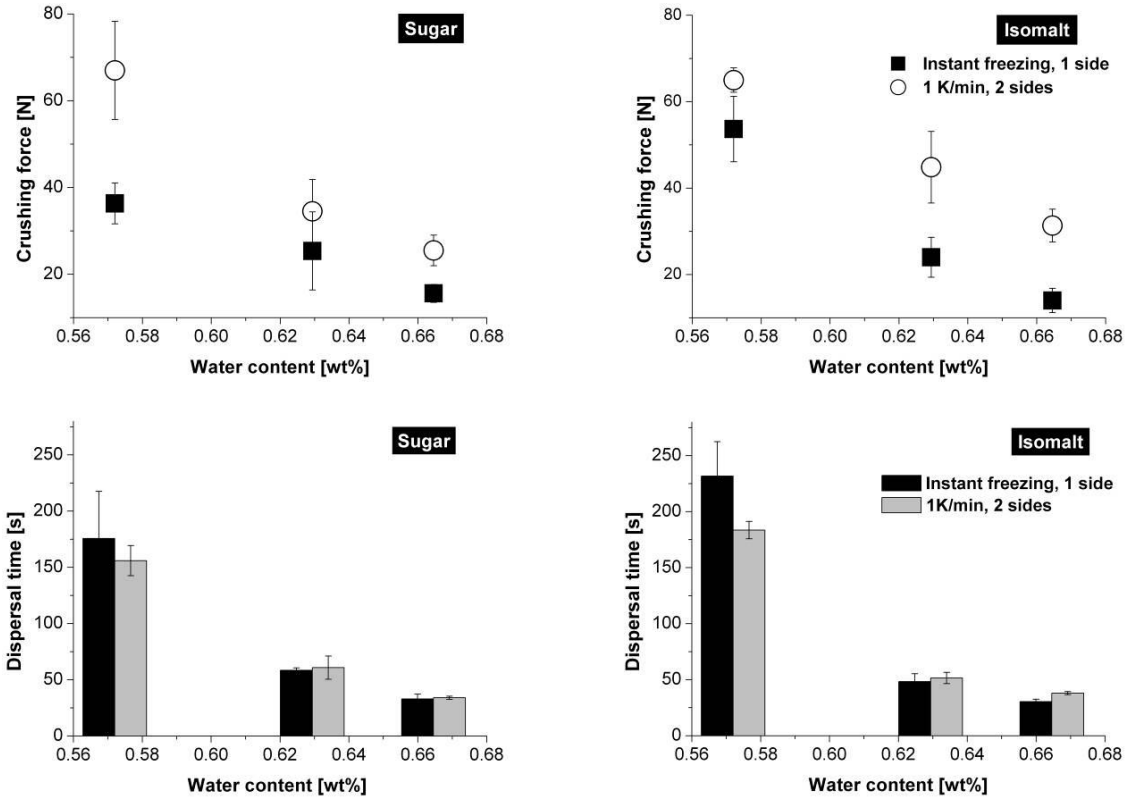


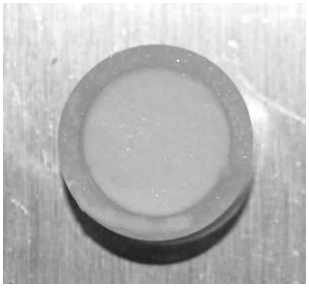
Fig. 5.1-28: The effect of water contents on the physical properties of the produced tablets.

5.2 System 2 – drug: paracetamol tablet

5.2.1 Trial test of tablet productions

Based on the experiences of the cocoa system, trials of paracetamol tablets' production were designed. The best conditions of the freeze casting process in the cocoa system were reused. The solid loading of 50 wt% was chosen after a simple screening of suspension behaviors. In Tab. 5-14 the summary of the operating conditions of freeze casting processes and the results of the first trials are presented.

Tab. 5-14: The operating conditions and the results of first trials of the paracetamol tablets' production using the freeze casting process.

Conditions: One side freezing, T_f = -24 °C, t_f = 4 h, T_d = -8.1 °C, t_d = 24 h. Suspensions: Water as the dispersal medium, solid loading: 50 wt%.		
Additive	Suspension	Tablet
No additive	mixable, stable	Cannot be produced → powder 
0.20 g*mL^{-1} sugar solution	mixable, stable	Get the tablet form Difficult to remove from the mold
0.20 g*mL^{-1} isomalt solution		

Firstly, it can be seen that without using an additive the paracetamol tablet cannot be produced. The solid body was obtained after the freezing step due to the crystallization of water, however, after the drying stage the tablet form was totally destroyed and a powder such as the original material was obtained. Secondly, an addition of isomalt or sugar as additive with the concentration of 0.20 g*mL^{-1} successfully maintained tablet forms. Unfortunately, the solid tablets were hard sticking to the molds that makes the removing of the tablets from the molds extremely difficulty. To overcome this problem, maize starch (starch 1500, Colorcon, UK) is added as a lubricant to produce the tablet. As to be expected,

the shrinkage of the maize starch aids to reduce the volume of the solid bodies that makes them easily to be separated from the molds. The overview of the tensile strength of the tablets in the function of the additive contents and starch contents is shown in Fig. 5.2-1. It can be seen that the addition of the maize starch significantly promotes the tensile strength of the tablets which can be even higher than the tensile strength of commercial tablets produced by conventional compression methods. However, the results of the dissolution tests of the produced tablets to be seen in Tab. 5-15 indicate that the produced tablets take extremely long times to be dissolved.

Tab. 5-15: The dissolution time of produced tablets.

Starch contents, *wt% of solid*	Dissolution time, min	
	0.20 g*mL^{-1} isomalt solution	0.40 g*mL^{-1} isomalt solution
10.0	75	40
20.0	105	50
Paracetamol Ratiopharm 500	10	

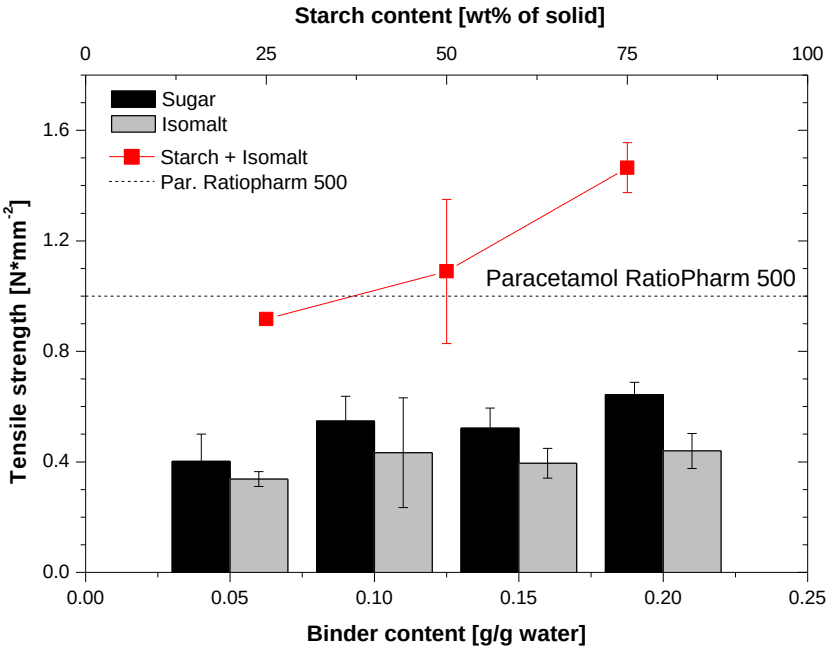


Fig. 5.2-1: The tensile strength of the produced tablets.

To promote both the tensile strength and the dissolution rate of the tablets, a soluble modified starch is chosen as additive for the further studies of the paracetamol system. Based on the observation of the trials it is found that it took just about 10 minutes for the

water to be crystallized and the periods of 2 hours is enough for the solidification of the suspensions. Therefore, the freezing time was shorted by 2 h for the later experiments of the paracetamol tablets' production. A brief summary of the parameters of the freeze casting process used for the later experiments of the paracetamol system is shown in Tab. 5-16. The related results will be presented in followings chapters.

Tab. 5-16: The parameters of the freeze casting process used for the paracetamol system.

Materials	Conditions
Solid: paracetamol	Freezing mode: instant 1-side freezing
Liquid medium: water	Freezing temperature (T_f): -24 °C
Additive: modified starch and sugar (optional)	Freezing time (t_f): 2 h
	Drying temperature (T_d): -8.1 °C
	Drying time (t_d): 24 h

5.2.2 Properties of suspensions

In this chapter, the results in relation to densities, rehological properties, surface tensions and thermodynamic properties of liquid dispersal media and suspensions in the paracetamol system are presented.

5.2.2.1 Density

Density measurements of the liquid dispersal media and the suspensions were carried out to know their density behavior in dependence of temperatures, solute concentrations and solid contents. Fig. 5.2-2 shows the density data of the liquid phases in relation to the modified

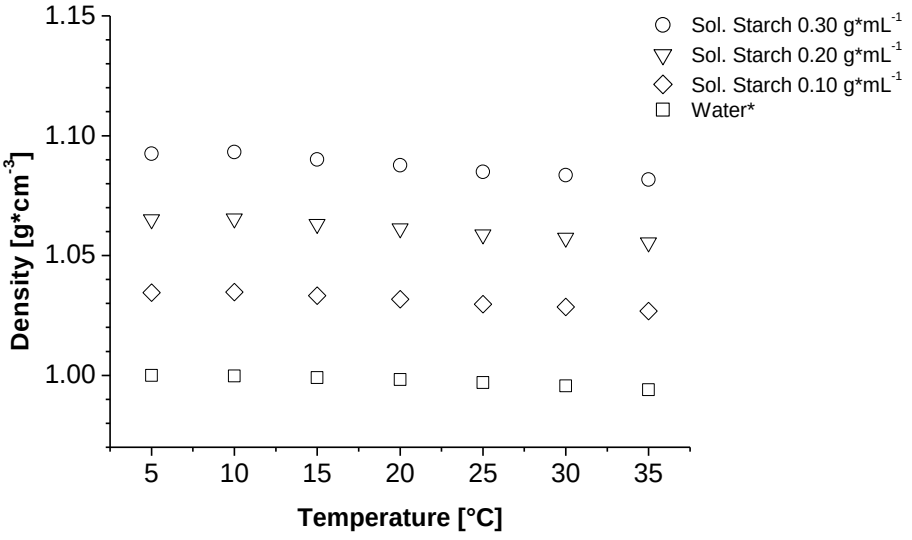


Fig. 5.2-2. Density of the modified starch solutions in various starch loadings. * - the water densities were collected from Weast, 1988 [Wes88].

starch contents and the temperatures. It is obvious to be seen that the density of all liquids slightly decreases according to an increase of the temperatures in the range of 5-35 °C. The higher the modified starch content is in the solution the higher is the density.

Due to the high viscose properties of the paracetamol suspensions, the process of degassing and stabilization of the suspensions took longer than the time limit of the D40 Density Meter. Therefore, the density of the paracetamol suspensions could not successfully be obtained by the density meter. To get reference values, the densities of the suspensions were simply determined by the weight of 5 mL suspensions at the temperature of 25 ± 0.5 °C. The weight was measured by a digital balance 4 digit. The volumes of suspensions were measured by a 5 mL cylinder with an accuracy of 0.1 mL. The measured results in comparison to the calculated data are plotted in Figs. 5.2-3 and 5.2.4.

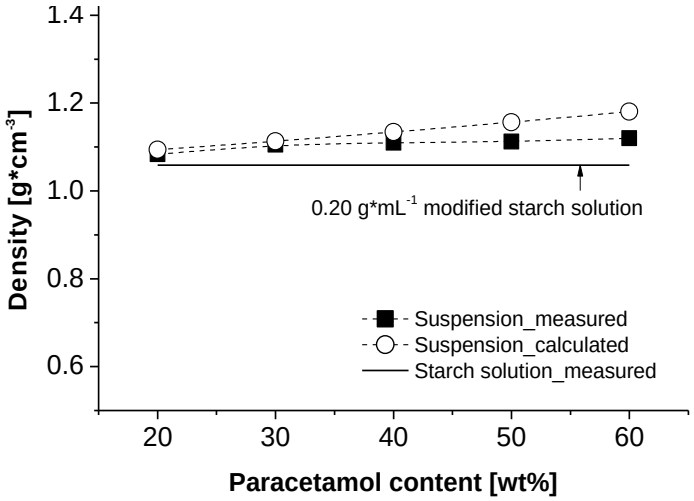


Fig. 5.2-3. Density of the paracetamol suspensions dispersed in the 0.20 g*mL^{-1} modified starch solution in the function of the solid loadings at 25 °C, 1.01 bar.

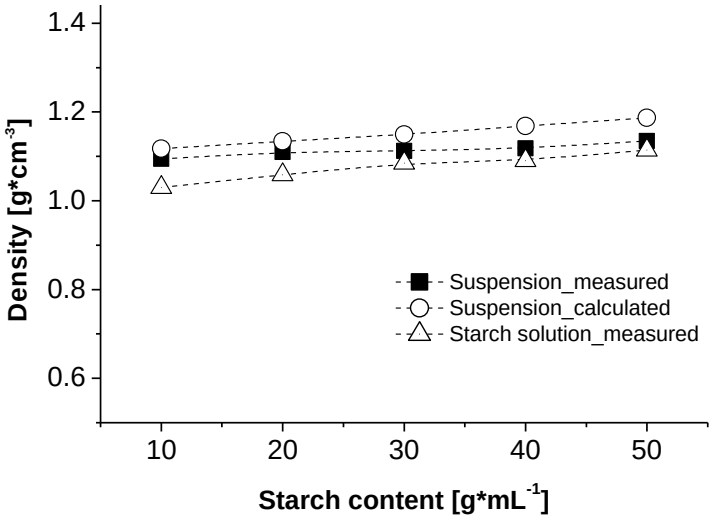


Fig. 5.2-4. Density of the 40 wt% paracetamol suspensions in the function of modified starch contents at 25 °C, 1.01 bar.

It was found that the density of suspension is around 1.1 g*cm^{-3}. In addition, the increase of the starch contents as well as the solid contents gives a slight increase of the density. The measured data are about 1 to 5 % lower than the calculated values.

5.2.2.2 Rheology measurements

The rheology measurements are focused to test influences of physical - chemical nature of substances, solid loadings, additive contents, time, shear rates and temperatures on viscosities of liquid phases and paracetamol suspensions. An experimental plan of measurements is listed in Tab. 5-17**.**

Tab. 5-17: The experimental plan of the rheology measurements of the paracetamol system at p = 1.01 bar.

Flow behavior T = 20°C D = 10-1000 s^{-1}				Time dependence T = 20°C D = 50, 200, 400, 600, 800, 900 s^{-1}				Temperature effect T = 5, 10, 15, 20, 25, 30, 35°C	
Effect of solid loadings		Thixotropy behavior		Effect of solid loadings		Effect of additive contents			
Paracetamol content, wt%	Modified starch 0.20 g*mL^{-1}	Paracetamol content, wt%	Modified starch 0.20 g*mL^{-1}	Shear rate, s^{-1}	Modified starch 0.20 g*mL^{-1}	Modified starch content, g*mL^{-1}	Paracetmol content: 40 wt%	Paracetamol content, wt%	Modified starch 0.20 g*mL^{-1}
20.0	X	0.0	X	20.0	X	10	X	0.0	X
33.4	X	20.0	X	33.4	X	20	X	20.0	X
44.4	X	50.0	X	44.4	X	30	X	50.0	X
50.0	X			50.0	X	40	X		
60.0	X								

Flow behavior and thixotropy phenomenon

Flow behavior of the paracetamol suspensions containing different solid loadings are exposed in Fig. 5.2-5. It is clear that by an increasing of the solid loadings, the viscosity of the suspensions will dramatically rise. The maximum practicable shear rates were reduced from 1000 to 150 s^{-1} when the paracetamol densities rise from 20 to 60 wt%. In addition, the flow behavior of the suspensions is clearly changed when the solid loadings of the suspensions are increased. At a solid loading of 20 wt%, the viscosity seems to be stable with an increase of the shear rates. When the solid loading is higher than 33.3 wt% the viscosity of the suspensions, however, rapidly increases to reach the maximum values, then gradually reduces as the shear rates were increased.

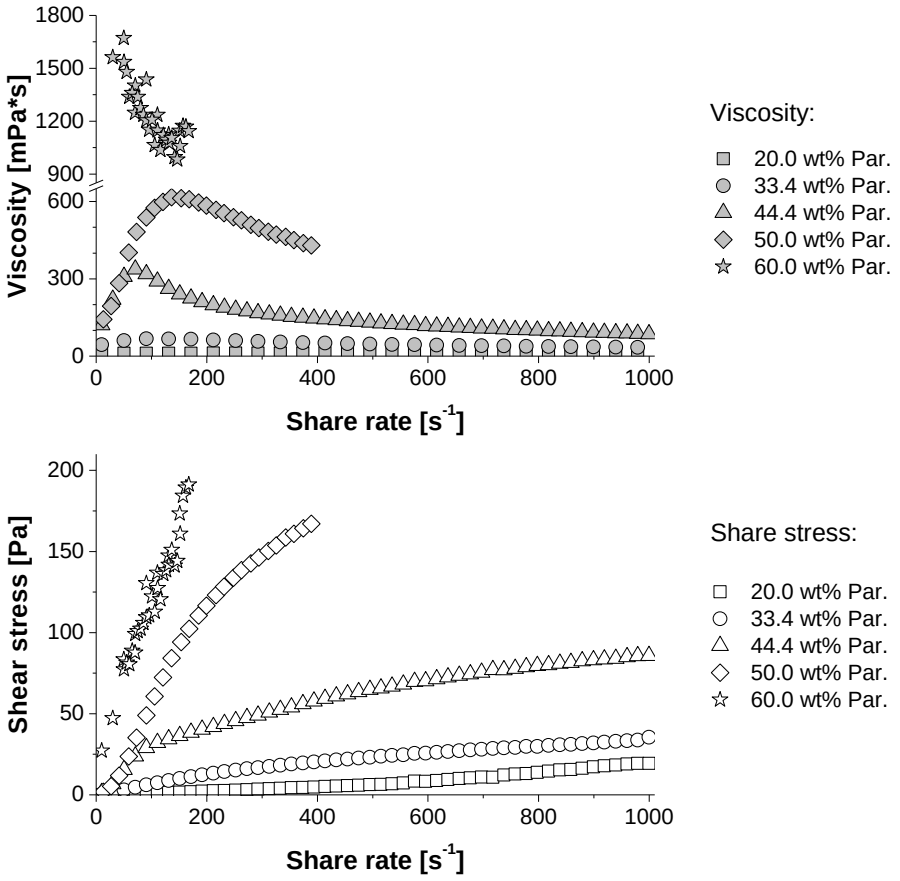


Fig. 5.2-5: Flow behaviors of the paracetamol suspensions containing different solid loadings dispersed in a 0.20 g*mL^{-1} modified starch solution.

To clarify the two kinds of the above observed flow behaviors, the two representative suspensions (20 and 50 wt% paracetamol) were chosen to test the thixotropy behavior. The viscosities and the shear stresses of the suspensions and the solutions were measured with a continuously increasing (up) and decreasing (down) shear rate in range of 10-1000 s^{-1}. The changing rate of the shear rates was kept constant at 33.3 s^{-1} per second. The results are show in Figs. 5.2-6 and 5.2-7.

The flow behavior of the 50 wt% paracetamol suspension shown in Fig. 5.2-6 performs a thixotropy phenomenon. This flow behavior is ensured by the exactly same results of the secondary measurement of the second sample at the same measuring conditions. The up and down curves of the viscosity and the shear stress in the first round are not identical. There are gaps between up and down curves. Surprisingly, this thixotropy phenomenon disappears when the shearing was continuously maintaining in the further retour circles.

The thixotropy phenomenon is not found in case of the 20 wt% paracetamol suspension (see Fig. 5.2-7) as well as the liquid dispersal phase – the 0.20 g*mL^{-1} starch solution (see Fig. 5.2-8). In these cases, the up and down viscosity curves of the continuous circles show the identical values, the shear stresses of the solution slightly increase corresponding to a shear

rate increase. The viscosity seems to be stable in the range of the low share rates and slightly rises thereafter when the shear rates were further increased.

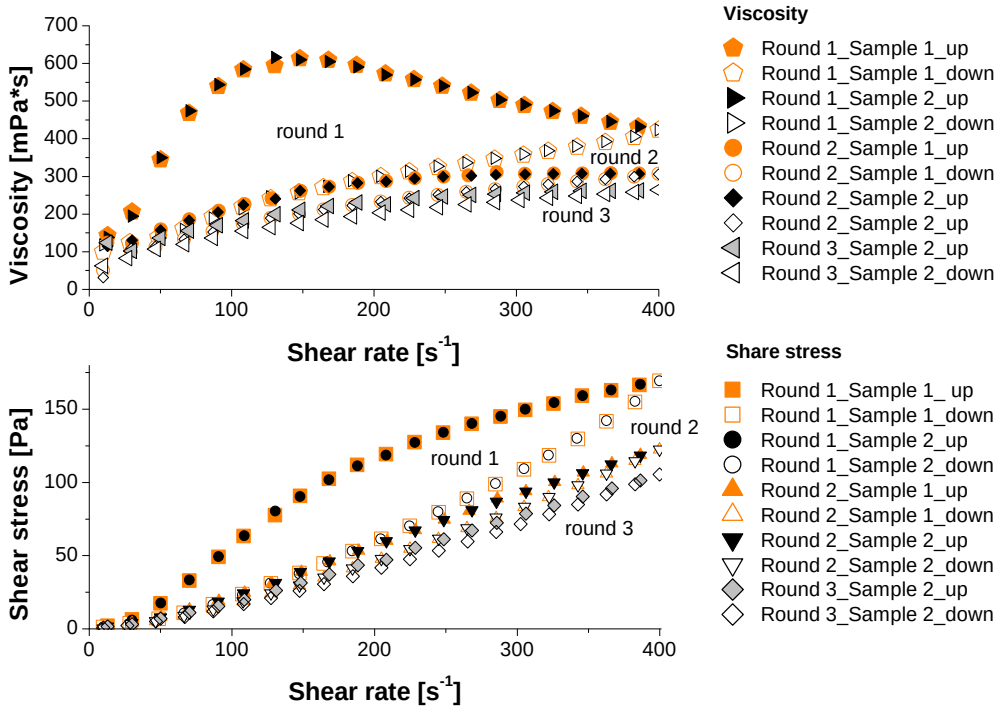


Fig. 5.2-6: Flow behavior of the paracetamol suspension with a paracetamol content of 50 wt% and a modified starch content of 0.20 g*mL^{-1}.

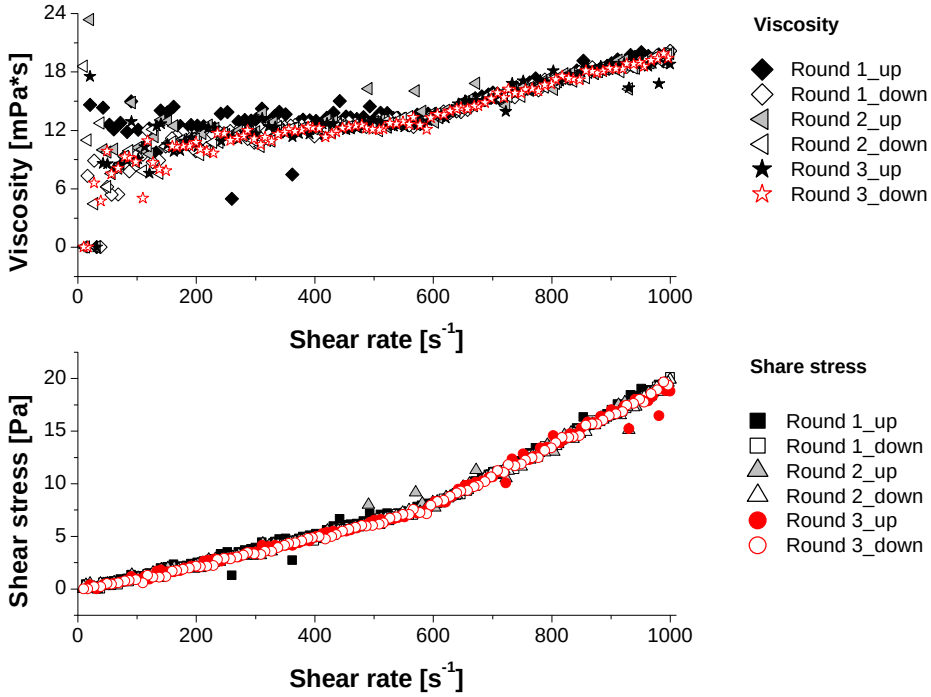


Fig. 5.2-7: Flow behavior of the paracetamol suspension with the paracetamol content of 20 wt% and the modified starch content of 0.20 g*mL^{-1}.

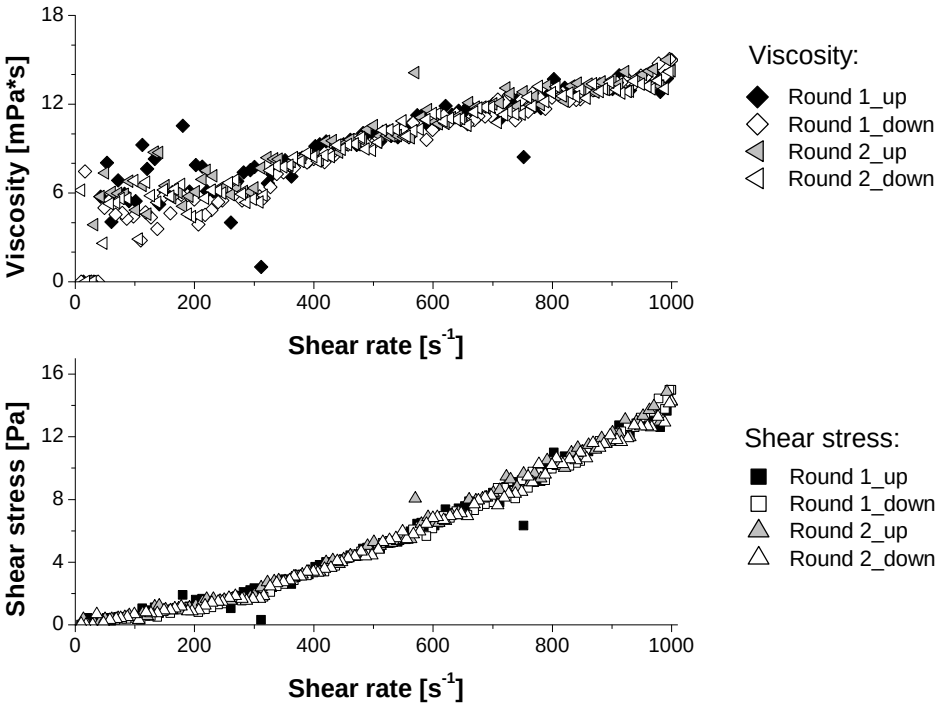


Fig. 5.2-8: Flow behavior of the 0.20 g*mL^{-1} modified starch solution.

Time dependence

The viscosities of many suspensions change with the shearing time at temperature of 20 °C and atmosphere pressure. The time dependences of the suspension viscosities are summarized in Tab. 5-18. Examples of the suspension viscosities vs. the shearing times are shown in Figs. 5.2-9 and 5.2-10.

Tab. 5-18: The time dependence of the suspension viscosity at 20°C, 1.01 bar.

Shear rate, s^{-1}	Paracetamol contents, wt%						Shear rate, s^{-1}	40.0 wt% Par., additive contents, g*mL^{-1}				
	20.0	33.4	44.4	50.0	54.5	60.0		0.10	0.20	0.30	0.40	0.50
50	X	√	√	√	√	√	50	√	√	√	√	√
200	X	√	√	√	√	–	200	√	√	√	√	√
400	X	√	√	–	–	–	400	√	√	√	√	–
600	X	√	√	–	–	–	600	√	√	√	–	–
800	X	√	√	–	–	–	800	√	√	–	–	–
900	X	√	√	–	–	–	900	√	√	–	–	–

X: independent, √: dependent, - : impracticable

It must be noticed that the viscosities of the suspensions with a solid loading equal or lower than 20.0 wt% are independent of shearing time. In contrast, viscosities of the suspension

with the solid loadings of equal or higher than 33.4 wt% are time dependent. The viscosities of these suspensions decrease corresponding to the time in a range of high shear rates. Only in the case of a low shear rate, i.e. 50 s^{-1}, the trend of the viscosity is reversed.

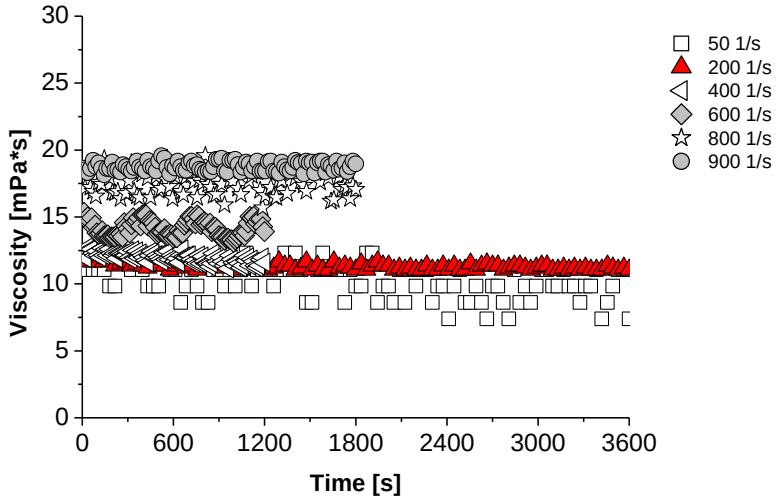


Fig. 5.2-9: Viscosity curves vs. elapsed time of suspension 20.0 wt% paracetamol.

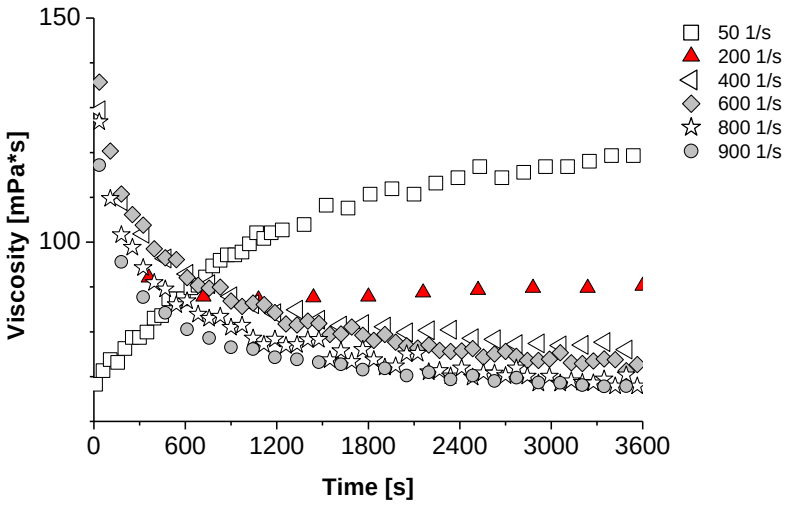


Fig. 5.2-10: Viscosity curves vs. the elapsed time of the 44.4 wt% paracetamol suspension.

Effect of solid loadings and starch contents

The viscosities of suspensions in function of the solid loadings and the starch contents are plotted in Figs. 5.2-11 to 5.2-12. Due to the reduction of the viscosity with time, here the presented viscosity data are the average values of the viscosities in the first hour of shearing. The error bars give the range of the maximum and minimum values. It can be seen that the higher the solid loadings as well as the more additive content is in the suspensions, the higher the viscosities of the suspensions are found.

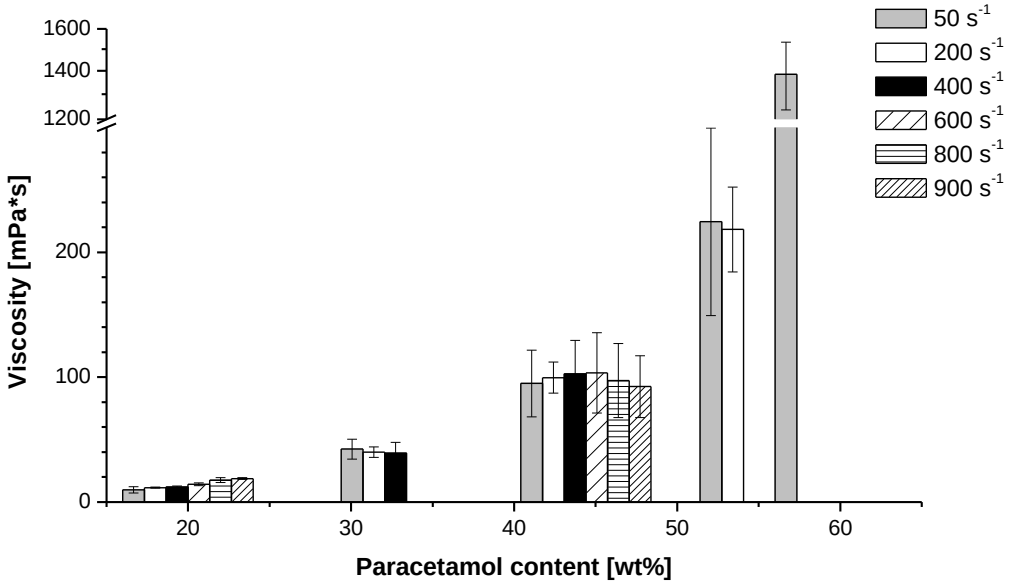


Fig. 5.2-11: Effect of the solid loadings on the suspension viscosities at 20 °C, 1.01 bar.

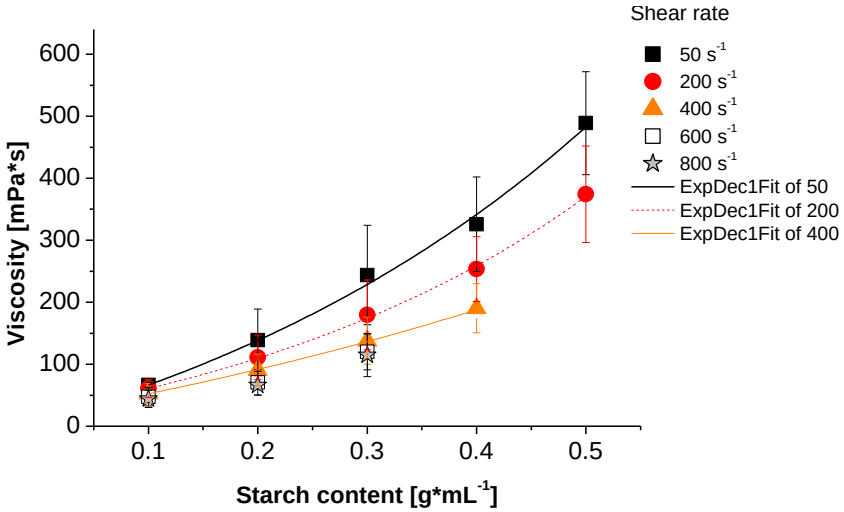


Fig. 5.2-12: Effect of the modified starch contents on the suspension viscosities of 40.0 wt% paracetamol at 20°C, 1.01 bar.

Temperature effect

The effect of temperatures in the range of 35 to 5 °C on the viscosities of the liquid dispersal medium and the suspensions was investigated. The examples of the viscosity profile of the liquid phase (the 0.20 g*mL^{-1} modified starch solution) and 20 wt% paracetamol suspension according to a defined temperature routine are presented in Fig. 5.2-13. The results are plotted in Fig. 5.2-14. It is demonstrated that the viscosities of the suspensions are significantly reduced when the suspensions are cooled.

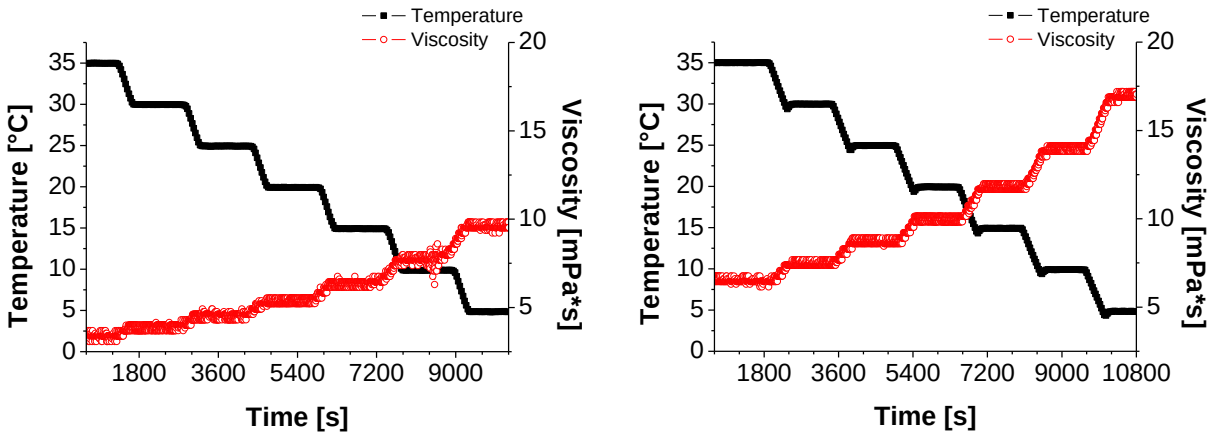


Fig. 5.2-13: The routines of the viscosities of the liquid dispersal medium – the 0.20 g*mL^{-1} modified starch solution (left) and the suspension – 20.0 wt% paracetamol suspension (right) in function of temperatures.

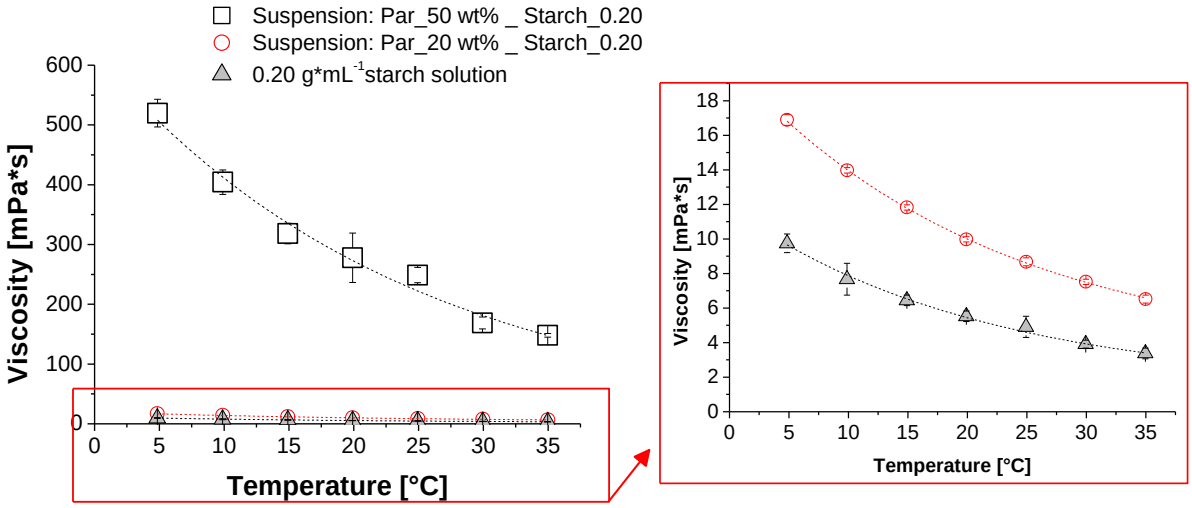


Fig. 5.2-14: Effect of the temperatures on the viscosities of the liquid dispersal medium - the modified starch solution (0.20 g*mL^{-1}) and the 20.0 and 50.0 wt% paracetamol suspensions.

5.2.2.3 Surface tension measurements

Surface tension measurements are focused on the influence of the solid loadings and the modified starch contents. The measured data of surface tensions are shown in Fig. 5.2-15. In the left graph, the surface tensions of suspensions is plotted in function of the solid contents at the temperature of 25 °C. The 0.20 g*mL^{-1} modified starch solution was used as the aqueous liquid dispersal medium. It is obviously that higher solid loadings in suspensions lead to higher surface tensions. The trend is reversed in the case of increasing the modified starch contents. In the right side figure, the surface tension of the liquid medium is significantly reduced when the modified starch was added into water. The surface tension of

the liquid media and the suspensions are gradually decreased according to the increase of the starch content in the range of 0.10-0.50 g*mL^{-1}.

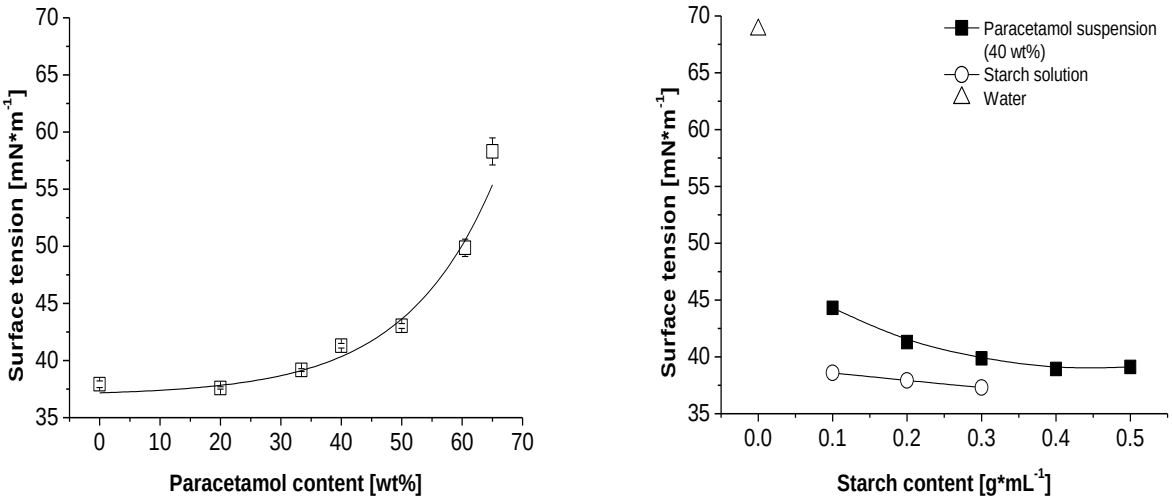


Fig. 5.2-15: Left: Surface tensions of the suspensions in function of the solid loadings at 25 °C, 1.01 bar. The starch content is 0.20 g*mL^{-1}. Right: Surface tensions of the liquid mediums and the suspensions in function of the starch content, at 25 °C, 1.01 bar.

5.2.2.4 Thermodynamic properties of paracetamol suspensions

Similar to the system 1, thermodynamic property measurements of paracetamol suspensions were carried out by DSC analysis. The effect of the solid loadings, the modified starch as well as the sugar contents on the freezing and melting points of suspensions were checked. The melting and freezing points of the suspensions are plotted in Fig. 5.2-16.

The results propose that the paracetamol content does not affect the freezing and melting point of suspensions. Using the 0.20 g*mL^{-1} modified starch solution as the dispersal medium, the suspensions with the solid loadings in range of 30 – 65 wt% give the freezing and melting points of around -15 or -16 °C and about -1 °C, respectively, (see Fig. 5.2-16a).

Modified starch slightly decreases the melting and freezing point of suspensions (see Fig. 5.2-16b). However, this effect is significantly pronounced when the sucrose is added into suspensions (see Fig. 5.2-16c). The higher sugar content in suspensions is the considerably lower are freezing and melting points. Freezing point of suspensions could be decreased down to -21 °C, while melting points could reach the temperature of lower than -5 °C.

Furthermore, the heat of fusions of the suspensions is determined and plotted in Fig. 5.2-17. The figure shows that modified starch seems to cause no effect on the heat of fusion of suspensions. Whereas a paracetamol or sugar content significantly decreases the heat of fusions of the suspensions.

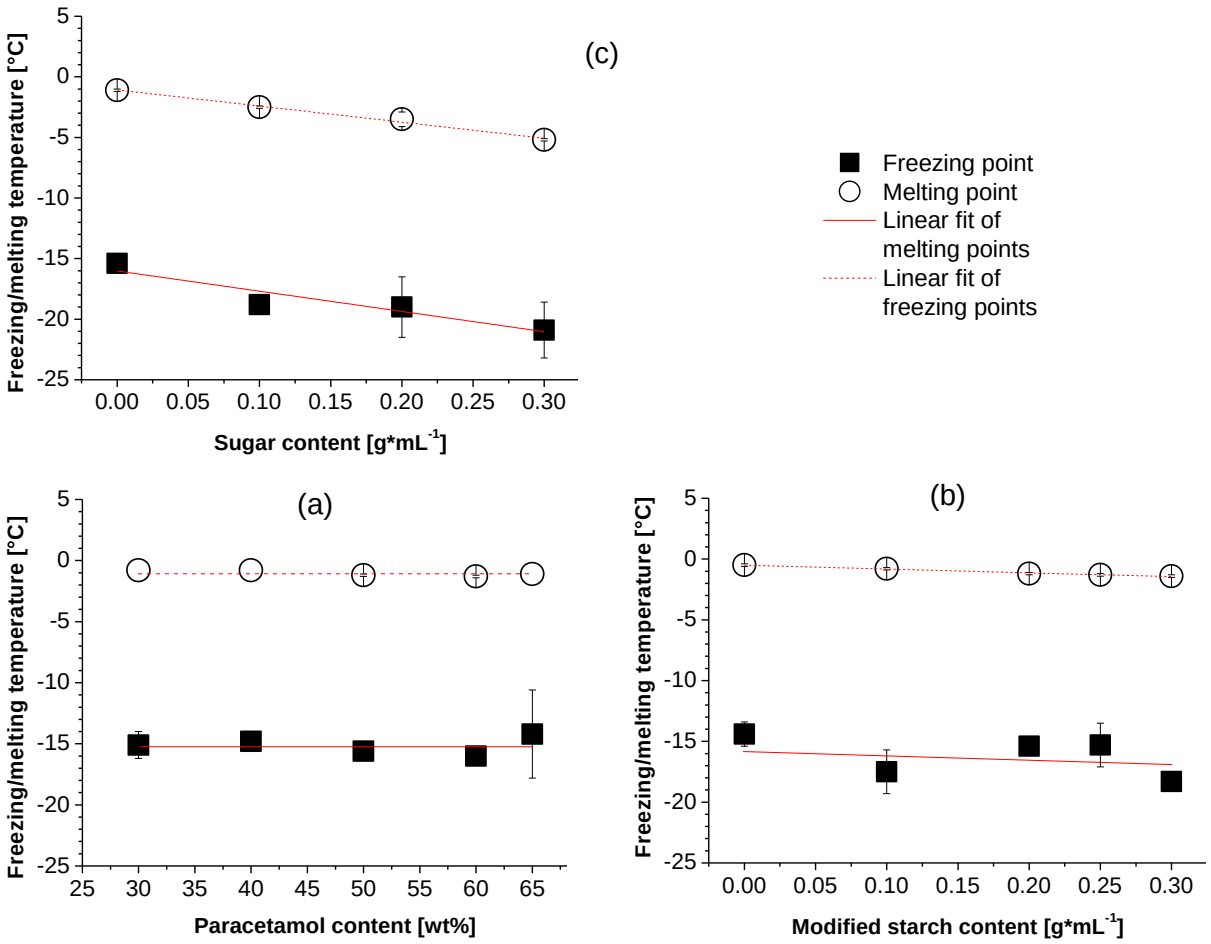


Fig. 5.2-16: The online freezing and melting points of the suspensions in function of: (a) the solid loading (the dispersal medium is the 0.20 modified starch solution), (b) the modified starch content (the paracetamol content 50 wt% was used for all suspensions), (c) the sugar content (the suspensions were prepared at the same paracetamol content of 50 wt% and the starch content of 0.20 g*mL^{-1}).

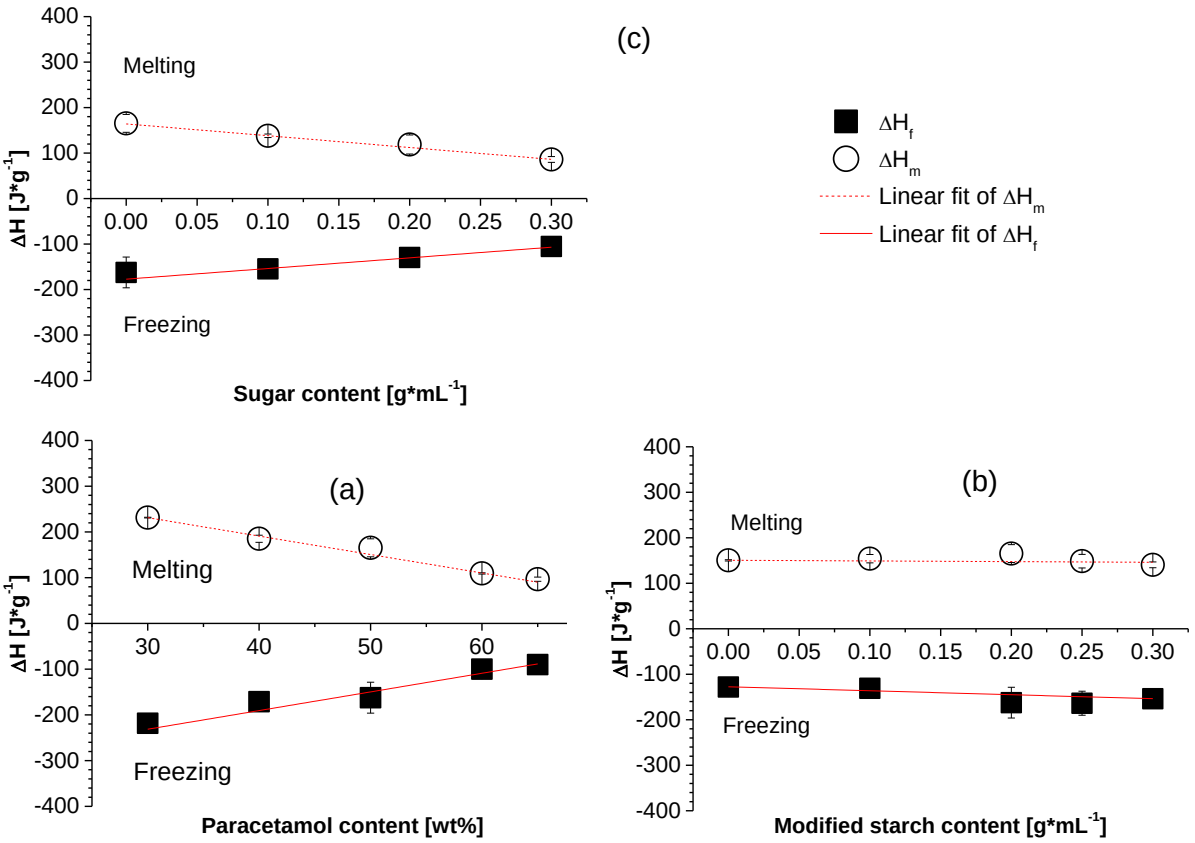


Fig. 5.2-17: The latent heat of fusions of the suspensions in function of: (a) the solid loading (the dispersal medium is the 0.20 modified starch solution), (b) the modified starch content (the paracetamol content 50 wt% was used for all suspensions), (c) the sugar content (the suspensions were prepared at the same paracetamol content of 50 wt% and the starch content of 0.20 g*mL^{-1}).

5.2.3 Effect of modified starch

Solid tablets of paracetamol containing modified starch as filler were successfully produced by means of the freeze casting process as depicted in Fig. 5.2-18. The summary of the compositions of the suspensions and the produced tablets are listed in Tab. 5-19.

All the tablets maintain their form after being removed from the molds and are easy to be handled. From a very first view (a first impression by eyes and a touching by hands), it is indicated that a higher modified starch content leads to a denser and harder tablet. However, with a starch content in the suspension equal or higher than 0.25 g*mL^{-1}, surface cracks started to occur in the produced big size (Ø16 mm) of tablets. No cracks were to be found in the small size (Ø10 mm) of tablets even when the starch content reaches the value of 40 g*mL^{-1} (see Fig. 5.2-18b).

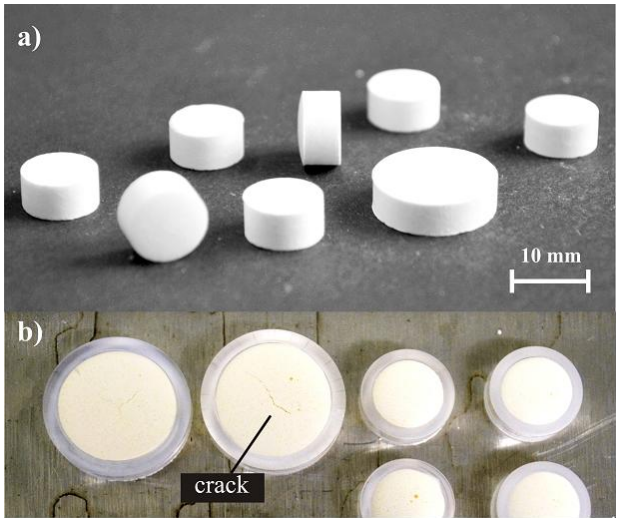


Fig. 5.2-18: Images of produced paracetamol tablets (a) and crack-like behavior (b) [Ngu15b].

Tab. 5-19: Compositions of samples in suspensions and in solid tablet forms [Ngu15b].

			Composition, wt%				
			In suspension			In tablet	
Sample	modified starch solution, g*mL^{-1}	paracetamol /water, g/g	modified starch	water	paracetamol	modified starch	paracetamol
1	10	1:1	4.76	47.62	47.62	9.09	90.91
2	15	1:1	6.98	46.51	46.51	13.04	86.96
3	20	1:1	9.09	45.45	45.45	16.67	83.33
4	25	1:1	11.12	44.44	44.44	20.00	80.00
5	30	1:1	13.04	43.48	43.48	23.08	76.92
6	40	1:1	16.66	41.67	41.67	28.57	71.43

To understand the characteristics of the produced tablets in more details, physical testes were carried out. Due to the non-crack behavior, the small size tablets were chosen to measure the tensile strength. The properties of the produced tablets are shown in Tab. 5-20 and in Fig. 5.2-19. It can be seen that, keeping the same ratio of paracetamol and water (1:1), the increasing modified starch content in the water from 0.10 to 0.40 g*mL^{-1} slightly decreases the water content from 47.62 to 41.67 wt% in the suspension. These changes in composition results in a slight reduction of porosities of the freeze casted tablets, from 63.55 to 56.79 % (see Tab. 5-20). Furthermore, the mercury porosimeter measurements indicated a pore size range from 2 to 10 µm for all tablets (see Fig. 5.2-19b). The estimated average pore diameters are reduced from 6.22 to 4.61 µm as the starch content in the tablets increases (see Tab. 5-20 and Fig. 5.2-19b).

Tab. 5-20: Properties of produced and reference tablets.

Sample	modified starch, g*mL^{-1}	Porosity, %	Average pore diameter, µm	Tensile strength, N/mm^2
1	10	63.55 ± 0.63	6.22 ± 0.62	0.57 ± 0.04
2	15	60.00 ± 0.62	5.67 ± 0.52	0.84 ± 0.09
3	20	57.51 ± 0.58	4.94 ± 0.49	1.05 ± 0.16
4	25	58.76 ± 0.60	4.85 ± 0.50	1.06 ± 0.15
5	30	56.79 ± 0.57	4.61 ± 0.46	1.05 ± 0.29
Ratiopharm 500				1.00 ± 0.15

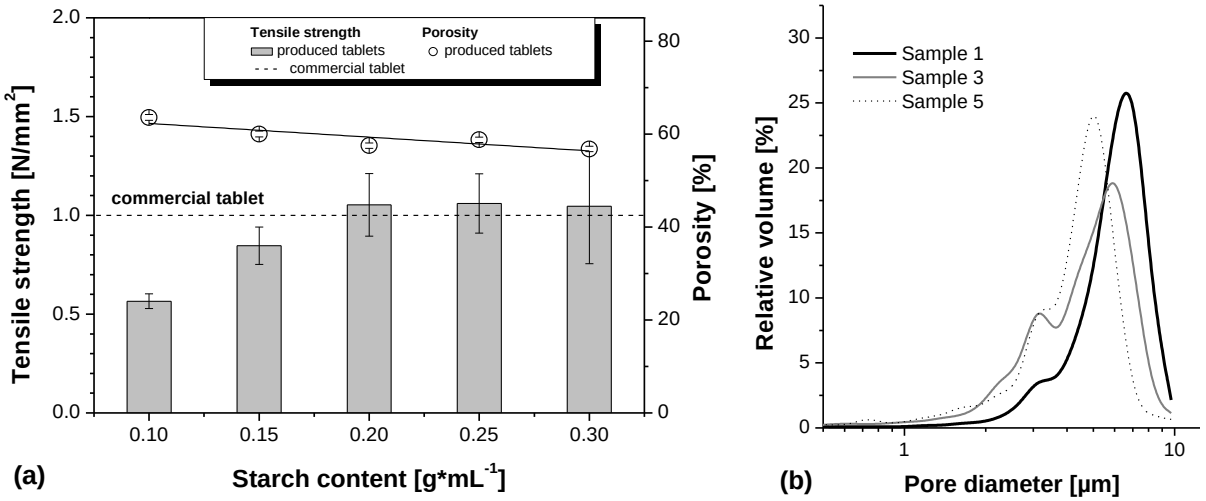


Fig. 5.2-19: Tensile strengths, porosities (a) and pore size distribution (b) of produced tablets by different modified starch contents. The commercial tablet is the Paracetamol – ratiopharm 500 [Ngu15b].

To know how the pore morphology and the microstructures of the solid bodies are, the SEM measurements were taken. To generate the cut through the tablets and to get new surfaces for SEM measurements, a knife with a sharp-narrow head is used to break the tablets. Only the parts of the samples in which no trace of the cutter were to be seen are collected for the microstructure measurement. The SEM images describing views of vertical-cut-surfaces of the freeze casted solid bodies of samples 1 and 3 are shown in Fig. 5.2-20.

It was found that the arrangement of solid particles in sample 3 is more organized than that of sample 1. The vertical channels of pores can be seen clearly in the pattern of sample 3. In addition, it must also be noticed that due to the higher modified starch content in sample 3, more bubbles (round bubble shape, see Fig. 5.2-20) have occurred in the suspension during mixing.

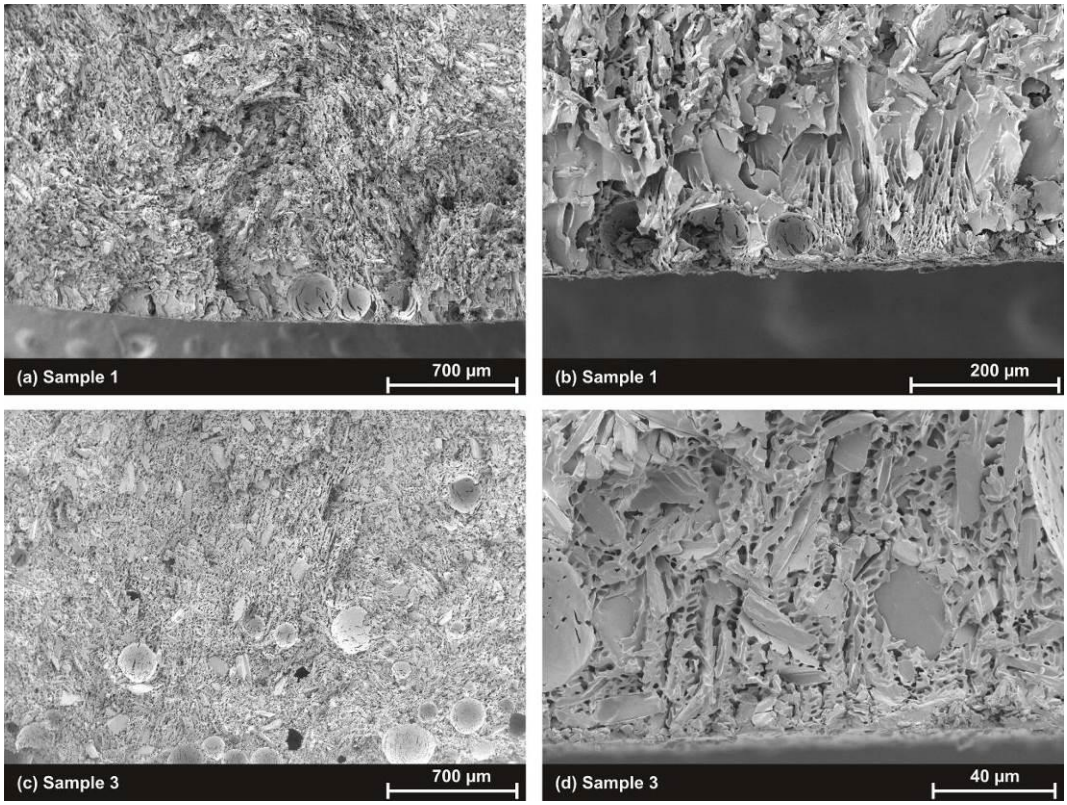


Fig. 5.2-20: SEM images of vertical-cut surfaces of samples 1 and 3 [Ngu15b].

To clarify the morphology of the pores and the behavior of the ice crystallization, magnified SEM images are shown in Fig. 5.2-21. It is clear that the network of pore channels is spreadingly distributed inside the tablets. The image of this network can be determined by a combination of the views from a top-surface (Fig. 5.2-21a) and a vertical-cut surface of the tablets (Figs. 5.2-21b and d). In Fig. 5.2-21c, the vertical tube channels which are the negative images of the grown ice crystals (in vertical direction) can clearly be seen. Figs. 5.2-21d and e propose a matrix glue connection of paracetamol particles in the tablets.

In addition, the particle morphology of the materials is shown in Fig. 5.2-22. It must be considered that in the matrix connection of particles in the tablets, no round shaped particles of the modified starch was found, there were only long rod-like particles of paracetamol distributed in a matrix as glues. The suspensions of the higher starch contents result in thicker glue layers which make the matrix of the solid needle-like paracetamol particles to be more embattled. This also results in a slightly lower porosity. A smaller pore sizes and a better matrix connection dramatically increases the tensile strength of the products from 0.6 up to more than 1 N/mm^2 as the starch content is increased (see Tab. 5-20). The tensile strengths are equal, or, to be precise, slightly higher, than those of the commercial tablets (Paracetamol – ratiopharm 500) produced by conventional compression (see Fig. 5.2-19).

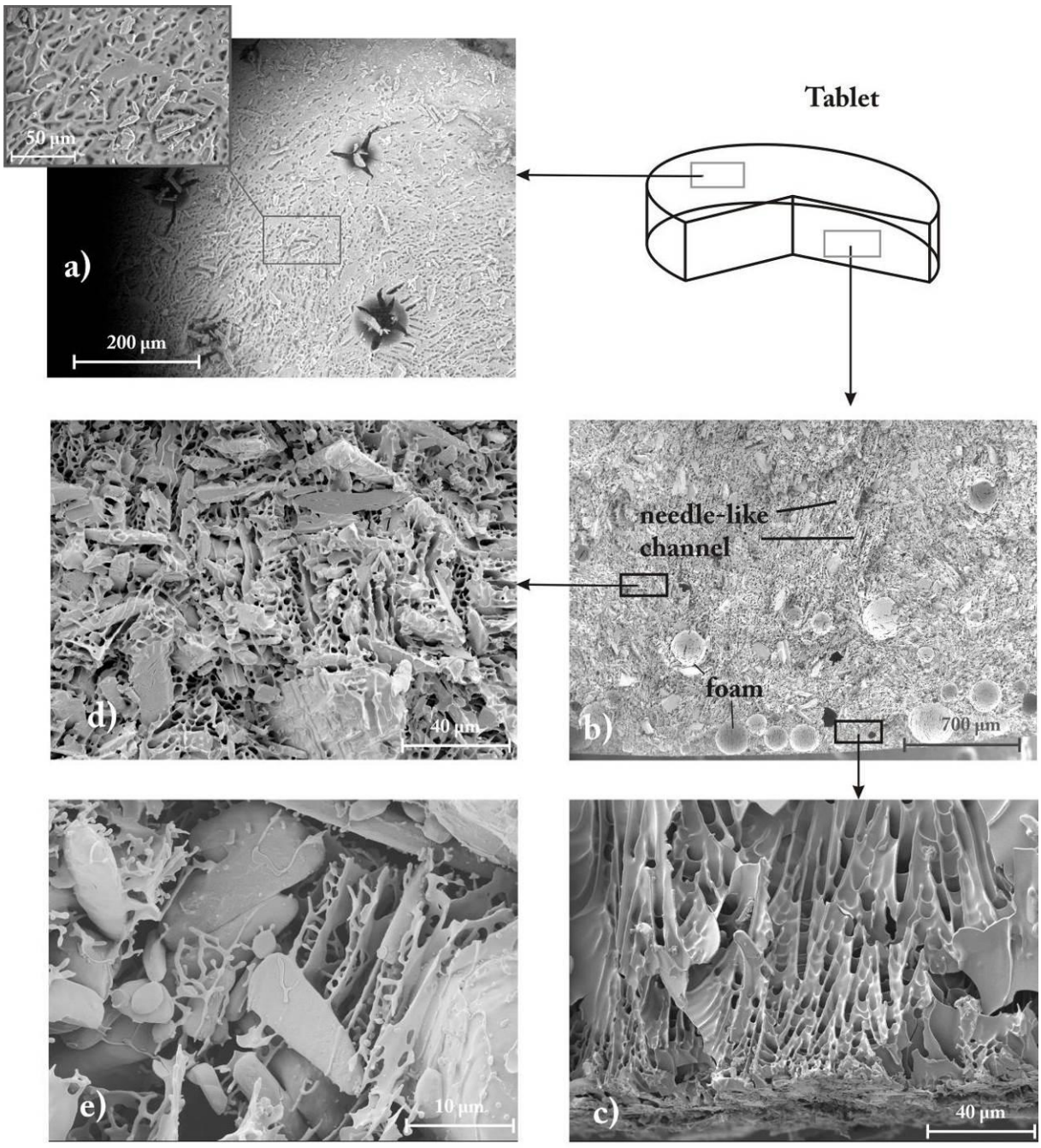


Fig. 5.2-21: SEM images of: a) the top surface, b) the vertical-cut surface, c) the magnified needle-like pore structure, d) the paracetamol (rod) particles in the network of the modified starch, e) the glued connection between paracetamol particles by the modified starch in sample 3 [Ngu15b].

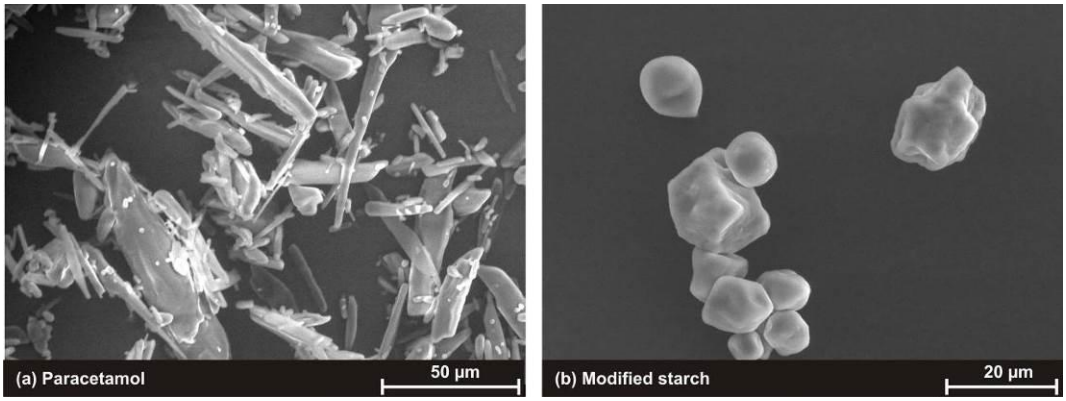


Fig. 5.2-22: The SEM images of paracetamol (a) and modified starch (b) particles in the material powder [Ngu15b].

Furthermore, in Fig. 5.2-23 the freeze casted products also demonstrate a remarkable faster dissolution behavior compared to the commercial products. The release rates of paracetamol in the freeze casted tablets are significantly faster than in compressed tablets. The time required for tablets to completely release the paracetamol in the freeze casted tablets is lower than 2, 3 and 5 minutes for samples produced from suspensions containing a modified starch content of 0.10, 0.20 and 0.30 g*mL^{-1}, respectively, while compressed tablets need almost 10 minutes to completely release the paracetamol.

Besides that increasing the modified starch content gives a slower drug release. At a starch content of 0.40 g*mL^{-1}, the rate of drug release turns to get much slower.

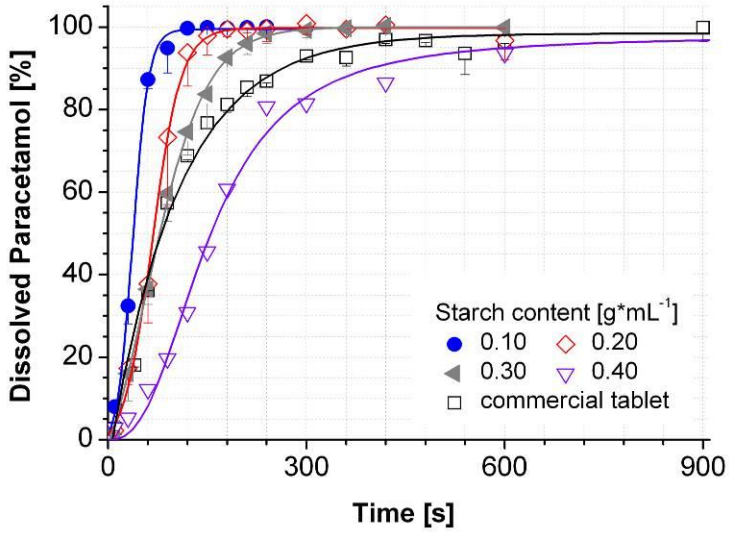


Fig. 5.2-23: Dissolution behavior of produced tablets in comparison to the commercial tablets [Ngu15b].

5.2.4 Effect of solid content

In the freeze casting process, the solid loading or water content is an important factor which can control the porosity, tensile strength and also dissolution/dispersal behavior of produced tablets. In order to make the effect of the solid loading in this system clear, the tablets produced from suspensions which contain a constant weight ratio of paracetamol to starch of 83.33:16.67 were investigated in various solid loadings. Because the modified starch was dissolved in water, the solid loading was generated by increasing the paracetamol contents in the water from 40 to 65 wt%. The properties of the produced tablets are shown in Figs. 5.2-24 and 5.2-25.

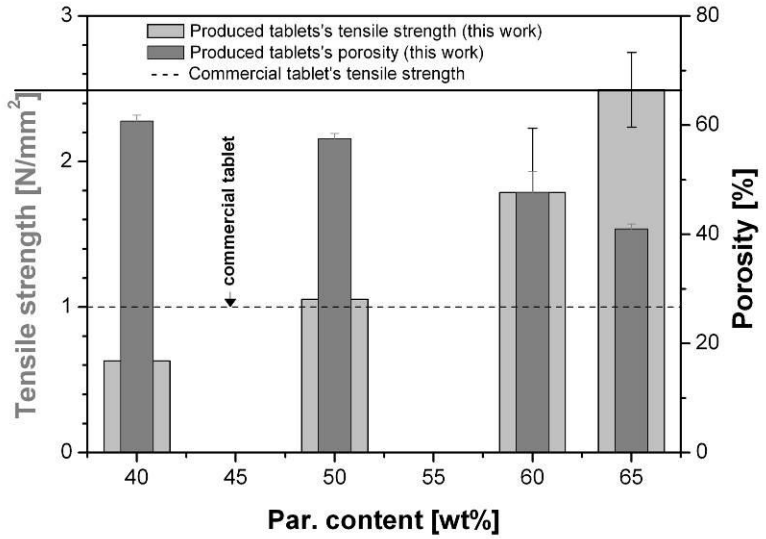


Fig. 5.2-24: Tensile strengths and porosities of produced tablets in function of solid loadings [Ngu15b].

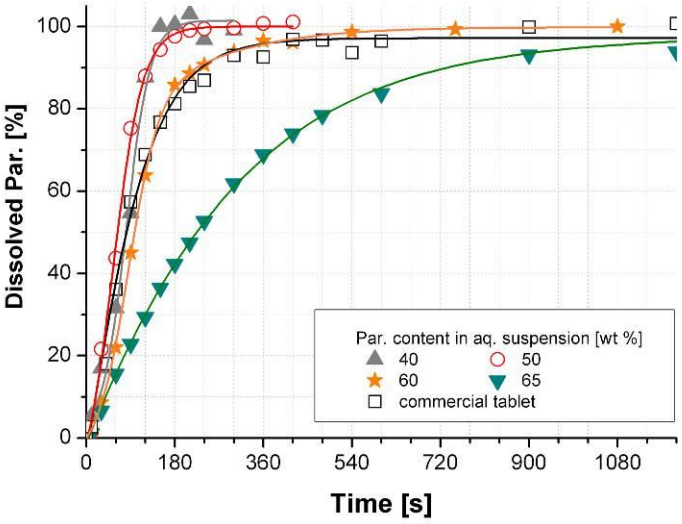


Fig. 5.2-25: Dissolution behaviors of produced tablets in function of solid loadings [Ngu15b].

As expected, the increase in solid loadings corresponds to the decrease of the water content in the suspensions which leads to an obvious reduction in the porosity and a dramatic improvement in the tensile strength of the produced tablets (see Fig. 5.2-24). However, at the same time a decrease in the dissolution rate was found (see Fig. 5.2-25).

5.2.5 Effect of sugar as additive

In the case study of the cocoa tablets, sugar presents as a good additive by improving both the tensile strength and the dispersal behavior of the produced tablets. In this chapter, results concerning the effect of sugar (sucrose) are presented.

The tablets are produced at the same process with the parameters as presented in Tab. 5-16. The solid loading was kept constant at 50 wt% and the starch content was maintained at 0.20 g*mL^{-1}. Sugar (sucrose) was added to the aqueous phase of the suspension in certain quantities from 0.00 to 0.40 g*mL^{-1}.

Fig. 5.2-26 shows the SEM images of vertical-cut surfaces of the produced tablets containing sugar. It is interesting to see that there is a complete change of the pore morphology when the sugar is added. As to be seen in Fig. 5.2-26, instead of the needle-like channel structure (as previously be reported in Fig. 5.2-21), a honey-comb-like structure was found in case of the use of 0.20 g*mL^{-1} sugar solution. The sizes of the pores seem to be larger in the top layer of tablets which is closed to the open surface.

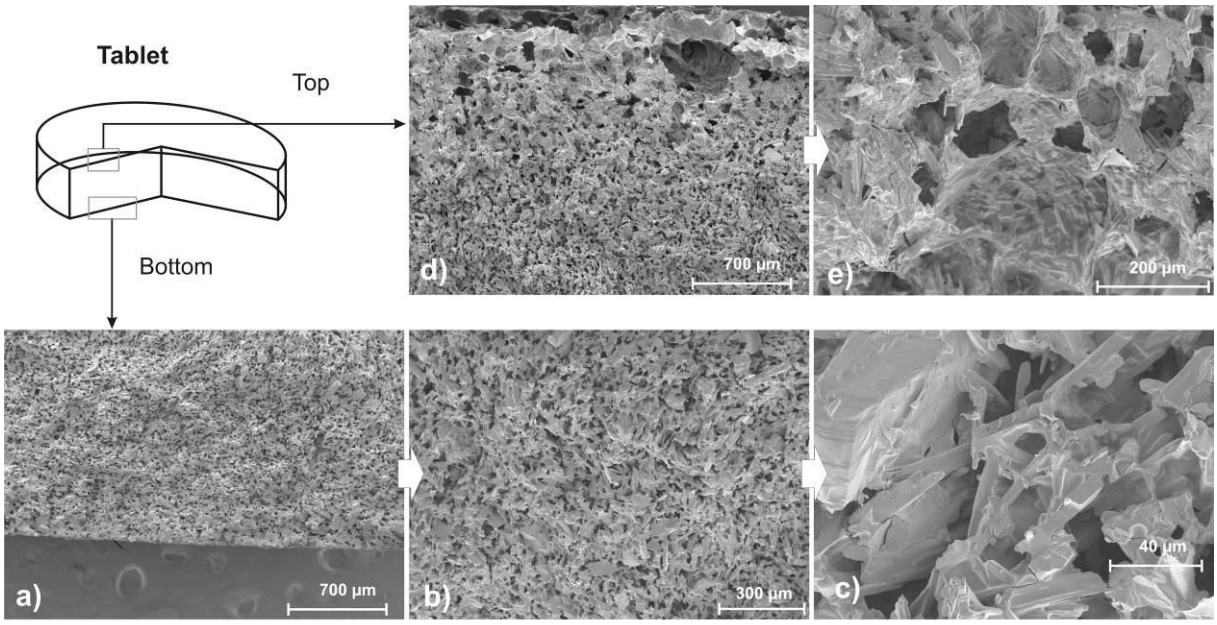


Fig. 5.2-26: SEM images of the vertical-cut surfaces of produced tablets with the addition of sugar.

In addition, the tensile strength tests in Fig. 5.2-27 propose that the tablets are more brittle. Whereas, the dissolution behavior shown in Fig. 5.2-28 was quite complex: At a sugar content equal or lower than 0.30 g*mL^{-1}, the dissolution rates of the produced tablets seem to decrease corresponding to an increase in the sugar contents. At a sugar content of 0.40 g*mL^{-1} the dissolution rate of the produced tablets suddenly rose up and surpassed the tablets containing 0 % of sugar.

To sum up, the produced paracetamol tablet containing sugar as a second additive may get a better dissolution rate, however, not a better tensile strength.

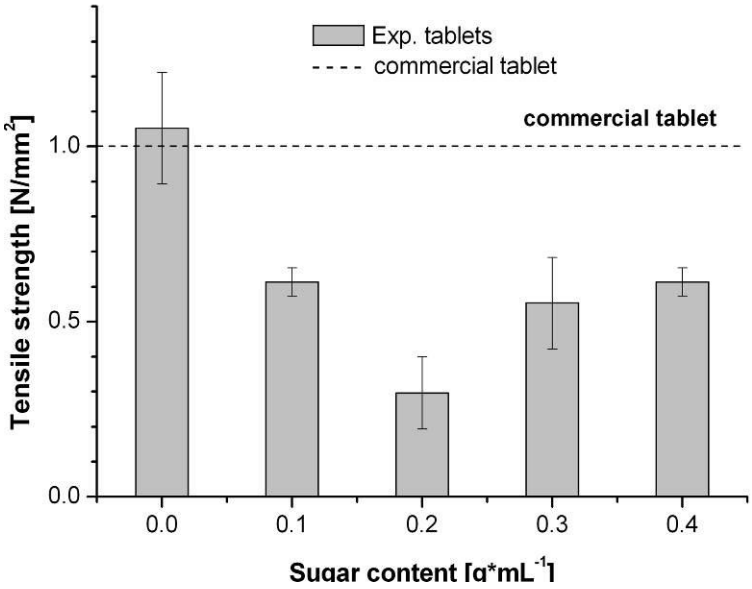


Fig. 5.2-27: Tensile strengths of produced tablets in function of sugar contents [Ngu15b].

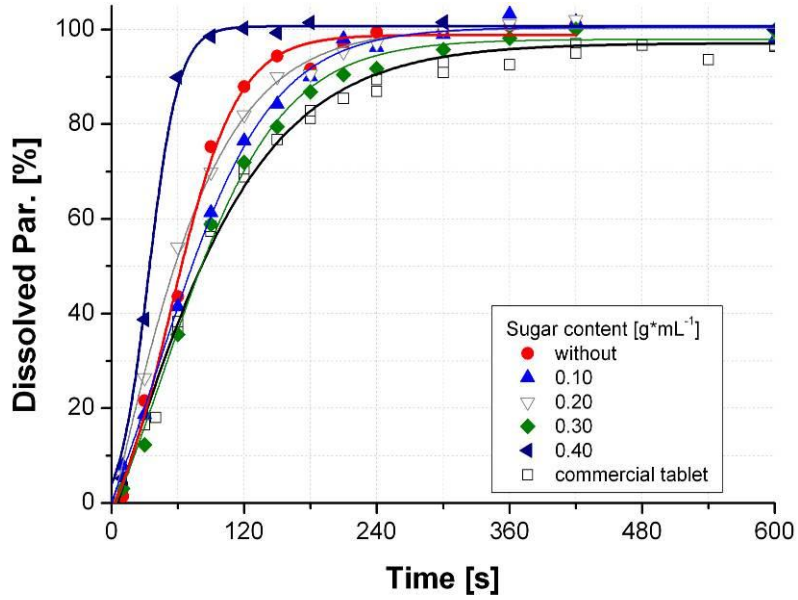


Fig. 5.2-28: Dissolution behavior of produced tablets in function of the sugar contents [Ngu15b].

6. Discussions

6.1 System 1 – food: cocoa tablet

6.1.1 Properties of suspensions

Density

As presented in section 5.1.1.1, in general, the density of the cocoa suspensions and the additive solutions stay in a range from 1.05 to 1.12 g*cm^{-3} in the temperature range of 5 - 35 °C. The difference in the density of the suspensions and the solutions in this small range do not significantly affect the processing of the freeze casting procedure. Nonetheless, here the detail of the influence of additives, solid contents and temperatures on the density will be discussed.

In Fig. 5.1-1, the densities of additive solutions are slightly higher than the one of water. This phenomenon is addressed by an addition of the solutes (i.e., additives) which have higher densities than water. When the same amount of a solute is dropped into a liquid, the density of the solution will dependently change based on the mass of the solution in a volume unit, which can be expected based on the real density of the solute. If the real density of the solute is higher than the density of the liquid, the density of solution may increase. In this case, the sucrose owns the real density (ρ = 1.6 g*m^{-3} presented by Rowe et al. [Row06] and ρ = 1.59034 g*m^{-3} measured in this presented work at 25 °C) higher than isomalt (ρ = 1.52 g*m^{-3} presented by Rowe et al. [Row06], ρ = 1.51558 g*m^{-3} measured in this presented work at 25 °C) and xylitol (ρ = 1.52 g*m^{-3} presented by Rowe et al. [Row06]), therefore the sucrose solution has a higher density than the isomalt and xylitol solutions at the same weight concentration. Even the real density of the solid phase of isomalt and xylitol shown by Rowe et al. [Row06] are equal, however, the density of the xylitol solution slightly lower than the one of isomalt.

In a similar way, due to the higher density than the solutions, when cocoa (ρ = 1.46536 g measured in this presented work at 25 °C) is dispersed in the solution, the density of the suspensions is increased. The higher cocoa content in suspension is, the higher suspension density is found (Fig. 5.1-1). At the same solid content in the suspensions, the order of the suspension density is kept the same as the order of the solution density (Tab. 5-2). Since the low dispersed solid content, the relative densities of these suspensions did not show a big difference in their values. The relative density of suspensions is in range of 1.02 to 1.06.

Furthermore, it is clear that owing to the thermal expansion of the liquid phase, the density of suspensions and solutions decrease according to an increase of the temperature in the studied range. This behavior is a well-known property of liquid phase.

Rheology measurements

The relationship between the dynamic viscosity, the shear stress and the shear rate is shown in equation 4-3. A Newtonian liquid has the constant viscosity even when the shear rate is changed (see chapter 4.2.2.2). The results of rheology measurements presented of the liquid media in Figs. 5.1-2 and 5.1-3 show the Newtonian liquid behavior when the shear rate is lower than 200 s^{-1}, after that the structure of liquids seems to be broken and the slope of the shear stress curve is continuously increased when the shear rate is increased. This leads to the continuous raise of the liquid viscosity. It is also to be noticed that the viscosity of the liquid media is really low in comparison to the viscosity of suspensions.

In the contrary, as to be seen in Fig. 5.1-4, the flow of all measured cocoa suspensions behaves like non-Newtonian liquids. The viscosity of all suspensions is significantly decreased when the shear rate is increased. Furthermore, even when the shear rate is maintained at a constant value, the viscosity of the suspensions is still continuously reduced with increasing the shearing time (see Figs. 5.1-5 and 5.1-6). This phenomenon is caused by the sedimentation of the solid cocoa in the suspensions, which occurs due to a density difference between the solid particles and the liquid phase when the mixing force is not high enough.

When the solid loading of suspensions is increased, the suspensions are thicker and denser, therefore, the viscosity of suspensions is dramatically increased (see Fig. 5.1-7). In this work, the solid loading is considered as the weight percent of the solid in the mixture of itself and the water. So, when the solid loading is kept constant and the additive is added into suspensions, it means that the total mass of the liquid phase is increased, which leads to an increase of the liquid volume. As result the real solid loading is reduced. Therefore, the viscosity of suspensions decreases as the additive is added into suspensions (see Fig. 5.1-7).

In addition, as the temperature is decreased, the thermal motions of molecules are slower and the volumes of liquid phases are decreased. All results in an increase of the suspension viscosity with the decrease of temperatures (see Fig. 5.1-8).

Thermodynamic properties

In the freeze casting process based on aqueous suspensions, the pores in the solid body are the negative image of the ice crystals that crystallize during the freezing step. This point is mentioned and proven by the previous studies (e.g., [Koc03, Don05, Dev08, Pac07a-c]). Therefore, in order to regulate the pore structure inside a solid body, the crystallization of ice crystals during the freeze casting process needs to be controlled. In crystallization, the nucleation and crystal growth are the primary particle formation processes, which determine the product size distribution [Sze07a, Don05]. Especially, applied in the freezing process, the crystallization of suspensions is often generated by freezing a suspension on the cooled

surfaces. Here, apart the nature of the cooled surface (i.e., type of material, roughness, etc.), the factor considered as the driving force of the nucleation and the crystal growth is the supersaturation (the supercooling). The needed supercooling profile is directly identified by the suspension composition, the applied freezing temperature, the cooling rate as well as the temperature gradient. In order to generate the wanted driving force, the thermodynamic properties of the suspensions need to be clarified.

As presented in chapter 5.1.1.4, the DSC analysis is investigated to figure out the thermodynamic properties of the suspensions. The related results were presented in chapter 5.1.1.4, and also be discussed in previous published works [Ngu13, Ng14a, Ngu15a].

The two clear peaks, respectively, the freezing and melting processes were found in the DSC curves in Fig. 5.1-10. This demonstrates that the freezing and melting points of the suspensions were easily identified by DSC measurements with the previously mentioned setting and there is no decomposition taken place during the freezing step.

It was found that the cocoa contents have a significant effect on the freezing and melting points of the suspensions in both cases, i.e. with and without additive (see Figs. 5.1-11 and 5.1-13). The freezing and melting points decrease when the cocoa contents were increased. This trend effect is different in comparison to previous studies. Pachulski and Ulrich [Pac07c] investigated the paracetamol system, and Witte and Ulrich [Wit10a-b] did a study on ibuprofen suspension. In both cases, no significant changes have been found in the melting and freezing points as a function of the solid content in aqueous suspensions. Here, the large decrease in the freezing points with increasing cocoa contents as to be seen in Figs. 5.1-11 and 5.1-13 should be the result of the rising content of soluble components in the cocoa material. The more cocoa powder is added, the higher concentration of the soluble components is in the suspension. Due to the higher soluble content in the water phase, the suspensions with higher cocoa content required a deeper temperature to crystallize or to melt.

Because the composition of the cocoa powder is quite complex, therefore, the concentration of soluble components in the cocoa material was not determined in this work.

Similarly, in Figs. 5.1-13 and 5.1-14, the increase of the soluble additive content also leads to the decrease of the freezing points and melting points of the suspensions. In other words, an aqueous suspension of higher sugar alcohol content requires a deeper temperature to be frozen and accepts lower temperatures for melted. This phenomenon is well-known in terms of the “freezing-point depression”.

For a high solute concentration, an equation proposed by Ge and Wang [Ge09a-b] can be applied to calculate the freezing-point depression. In case of an ideal diluted solution, the depression in the freezing point is proportional to the molarity of solutes following the Blagden’s law:

$$\Delta T = K * m * i \quad \text{(Eq. 6-1)}$$

where, ΔT, the freezing point depression, is defined as $T_{(pure\ solvent)} - T_{(solution)}$. K, the cryoscopic constant, which is dependent on the properties of the solvent, not the solute, i.e. for water, K_F = 1.853 K*kg*mol^{-1} [Ayl02]. m is the molality (mol solute per kg of solvent) and i is the Van 't Hoff factor.

Because the additive concentrations in the suspensions used in this work was not so high (< 0.58 M) and due to the straightforward form of the equation, here, Blagden's law is applied to simply evaluate the results. With the assumption that the liquids are ideal solutions, sucrose, isomalt and xylitol are considered as non-electrolytes (i =1). Therefore, a linearly decreased trend of the freezing and melting points in function of the additive content in Figs. 5.1-13 and 5.1-14 is reasonable. It is to notice that in this work, the additive contents are named in weight concentration. Consequently, at the same additive content xylitol depresses the freezing and melting point of suspensions more than sugar and isomalt do, because of its higher molarity according to lower molecular weight. With the similar molecular weight, whereas, sugar (sucrose) and isomalt have likely an identical effect on the freezing and melting points of the suspensions [Ngu15a].

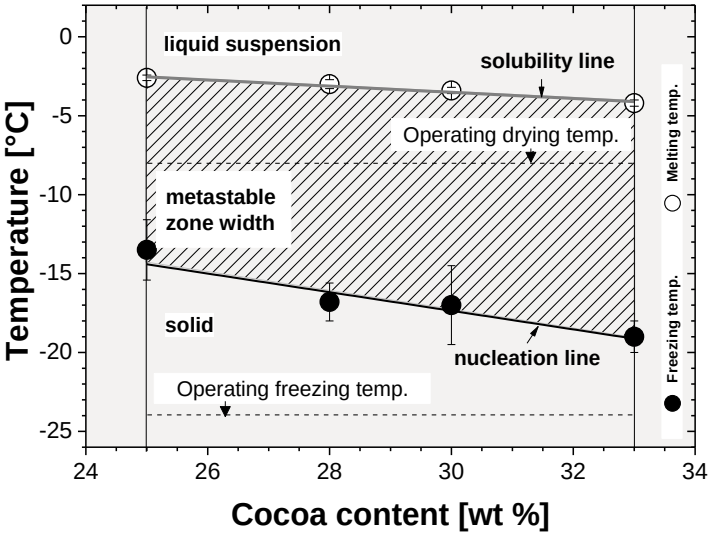


Fig. 6.1-1. Phase diagram of the aqueous cocoa suspensions and experimental design of the freeze-casting process [Ngu14a].

Furthermore, based on the DSC data of the cocoa suspensions, the metastable zone width can be determined by the difference between the freezing point and the melting point of the suspensions. An example of the metastable zone width's determination is proposed in Fig. 6.1-1 which was presented and discussed by Nguyen and Ulrich [Ngu14a]. This figure provides a simple overview concerning the phase behavior of the aqueous cocoa slurry during the freeze-casting process. Based on the melting and freezing points, the solubility and nucleation lines were defined. Therefore, the metastable zone width between these two

lines was determined. Due to the depression in the freezing points in function of the cocoa content is more than in the melting points, the width of the metastable zone is bigger (see Fig. 6.1-1).

Whereas, the effect of additives on the depression of the freezing and melting points of suspensions is quite equal. Therefore, the metastable zone of suspensions is similar in the width, but their positions are lower in the graphs (see Figs. 5.1-13 and 5.1-14). In general, the metastable zone width is in the range of 11 to 15 K.

Based on Fig. 6.1-1, in order to ensure that the suspensions are completely frozen, the operating freezing temperature should be lower than the upper limit of metastable zone or named the nucleation line. Likely, the drying process needs to be generated at the temperature below the the solubility line to guarantee that the water is removed from the solid bodies by a direct transition from a solid state into gas without going through a mediate liquid phase.

Tab. 6-1: Summary of heat of fusions of the suspensions and predicted heat required for tablets containing 1 g cocoa produced from suspensions in different compositions.

Studied factor			measured data, per 1 g of suspension		calculated data, per 1 g cocoa	
			$\Delta H_{f,}$ J	ΔH_m, J	ΔH_f, J	ΔH_m, J
w/o additive	Cocoa content, wt%	25.00	-197.6 ± 26.5	196.5 ± 24.7	-790.3 ± 106.0	785.9 ± 98.9
		28.00	-221.2 ± 30.3	230.0 ± 24.6	-790.1 ± 108.3	821.4 ± 87.8
		30.00	--180.5 ± 26.0	180.5 ± 13.5	-601.5 ± 86.7	601.5 ± 45.0
		33.00	-157.3 ± 26.4	161.3 ± 15.0	-476.7 ± 80.0	488.8 ± 45.5
With additive	Sugar content, g*mL^{-1}	0.00	-221.2 ± 30.3	230.0 ± 24.6	-790.1 ± 108.3	821.4 ± 87.8
		0.05	--219.8 ± 21.7	220.8 ± 19.1	-813.3 ± 80.4	816.9 ± 70.7
		0.10	-166.2 ± 6.6	156.1 ± 3.1	-636.1 ± 25.2	597.6 ± 11.9
		0.20	-164.0 ± 7.8	144.5 ± 5.8	-669.9 ± 32.0	590.4 ± 23.6
	Xylitol content, g*mL^{-1}	0.00	-221.2 ± 30.3	230.0 ± 24.6	-790.1 ± 108.3	821.4 ± 87.8
		0.05	-205.4 ± 22.9	210.4 ± 15.0	-760.1 ± 84.6	778.3 ± 10.9
		0.10	-186.3 ± 2.6	187.8 ± 2.1	-713.1 ± 10.0	719.0 ± 8.1
		0.15	-169.3 ± 8.5	162.4 ± 8.0	-669.9 ± 33.5	642.7 ± 31.8
		0.20	-143.3 ± 11.2	123.4 ± 20.1	-585.4 ± 45.9	504.0 ± 82.0
	Isomalt content, g*mL^{-1}	0.00	-221.2 ± 30.3	230.0 ± 24.6	-790.1 ± 108.3	821.4 ± 87.8
		0.05	-193.4 ± 12.4	210.4 ± 15.0	-715.5 ± 45.9	629.4 ± 83.8
		0.10	-179.3 ± 7.2	187.8 ± 2.1	-686.3 ± 27.4	636.3 ± 16.8
		0.15	-169.6 ± 9.7	162.4 ± 8.0	-671.1 ± 38.2	633.1 ± 96.7
		0.20	-150.8 ± 4.2	123.4 ± 20.1	-616.1 ± 17.0	440.1 ± 47.5

Not only influence on the freezing point and melting points of suspension, the solid loading (cocoa content) and additives (sugar and sugar alcohols) but also change the latent heat of fusion of suspensions. As be seen in Figs. 5.1-12 and 5.1-15, the more cocoa or additive content in suspension is, the higher heat of fusion upon freezing will be. Based on these results, the heat required for freezing and melting of suspensions in cocoa production is predicted and shown in Tab. 6-1. From this data, an overview of energy cost can be estimated.

Since the compositions of these cocoa suspensions were quite complex, the DSC measurements were only meant to ensure that the process temperature was low enough to freeze the aqueous suspensions and to sublimate the ice crystals. In comparison to the thermodynamic results of the all cocoa suspensions with the various compositions including the different solid loadings as well as additive contents, the operating freezing temperature (the temperature of the cooling plate surface) of -24 °C and the operating drying temperature of -8.1 °C were found to be low enough and can be applied for all experiments.

6.1.2 Effect of freezing conditions

Freezing temperature

As mentioned in previous chapters, the freezing temperature directly affects the supercooling profile known as the driving force of the crystallization. With the same composition of the suspensions, a decreasing freezing temperature increases the supercooling which leads to the increase of the supersaturation. As a result, a faster nucleation and growth of crystals occurred which induces the decrease in the size of ice crystals according to the reduction of pore sizes as to be seen in Tab. 5-8. Furthermore, the fast crystallization also results in a less compact structure (see Fig. 5.1-16) which causes the reduction in the tensile strength, but there is an improvement in the dispersal/dissolution behavior as to be seen in Fig. 5.1-17. The change in the tensile strength of tablets in the horizontal direction was not pronounced. The small difference in the mechanical strength was not enough to be determined by the sensor of the crushing force tester.

Based on the properties of the produced tablets, it can be concluded that a further decrease of the freezing temperature will not propose a visible change of the channel pore structure or a clear improvement in the tensile strength and the dispersal/dissolution behavior of the tablets. The freezing temperature of -24°C is low enough to get a good performance of tableting.

Effect of the freezing modes and the cooling profiles

Solidification of the prepared suspensions is the most critical step during the freeze-casting process. Crystal nucleation and growth, the interaction between the moving solidification front and the particles, and the freezing modes (homogeneous or directional) are key issues

that control the solidification behavior of a disperse medium [Li12]. The microstructure of channel pores can be categorized by different morphologies, depending on the nucleation and growth rates of the ice crystals. By regulating the heat transfer and the temperature gradient, the ultimate size of the ice crystals and thus the porous solid body can be controlled [Sze07b].

As been presented in Fig. 5.1-18, two morphologies of pores, the needle columnar and planar-lamellar structure are found. These morphologies are the results of the different growth mechanisms which are caused by different temperature gradients. The crystallization of the aqueous phases in the freeze-casting process is similar to the crystallization in a solid layer melt crystallization process. The crystal surface is flat when it undergoes a stable growth process, while it gets rough when the growing conditions are far from the equilibrium and the growth process is fast [Chi03]. The needle-like behavior of ice is the result of a dendritic growth since the growth rate is considerably high due to the high supercooling resulting from the applied supercooling and a supercooling resulting from the enriched impurity content in the boundary layer which is named “constitutional supercooling”.

The behavior of the ice crystallization in the freeze casting process of aqueous suspensions was well studied and presented in previous works [Pac07a-c, Dev09, Wit10a-b, Was11, Li12]. In general, heterogeneous nucleation occurs near to the cold surface where the sample is placed for directional freeze casting. The initial ice crystals are randomly oriented and the growth rate is high enough to engulf all the particles for a dense microstructure to form. Then, ice crystals both along the freeze direction and randomly oriented ones grow with the diminishing ice front velocity. Due to the effect of directional temperature gradient, the unidirectional growth of ice crystals occurs which causes an obvious ice morphology transition. Above described behavior is the right explanation for the change of pore morphologies in Fig. 5.1-18b where the one-side freezing at the cooling rate of 1 $K*min^{-1}$ is applied.

In the case of the instant freezing from one side (see Fig. 5.1-18a), due to the faster and stronger directional freezing, the unidirectional temperature gradient was generated in a very early stage of the ice crystallization. Therefore, the layer of the dense microstructure near the bottom seems to be thin and invisible. The growth of ice crystals was proposed to occur in the vertical direction and result in needle-like crystals. This pore morphology is the most common appearance of pores obtained from the needle shape growth of ice crystals, which is already well known from the one-side freeze-casting processes of previous studies [Pac07a-c, Wit10a-b, Was11]. Furthermore, it is well compatible with the simulated image of ice crystallization generated by Witte and Ulrich [Wit10a-b], see Fig. 6.1-2.

Deville et al. [Dev08] and Pachuski and Ulrich [Pac07a] proved that the size of needle-like crystals was bigger as their distance from the bottom was increased due to a slower growth rate. It was written by Pachuski and Ulrich [Pac07a] that *“due to the temperature difference between the bottom and the top of the sample of the suspension in the mould, the porosity*

and the pore size in the sample changes with the height in the sample. On the bottom, where the temperatures are lowest, many ice crystals appear. With increasing heights and therefore rising temperatures, the ice crystals grow slower and slower. The pores created are therefore bigger in size". The size distribution of the pores in a function of the height of the tablets was not investigated in this work, however, the increase of the size of the pore channels is visible in the images of tablets in a vertical view (see Fig. 5.1-18a) or at the horizontal surfaces (see Fig. 5.1-19).

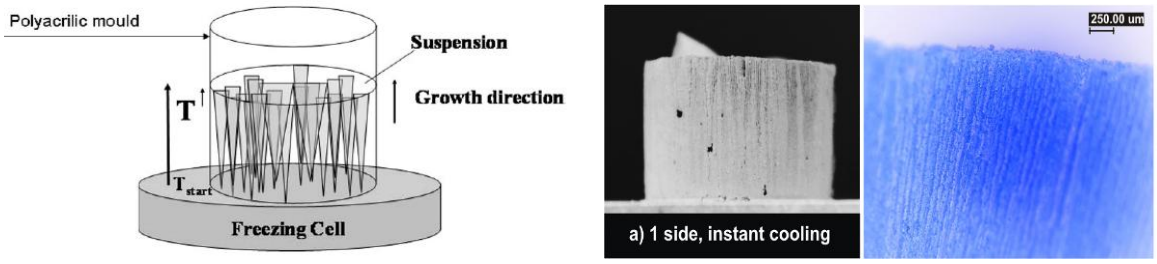


Fig. 6.1-2: Scheme for the growth of the ice crystals [Wit10, Pac07c] and the needle-like microstructure of pores (according to Fig. 5.1-18).

With a slower freezing mode in the case of two-side freezing with a cooling rate of 1 K*min^{-1}, the driving force is less than in case of a one side freezing and by the two-side freezing, the temperature gradient was not totally directional. Here, due to the short distance (just equal the height of tablets, 10 mm) between both cooling surfaces, it can be considered as the homogenous freezing. Therefore, the growth of ice crystals is not fast and unidirectional in comparison to the instant freezing mode. As the result, the denser planar-lamellar structure was found in whole tablets (see Fig. 5.1-18d). This behavior is in good agreement with the previous studies of ice-template structure formation during freeze-casting [Was11].

The horizontal splitting in the middle area of the tablet in the case of instant two-side freezing can be explained by the fast growth of ice crystals from both sides. The forward pushing of the impurities (which are the insoluble and, at the end of the solidification process, also the soluble (additive or others) components) by the pure ice crystals will result in a meeting of all impurities in the middle of the tablet. As to be seen in Fig. 5.1-16 the breaking behavior occurs in all samples in the case of the instant two-side freezing and becomes clearer as the freezing temperature was reduced. This evidence again confirmed the above explanation. With the same suspension composition, a lower freezing temperature proposes a higher supercooling which lead to a faster growth of ice crystals from both sides and results in a stronger pushing up impurities in the middle area. When the freezing is contemporaneously applied to both sides of the tablets, the crystallization of suspensions is almost twice as fast. The crystallization of aqueous suspensions in this case can be considered as the crystallization of two tablets. In that case it is like a one side freezing from opposite sides, where each side owns a haft of the height in comparison to the original tablets. The growth of

the ice crystals in each side needed to pass only a haft of the tablet's height to finish the solidification. In addition to, due to the short distance between both cooling surfaces, a homogeneous crystallization can occur. Therefore, the size of ice crystals was small which results in the dense surfaces in the middle parts (see Fig. 5.1-20).

With the dense microstructure of pores, the pore sizes of the tablets produced by the two-side freezing mode are significantly smaller in comparison to those of the one-side freezing mode (see Tab. 5-9). In theory, the volume expansion of water during the solidification will induce a pressure which compresses the solid particles together, especially, when rigid moulds are used. Here, the top surface of the tablets is opened during the freezing step in the one-side freezing mode, therefore, after freezing the tablets expand their height. This capability was not possible to occur in a both-side freezing mode in which there is no open surface surrounding the tablets during the freezing step. For this reason, the tablets produced by the two-side freezing mode at the cooling rate of 1 $K*min^{-1}$ are more compacted than the tablets produced by the one-side freezing mode. In other words, the porosity of tablets in the case of a one-side freezing mode is theoretically higher in comparison to the two-side freezing mode. However, the practical porosity in both cases shown in Tab. 5-9 is not considerably different. The porosity of tablets produced by the one-side freezing was even a little bit lower than the ones in the case of the two-side freezing mode. The decrease in the porosity of the tablets produced by the instant one-side freezing mode may be the results of the omission of the big-open pores in the top area of tablets which are easy filled by mercury without the applied pressure during measuring.

As to be discussed, the freezing mode and cooling profile strongly influence the pore morphologies, hence it also affects the tensile strength and the dispersal behavior of the produced tablets. With the small size pores and dense microstructures, the two-side freezing mode has the ability to improve the tensile strength of the tablets, however, as a consequence the slower dispersal/dissolution behavior was accompanied (see Fig. 5.1-21). Furthermore, because of the unidirectional growth of ice crystals, the binding of solid particles is also preferred to be formed in a vertical direction. Thus, it is more difficult to break the tablets in the vertical direction. Due to a less strong connection of solid particles in the horizontal direction compared to the vertical direction, the tensile strength of produced tablets is extremely lower in the horizontal direction.

Based on the presented results it can be concluded that the fast freezing such as the instant freezing is not suitable to produce tablets using the both-side freezing mode. The instant freezing produces the needle-like open pores which can enhance the dispersal behavior of produced tablets. Whereas, both sides freezing can improve the tensile strength of the tablets, however, a slower dispersal/dissolution behavior is in parallel.

6.1.3 Effect of additives

As to be seen from chapter 6.1.2, the freezing mode and the cooling profile significantly define the pore morphologies and the pore structures, which directly affect both the tensile strength and the dissolution/dispersal behavior of the produced tablets. However, controlling the freezing condition and the solid loading is still not sufficient to obtain a tablet with properties required for fast dissolving tablets: Acceptable tensile strength with short dispersal time. In the freeze casting process, the tensile strength of the produced tablets is inversely linked to their dissolution rate. To improve both the mechanical strength and the dispersal (dissolution) behavior of a tablet, a water-soluble additive should be used [Ngu15a]. The main requirements for an additive for fast dissolving tablets in the food field are a high aqueous solubility, a fast dissolving rate, a good taste, a well interaction with the solid particles and to be food proved. Moreover, nontoxic, easy to find and low cost are the extra considered properties. In previous studies, Pachulski and Ulrich [Pac07a] concluded that an increase of the additive ascorbic acid results in an increased crushing force but a slower dissolution rate. In contrast, Witte and Ulrich [Wit10b] presented that using lactose as an additive can improve both the tensile strength and the dissolution behavior of ibuprofen tablets.

In the case study of cocoa tablets, lactose has the high solubility in water, however, the dissolution rate was slow. Without mixing, it might take hours to dissolve the lactose in water at a concentration of 0.20 g*mL^{-1}. Such a slowly water-soluble substance is not suitable to be used as an additive for a fast dissolving tablet which is often required a dissolving/dispersal time of less than one minute [Eur01, Sch02]. Citric acid has a high solubility and a fast dissolution rate, but it owns a sour taste which is not suitable for cocoa drinks. Sugar (sucrose) and sugar alcohols including isomalt and xylitol are not only fast and easy solutes in water or milk, but also are sweeteners which improve the taste of cocoa beverages. For this reason, they were chosen for the further steps of this work.

The results presented in chapter 5.1.4 indicate that sugar and sugar alcohols are potential additives for the production of fast dissolving cocoa tablets. Here, sugar and sugar alcohols improve both the tensile strength and the dissolution/dispersal behavior of tablets. Furthermore, the morphology of pores was changed. To explain these phenomena, the effect of the sugar and sugar alcohols on the properties of the aqueous phases and the suspensions, as well as on the crystallization of the aqueous solutions has to be considered.

In theory, the nucleation rate of the primary nucleation is mainly depended on supersaturation (S) and the specific surface energy (γ) such as in following equation [Mul01]:

$$J = A\exp\phi\left[-\frac{16\pi\gamma^3\nu^2}{3k^3T^3(\ln S)^2}\right] \qquad \text{(Eq. 6-2)}$$

where, A is the pre-exponential factor, k is the Boltzmann constant. T is the freezing

temperature. ν is the molecular volume. ϕ is the factor, for the homogeneous nucleation: $\phi = 1$, for the heterogeneous nucleation: $\phi < 1$.

As to be seen from equation 6-2, the nucleation rate is sensitive to the level of supersaturation and freezing temperature. It is rapid once a critical level of temperature and supersaturation is exceeded [Chi03]. A very important factor is also the surface free energy which is also called the interfacial tension, i.e., between the developing crystalline surface and the supersaturated solution in which it is located [Mul01]. This value is extremely difficult to be measured and it is up to now not possible to determine by experiments. It is related to the nature of the solution and is strongly influenced by the presence of admixtures, i.e. impurities and additives.

Even though the freezing temperature was kept constant, here, the presence of sugar and sugar alcohols in the suspensions decreases the freezing points of the suspensions (see chapters 5.1.1.4 and 6.1.1). Thus, the degree of suspesaturation is reduced since the sugar alcohol content is increased. Furthermore, when the sugar and sugar alcohols are added the viscosity of aqueous solutions is increased (see Fig. 5.1-5). Even though the interfacial tension is not determined and it is unknown how much it changes, it can be expected that the addition of the sugar and sugar alcohols do affect the interfacial tension between crystalline surface and the supersaturated solution, the interparticle forces between solid particles, as well as between the solid particles and the supersaturated suspension. Based on the higher viscosity and the “glue” property of the sugar and sugar alcohols, the interfacial tension in this case is expected to rise according to the higher sugar alcohol content.

In summary, an addition of sugar and sugar alcohols as additives decreases the supercooling and leads to a higher interfacial tension. A lower degree of supersaturation and a higher interfacial surface tension lead to a slower nucleation rate. A lower supersaturation degree also induces a slower growth rate. Here in this study, the kinetics of crystallization was not examined in the detail. However, the overall crystallization time which is needed for the ice crystals are formed from the bottom to the top of tablets, is considered. The time required for the solidification of tablets of the same height in the case of use of additives is significantly longer in comparison to the case without using additives. The delay time is about 2 to 10 minutes depended on the sugar and sugar alcohols contents (from 0.05 to 0.20 $g*mL^{-1}$), as well as the type of additive. Consequently, the morphology of ice crystals is different, the needle-like crystals which are induced from the very fast and unidirectional freezing gradually disappeared. It is interesting that the new sphere-like pattern of pores in Fig. 5.1-24 is well met with the morphologies of ice crystals in ice cream when the sweeteners were added, which was reported by Hagiwara and Hartel [Hag96] (see Fig. 6.1-3). However, there is a possibility that these big sphere-like pores were images of bubbles which often occurred in the suspension preparation due to mixing when sweeteners are added into the water phase [Ngu15a].

The closed up view of the pore structure in the SEM images in Figs. 5.1-25 and 5.1-26 proposes a mechanism of the tablet strengthening. It is shown that there are connections which link the solid particles into a network growing in various directions, not only in the vertical direction such as to be seen in case of “without” additive. This phenomenon can be explained by the binding function of additives, i.e. sugar and sugar alcohols. During the freezing step, when the pure ice crystals are formed, it means the water is removed from the liquid phase. Thus, the concentration of the sugar solution remaining in the suspensions is increased. In combination with the effect of a temperature decrease, the sugar solution is rapidly reaching and even passing the saturated point of the solution. Therefore, besides the crystallization of water, sugar is also simultaneously crystallized in the network of ice crystals and solid particles. The forming sugar crystals are located in between solid particles and form the bonds to connect them. Consequently, the undefined shaped holes were formed and distributed in the middle surrounded by solid chains connected by the additives. This behavior is different from the directional orientation connection in case of the one side freezing mode of suspensions without additives (see Fig. 5.1-25). Therefore, by a vertical cutting, layers bordered by needle channels were easy to be separated without a destruction of the layer structure (see upper left image in Fig. 5.1-25) [Ngu15a].

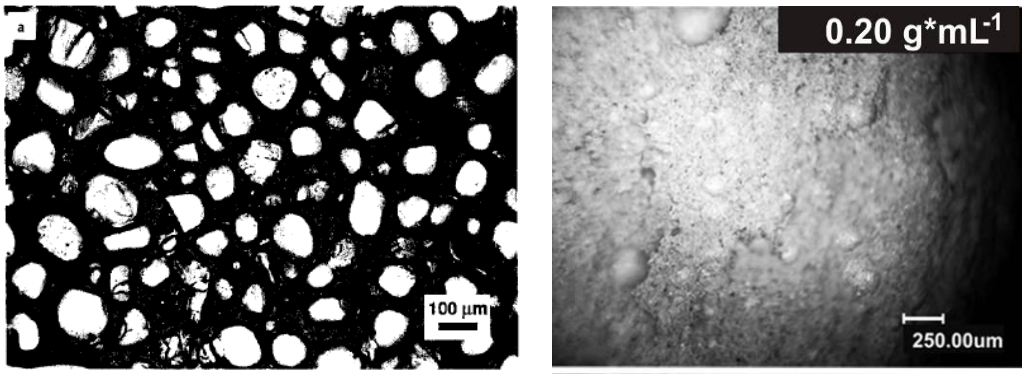


Fig. 6.1-3: The ice morphology of ice crystals in ice cream with sucrose as sweetener in the absence of a stabilizer [Hag96] and the sphere-like pores inside the produced tablet (according to Fig. 5.1-24).

In addition, the presence of sugar crystals can be considered as impurity which also may affect on the heterogonous nucleation, as well as interrupt the unidirectional growth of water. As result the morphology of ice crystals is totally different and a stronger binding connection by the additives is formed. That explains why the tablet containing additives has a better mechanical strength than the tablets without additives (see Fig. 5.1-22).

Based on SEM images, it is obvious that the sugar and sugar alcohols reinforce the porous solid bodies by creating multi directional bindings between solid particles and change the morphology of pores. It is also noticeable that when additives were added, solid particles in tablet bodies tend to behave as round corner particles instead of sharp edged particles which were often seen in case of no additive use. There are also tiny particles attached to big solid

particles, however, it could not be determined up to now whether they are the crystal additives or not [Ngu15a].

As mentioned at the beginning of this section, the mechanical strength and the dissolving/ dispersal behavior compeat each other. Owing a higher hardness (see Fig. 5.1-22), means the dissolution rate of the produced tablets was estimated to be slower. However, the hardness of tablets, here, is improved by the formation of matrix bonds which are formed by fast water-soluble solutes, i.e. sugar (sucrose), isomalt and xylitol. The big size porous structures (see Fig. 5.1-24) and water-soluble sugar and sugar alcohols distributed in the tablets aids water to easily diffuse from the contact surfaces into the cocoa tablets. The tablets are easily wetted, therefore, the binding channels between cocoa particles formed by the sugar and sugar alcohols can also rapidly be destroyed in water [Ngu15a]. All aid to enhance the dissolution or dispersal rate of tablets such as being seen in Fig. 5.1-27.

It is clear that sugar and sugar alcohols can be used as the binders which can enhance the hardness of tablets. However, it is noticed that they also cause a change of porous properties and the pore sizes of tablets. The more sugar and sugar alcohols are added, the bigger and more open pores are occurring which reduce the hardness of tablets. Such as to be seen in the case of xylitol with a content of 0.20 $g*mL^{-1}$, the porous structure was increased so strong that the result is a very porous tablet body (see Fig. 5.1-23(d)) leading to a reduction of the hardness (tensile strength) (see Fig. 5.1-22(c)). This means that there is a critical maximum additive content where the hardness of tablets reaches the maximum value.

Furthermore, in the porosity measurement, the large and open pores might be easy to be missed because the mercury can easily fill the hole at the beginning of the measurements when no pressure was applied. Therefore, even though the tablets with additives have a more porous look, they show a lower measured porosity of about 5 to 10 % lower than the tablets without additives and just a small increase in measured pore sizes were found (see Tabs. 5-11 and 5.12)

A dispersal time lower than 1 min (45.5 and 51.5 s in case of isomalt, 58.5 and 60 s in case of sugar) meets the standard value in European Pharmacopoeia [Eur01] and is seen as an good dispersal time for fast dispersal (dissolution) tablets [Sch02, Goe08]. Furthermore, the maximum crushing force value of 44.8 N (i.e. 0.18 N/mm^2 diametral tensile strength) in case of isomalt and 34.5 N (i.e. 0.14 N/mm^2 diametral tensile strength) in case of sugar show a good mechanical strength compared to others in the case study for lyophilized fast dispersal/dissolution tablets (see Chadrasekhar et al. [Cha09]). As discussed by Nguyen and Ulrich [Ngu14a], these tensile strength values are still much lower than the standard for compressed tablets, however, they are adequately stable for food use and are thus easy to be handled and to be stored.
In summary, it is confirmed that the dissolution rates as well as mechanical strengths required for fast dispersal tablets are met in case of the use of an additive, e.g. isomalt and sugar.

6.1.4 Effect of solid loadings

The effects of solid loadings on the physical properties of tablets in the case of “with” and “without” additive were presented in chapters 5.1.5 (Fig. 5.1-28 and Tab. 5-13) and 5.1.3 (Fig. 5.1-21 and Tab. 5-9), respectively. In both cases the presented results demonstrate that the solid contents have a strong effect on the properties of the produced tablets. A higher solid content in suspension is according to a lower water content which induces a lower porosity, smaller pore sizes in produced tablets and thus a high tensile strength and a slow dispersal/dissolution behavior as well. This means that not only the additive content, but also the hardness, the porosity as well as the pore size are very important factors which determine the dissolution/dispersal behavior of the produced tablets. A balance of the tensile strength and the porosity needs to be considered to get the optimized dissolution/dispersal behavior.

From the view of the process control, the additive content and the solid loading are the key factors which are needed to be considered to adjust the tensile strength as well as the dissolution/dispersal behavior of produced tablets. The suspension with the solid loading of 28 wt% and additive content of 0.2 $g*mL^{-1}$ shows the best performance of produced cocoa tablets in both terms of the tensile strength and dissolution/dispersal behavior.

6.2 System 2 – pharmaceutical: paracetamol tablet

6.2.1 Properties of suspensions

Density

The density data of paracetamol suspensions were presented in chapter 5.2.2.1. Similar to the case study of cocoa tablets, in general the density of paracetamol suspensions with the modified starch as an additive stay in range of 1.1 to 1.2 g*cm^{-3}.

Due to the higher density of the modified starch (ρ = 1.500 g*cm^{-3} [Ing14]) in comparison to water (ρ = 1 g*cm^{-3} [Mor07]), the density of liquid medium is slightly increased as the modified starch is added into the water. Because of thermal expansion of liquids, the density of solutions is slightly decreased when the temperature of solutions is increased from 5 to 35 °C (see Fig. 5.2-2).

The densities of suspensions are higher than those of respective liquid phases due to the higher real density of solids. With higher density, modified starch (ρ = 1.500 g*cm^{-3}) raises the density of the suspensions stronger in comparison to paracetamol (ρ = 1.293 g*cm^{-3} [Cae13]) (see Figs. 5.2-3 and 5.2-4).

As to be mentioned in chapter 6.1.1, the small difference in the density of the suspensions and solutions do not significantly affect the processing of the freeze casting. However, the measurements of densities are still necessary to be carried out to know how much they are.

In Figs. 5.2-3 and 5.2-4, the lower values of the measured density as compared to calculated density of paracetamol suspensions can be explained by the appearance of the gas inside the suspensions when a degassing process could not carried out in the simple density measurement. Furthermore, systematic and random errors could also occur during measurements, therefore a double check is advised.

Rheology measurements

For the liquid phases and suspensions with the paracetamol content lower than 20 wt%, the flow behavior in the low shear rate ranges is close to the one of the Newtonian liquids (see Figs. 5.2-7 and 5.2-8): The viscosities of the studied systems seem to be stable in a certain range of the shear rate (< 300 s^{-1} for the 0.20 g*mL^{-1} modified starch solution and < 600 s^{-1} for the 20 wt% paracetamol suspension). When the shear rate is further increased, the slopes of the shear stress curves are bigger and the viscosity of substances gradually rises. This phenomenon may be caused by the break of the liquid structure. Normally, the viscosity of the liquids should decrease when the structure of a liquid in this system is destroyed. However, in this case study, with the high shear rate, the viscosity is increased. These flow behaviors of liquids and suspensions are complex. However, this exactly same behavior was

presented by Pachulski [Pac07c] with the paracetamol system using Bindzil as the liquid medium.

The suspensions with equal or higher solid loadings of 33.4 wt % behave as non-Newtonian liquids (see Fig. 5.2-5). The viscosities of suspensions are not constant with increasing shear rate. At the low shear rate range, the viscosity of systems increases. As increasing the shear rate, the shear stress of system is also increased. After the maximum value of viscosity is reached, the thinning flow behavior occurs. The viscosities of the suspensions quickly decrease according to the increase of the shear rate. The reason for the shear thinning flow behavior is that an increased shear rate deforms and or rearranges particles, resulting in lower flow resistance and consequently a lower viscosity. The solid particles in the suspensions are also settling down during the shearing. Therefore, the viscosities of suspensions are significantly decreased with an increased shear rate and increasing shearing time.

Furthermore, the thixotropy behavior is also found in the suspensions with the solid loading equal or higher solid loading of 33.4 wt %. The viscosities of the suspensions are dependent not only on the shear rate but also the shear time. The example of the thixotropy test is proposed in Fig. 5.2-6. This behavior did not occur with the suspensions with the solid content equal or lower than 20 wt% as well as the starch solutions in the studied concentration range. The thixotropy behavior of suspensions can be explained by the gel properties of the modified starch in the thick suspensions.

The results of the time dependence tests of the suspension viscosity with the constant shear rates are presented in Tab. 5-18 and Fig. 5.2-10 and demonstrate that the viscosities of the suspensions are significantly dependent on the shear time. It means that the structure of suspensions is easy to be destroyed and due to the difference in the density, the solid particles easy settle in the suspensions. To maintain the structure of the suspensions, a reasonable mixing is necessary during processing or the suspensions need to be remixed after resting in a long time.

In general, as can be predicted, the solid loadings and modified starch contents strongly affect the viscosity of the suspensions (see Figs. 5.2-11 and 5.2-12). The higher the solid loading or the higher the modified starch content is the thicker the suspensions with higher viscosity value will be. The maximum paracetamol loading in the 0.20 $g*mL^{-1}$ starch solution is 65 wt%. However, to be easier to control the flow of the suspensions during processing, the paracetamol content equal or lower 60 wt% is highly recommended. High modified starch contents do not cause any disadvantage on the flow properties of suspensions.

Similar to the cocoa system, the viscosities of the liquid phases and suspensions are significantly influenced by the measuring temperature. When the temperature is decreased the thermal motions of liquid molecules are slower and make them less active, which leads to a decrease of the volume of liquids and suspensions, and results in the increase of the

viscosity. Figures 5.2-13 and 5.3-14 show that the effect of the temperature on the viscosities of the suspensions is stronger than the liquid solutions and this effect is more significant when the solid loading of the suspensions is higher.

Thermodynamic properties

Unlike cocoa, paracetamol has a higher purity. With a solubility of 14 $g*L^{-1}$ [Cae13], the solid content of all studied suspensions is higher than the paracetamol amount required to form the saturated solution. Therefore, in all suspensions, the liquid phase is saturated by paracetamol, and the changing of solid contents does not alter the composition of the liquid phase. As result, the freezing and melting point of suspensions are independent with respect to the solid loading (see Fig. 5.2-16a). The melting points of the suspensions are around -1 °C, and the freezing points are suppressed to -15 °C. Also, the latent heat of fusion of suspensions is reduced (see Fig. 5.2-17a), which is accounted by the decrease of the water content when the solid content in suspensions is increased. This means that suspensions with the different solid loadings can be frozen at the same freezing temperature, however, the release heat upon freezing of water will increase according to the water content in suspensions. If the power of the thermobath is kept constant, with the tablets containing the same paracetamol amount of 500 mg, the tablets with a higher solid content need a shorter time, less energy to be completely frozen as well as to be completely sublimated.

Similar to the cocoa system, sugar used as additive strongly drops the freezing and the melting points of the suspensions (see Fig. 5.2-16c). With the sugar content up to 0.30 $g*mL^{-1}$, it can reduce both the freezing and melting temperature an amount of up to 5 °C. Whereas, the modified starch causes a slight depression on the freezing and melting points (see Fig. 5.2-16b) and non-change in the latent heat of fusions (see Fig. 5.2-17b) of the suspensions at the same concentration. The freezing/melting point depression was described in equation 6-2. The smaller freezing/melting-point-depression effect of the modified starch in comparison to sugar can be explained by the difference in the molarity of solutes. With very big molecule structure, the modified starch has the extremely high molecule weight (M > 10000) as compared to sugar (M = 342.3), therefore as the same $g*mL^{-1}$ concentration, the sugar molarity is much higher than the molarity of the modified starch. Furthermore, all the suspensions in the case of sugar addition include the modified starch at the same concentration of 0.2 $g*mL^{-1}$. Therefore, the depression effect in the case of suspensions containing sugar is the conjugate effect from both sugar and the modified starch.

Not only significantly depresses the freezing and melting points of the suspension, sugar but also outstandingly reduces the latent heat of fusions of suspensions. As to be seen in Fig. 5.2-17c, the more sugar content in suspensions the higher heat of fusion upon freezing is. It means that the heat release upon freezing of suspension is lower. In the other words, the

freezing and drying processes of suspensions containing sugar take longer time than the suspension without sugar.

Based on the latent heat of fusions of suspensions, the heat of fusion required for one tablet are predicted and summarized in Tab. 6-2. Similar to the cocoa system, based on this data, the energy cost can be estimated.

Tab. 6-2: Summary of heat of fusions of the suspensions and predicted heat required for one 500 mg tablets.

Studied factor		measured data, per 1 g of suspension		calculated data, per one tablet = 500 mg paracetamol	
		$\Delta H_{f,}$ J	ΔH_m, J	ΔH_f, J	ΔH_m, J
Modified starch content, g/mL	0.00	-128.0 ± 2.1	150.4 ± 1.3	-128.0 ± 2.1	150.4 ± 1.3
	0.10	-130.8 ± 5.3	154.1 ± 9.2	-137.3 ± 5.6	161.8 ± 9.7
	0.20	-162.4 ± 33.9	165.3 ± 19.6	-178.6 ± 37.3	181.9 ± 21.5
	0.25	-163.7 ± 26.4	148.6 ± 14.8	-184.2 ± 29.8	167.1 ± 16.6
	0.30	-153.7 ± 0.6	140.6 ± 6.3	-176.8 ± 0.7	161.6 ± 7.2
Sugar content, $g*mL^{-1}$	0.00	-162.4 ± 33.9	165.34 ± 19.6	-178.6 ± 37.3	181.9 ± 21.5
	0.10	-154.5 ± 6.0	138.0 ± 3.8	-173.0 ± 6.7	154.6 ± 4.3
	0.20	-129.6 ± 20.0	118.8 ± 20.9	-147.7 ± 22.9	135.5 ± 23.8
	0.30	-105.3 ± 17.2	86.0 ± 6.3	-122.1 ± 20.0	99.8 ± 7.3
Paracetamol content, wt%	30.00	-218.3 ± 6.9	213.3 ± 0.8	-414.8 ± 13.0	439.5 ± 1.4
	40.00	-171.3 ± 12.6	185.1 ± 7.8	-239.9 ± 17.7	259.2 ± 10.9
	50.00	-162.4 ± 33.9	165.34 ± 19.6	-178.6 ± 37.3	181.9 ± 21.5
	60.00	-100.1 ± 3.4	109.4 ± 1.4	-90.1 ± 3.0	98.5 ± 1.3
	65.00	-90.1 ± 5.0	96.7 ± 4.5	-74.1 ± 4.1	79.6 ± 3.7

6.2.2 Tablet production

The paracetamol tablet is not able to keep the tablet form without using an additive. The phenomenon may be addressed by the weak interaction force between the paracetamol particles, the big particle size, the higher bulk density of particles as well as the structure of the surface of the solid particles. Due to the big particle size, high bulk density and lower interactions in the water medium, the paracetamol is less distributed in water than cocoa. In addition, in the original paracetamol material there is no soluble impurity which can play a role of an additive such as in the case of cocoa tablet. All these reasons lead to the unsuccessful tableting by freeze casting without additives.

Paracetamol shows no shrinking behavior while drying. Therefore, even in combination with sugar and isomalt, after freezing, the volume of system is increased, which makes the solid

materials, especial, the additives (sugar and isomalt) stick to the polyacrylic molds and leads to an extremely difficult removing of tablets from the molds.

Therefore, to successfully produce paracetamol tablets by a freeze casting process, it is necessary to add a water soluble additive to the suspension which has a shrinkage behavior while drying. Modified starch is a good candidate for this case.

Effect of modified starch

As presented in chapter 5.2.3 and discussed by Nguyen and Ulrich [Ngu15b], modified starch is a potential additive to produce a high tensile strength tablet, e.g. the paracetamol tablet. Here, in this section, the function of the additive and the binding mechanism of the modified starch will be discussed.

Previous studies [Pac07a-b, Sze07a, Wit10b] demonstrated that the water soluble additives recrystallize during solidification and modify the structure of the solid body by building the connection between solid particles [Sze07a]. This phenomenon is clearly seen in the case of cocoa system using sugar and sugar alcohols as additives. However, here with modified starch the mechanism is a different one.

When a comparison is carried out between the morphologies of the original materials and their morphologies in the tablets (see Figs. 5.2-21 and 5.2-22). It is clear that there is no round-shape particle of the modified starch (see Fig. 5.2-22b) or any new particles which can obviously be seen in the SEM images of the freeze casted solid bodies (see Fig. 5.2-21d). It seems that almost all modified starch is dissolved in water and solidified in the process without recrystallization as starch crystals. Modified starch distributes in the matrix of paracetamol particles (the particles in long rod shape) and the ice crystals and plays its part as a glue to cover and connect the solid paracetamol particles (see Figs. 5.2-21d and e).

Different compared to the sugar and the sugar alcohols, the morphology and the growth of ice crystals are not strongly affected by an addition of modified starch as filler or additive. The needle channel structure of ice crystals is still remaining. This behavior is very interesting and useful to design a customized pore structure of freeze casted solid bodies.

With a higher content of the modified starch in sample 3, the layer of glue is thickier which makes the matrix of the solid needle-like paracetamol particles to be more embattled (see Fig. 5.2-20). This also results in a slightly lower porosity, smaller pore sizes and better matrix connection which dramatically increases the tensile strength of the products (see Tab. 5-20 and Fig. 5.2-19). However, it also leads to a reduction in the dissolution or disintegration behavior of produced tablets (see Fig. 5.2-23).

Furthermore, a higher content of modified starch also creates cracks on the surface of tablets as to be seen in Fig. 5.2-18. This phenomenon is proposed to be caused by a shrinkage of the modified starch during drying. Shrinkage in the field of casting/molding is defined as a

slight dimensional reduction brought about by the reduction in volume of the cast or molded material as it cools and solidifies. A reasonable shrinkage actually makes the removal of tablets out of their mold easier, however, a too strong shrinkage is likely to cause cracks as observed in the present experiments. Here, the shrinkage level rises proportionally to the starch content in the tablets [Ngu15b]. However, if the modified starch content is chosen in a reasonable grade, the best performance of paracetamol tablets in both terms the dissolution/disintegration behavior and the tensile strength can be achieved.

As to be seen in Fig. 5.2-23 the freeze casted products own a remarkable higher dissolution behavior compared to the commercial product. The release rates of paracetamol in the freeze casted tablets are significantly faster than in the compressed tablets as the paracetamol content is lower than 0.40 $g*mL^{-1}$. In addition, the dissolution or disintegration rate can be adjusted in the freeze casting process by means of the justification of the modified starch content. The tensile strength of freeze casted tablets can beat the commercially compressed tablets with respect to the dissolution/dispersal time and the tensile strength when the modified starch content in the suspensions is equal or higher than 0.20 $g*mL^{-1}$.

There is no doubt that by controlling the modified starch content in suspensions as well as in tablets, freeze casted tablets can be produced fulfilling a faster dissolving time and a higher tensile strength in relation to conventional tablets. The fixed 1:1 (wt:wt) ratio of paracetamol and water in an aqueous suspension containing 0.20 $g*mL^{-1}$ modified starch was found to give the best results of the produced tablets. These results demonstrate that the produced freeze casted tablets can perform better than the commercially compressed tablet in both terms of dispersal time and tensile strength.

Here, similar to the sugar and the sugar alcohols, the additive modified starch is in charge as a multifunctional additive. They are not only an additive to enhance the mechanical strength of freeze casted tablets, but also a disintegrant which improves the dissolution/dispersal rate of the produced tablets.

The result indicates that it is possible to enhance and control the release of paracetamol via controlling the additive and solid contents in freeze casting tablets. However, for a drug substance, the release profile of drug substance is extremely important for the treatment. Depending to the specific requirements of defined active pharmaceutical substance, the dissolution/dispersal profile of tablets is advised to be strictly further investigated to get an optimized dissolution/dispersal rate which is successful, effective and harmless in the treatment.

Effect of solid loading

Similar to the cocoa system, here again the solid loading confirms its significant role on the physical properties of produced tablets. A higher solid loading is in parallel with a lower water

content in the suspension. It means that the density of ice crystals frozen in a solid body is smaller and afterwards there is a lower porosity as well as a smaller pore size. The changes in the structure of solid bodies directly enhances the tensile strength but slows down the disintegration/dissolution behavior of produced tablets (see Figs. 5.2-24 and 5.2-25). Therefore, to get the balance between the tensile strength and the disintegration/dissolution behavior of freeze casted tablets, the solid loading of initial suspensions need to be optimized. Based on the presented results in chapter 5.2.4, the solid loadings in the range of 50 – 60 wt% are found to be the best compositions to produce tablets which can perform better than the commercially compressed tablets in both aspects: The tensile strength and the dissolution rate. The experimental tablets which are produced from suspensions of 50 wt% of solid loadings own a tensile strength slightly higher than one of the commercial tablets while the dissolution time is more than three time shorter. When the solid loading reached 60 wt%, however, the tensile strength of the produced tablets is almost doubled while the dissolution behavior equals to the commercially compressed tablets.

Effect of sugar as additive

As presented in chapters 5.2.2.4, 5.2.5 and 6.2.1, sugar or sugar alcohols used as additives, here, e.g. sugar in paracetamol tablets shows similar effects concerning the thermodynamic properties (see chapters 5.1.1.4 and 6.1.1) and morphologies of the pores (see chapters 5.1.4 and 6.1.3) in comparison to the cocoa system. Instead of the needle-like channel structure (as previously be reported in Fig. 5.2-21), in Fig. 5.2-26 a honey-comb-like structure was found in case of the use of 0.20 $g*mL^{-1}$ sugar solution. This pore morphology exactly matches with the cellular structure of freeze-dried sucrose which is reported by Devi and William [Dev14]. This behavior is also well explained by Nguyen and Ulrich [Ngu14b, Ngu15a] and Hagiwara and Hartel [Hag96]. The sweeteners, here sugar as an example, affect the ice crystallization primarily by the depression of the freezing point (for cocoa: see chapters 5.1.1.4, 6.1.1, for paracetmol: see chapters 5.2.2.4 and 6.2.1). They also influence viscosity and glass transition temperature and can show specific growth inhibition effects on the ice crystals. Sugar (sucrose) depresses the freezing point of both cocoa and paracetamol suspensions. Therefore, it indirectly decreases the supersaturation (or supercooling) of aqueous suspensions and reduces the crystal growth of the ice. At the end, the needle-like channel structure, which is often obtained from a fast and directional growth of ice, was completely replaced by another morphology, i.e., honeycomb-like structure. This morphology of pores makes the tablet surface also look more porous.

Also can be seen in Fig. 5.2-26, the sizes of the pores seem to be larger in the top layer of tablets which is close to the open surface. This behavior can be explained by the formation of the film of the sugar solution which covers the open surface of tablets and prevents the release of gas (water vapor) in the beginning of the drying step (sublimation). When the gas gathered on the top surface and created a high enough pressure to destroy the film layer, the

gas is released and thereafter bigger pores remain in comparison to other parts of tablets. This behavior occurs when the sugar content in suspensions is high. In that case the sugar solution is viscous and the melting point of suspension is near to drying temperature. Or the temperature on the surface is accidently lower than melting point of suspensions.

However, although the pore morphology was changed in the same way in the current work, it has to be noticed that effects of sugar (sucrose) on the key properties of tablets are different. In case of the soft cocoa tablets, sugar (sucrose) improves both the tensile strength and the dissolution behavior of the produced tablets. However, in case of “normal” tablets, it did make the tablets more brittle as shown in the tensile strength tests (see Fig. 5.2-27).

The sugar content also causes a quite complex effect on the dissolution behavior in Fig. 5.2-28. At a sugar content lower than 30 g/100 g water, the dissolution rates of the produced tablets seem to decrease corresponding to a right-side shift of dissolution curves in Fig. 5.2-28. At a sugar content of 40 g/100 g water the dissolution rate of the produced tablets suddenly rose up and surpassed the tablets containing 0 % of sugar. This behavior is explained based by the bigger pore sizes and the increase in the sugar content which is already presented by Nguyen and Ulrich [Ngu15b]. Increasing sugar contents results in three phenomena: (1) an increase of the pore size, (2) an increasing additive connection, and (3) a rise in concentration of soluble components. These phenomena affect the tensile strength and the dissolution behavior in a complicated and interactive relation. Increasing sugar contents may increase the pore size which can lead to the decrease of the tensile strength and a rise of the dissolution rate by improving the water diffusion inside the tablet, subsequently an increase in the wetting rate. However, increasing the sugar content also reinforces the channel structure by adding more additive channels, which may also lead to the improvement of the tablets’ tensile strength. The produced tablet may get a better dissolution rate, a better tensile strength in the case the very soft tablets, i.e. cocoa tablets. However, in the case of a paracetamol tablet, the balance between tensile strength and dissolution rate was not successfully generated and controlled by the sugar content. The produced tablet may get a better dissolution rate, but not a better tensile strength for a hard tablet such as paracetamol tablets.

6.3 Summary

To sum up, the flow chart of the development of a freeze casting process to produce a fast dissolving tablet used in this work is show in Fig. 6.3-1.

A short overview of the obtained results is presented in Tabs. 6-3 and 6-4.

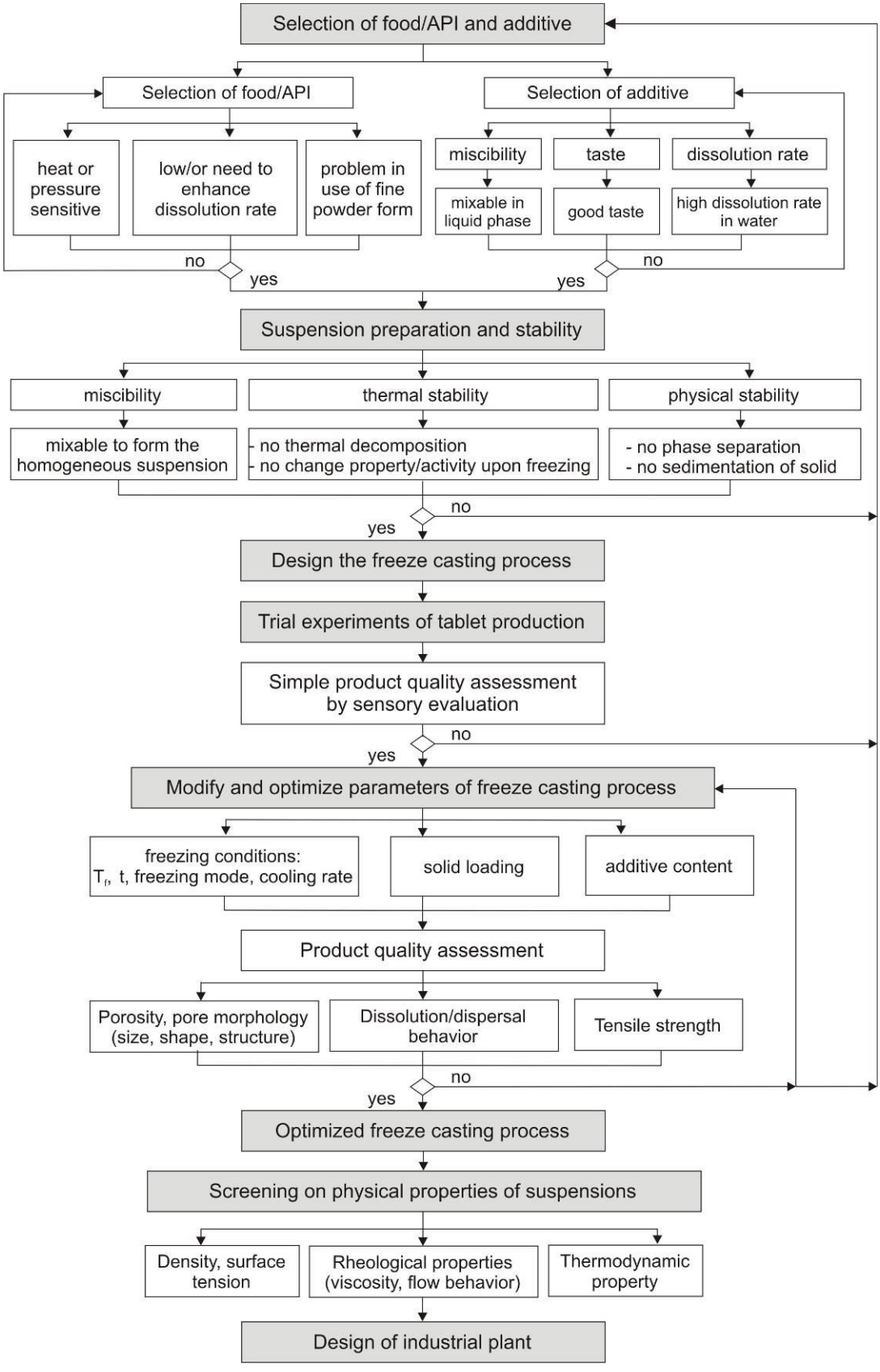


Fig. 6.3-1: The flow chart of the development of a freeze casting process of foods/APIs.

Tab. 6-3: The overview of results.

Note: *↑: slightly increase* *↓: slightly decrease* **: instant freezing* ***: cooling rate at 1 K*min^{-1}*
↑↑: moderately increase *↓↓: moderately decrease*
↑↑↑: strongly increase *↓↓↓: strongly decrease*

1. Case study 1: Fast dissolving cocoa tablets					
1.1 Composition and general conditions					
Composition: In suspension: - Solid: Cocoa : 25 ÷ 33 wt% (based on weight of mixture with water) - Additive (isomalt, sucrose or xylitol): 0 ÷ 0.40 g*mL^{-1} (based on water)					In tablet: - Additive: 0 ÷ 44.82 wt% - Cocoa: 100 ÷ 55.18 wt%
Condition: - Freezing mode: 1-side and 2-side freezing - Cooling rate: instant and 1 K*min^{-1} - Freezing temperature (T_f): -24 ÷ -34 °C, mainly -24 °C - Freezing time (t_f): 4 h - Drying temperature (T_d): -8.1 °C - Drying time (t_d): 24 h					
1.2 Suspension properties					
Property	General	Effect of critical factors			
		↑ Solid loading 25 ÷ 33 wt%	↑ Additive content: 0 ÷ 0.40g*mL^{-1}		↑ Temperature 5 ÷ 35 °C
			isomalt	sucrose / xylitol	
Density, g*cm^{-3}	1.05 ÷ 1.12	↑↑	↑, xylitol < isomalt < sucrose		↓↓
Surface tension, mN*m^{-1}	35.05 ÷ 45.7	↑	↑, similar effect		-
Viscosity, mPa*s	< 50 ÷ > 600, at D = 200 s^{-1} - non-Newtonian liquids - strongly increase with increasing solid loading - rapidly decrease with shearing time, solid can settle down to the bottom - strongly dependent on temperature	↑↑↑	↓, similar effect		↓↓↓
Latent heat of melting, J*g^{-1}	100 ÷ 230	↓↓↓	↓↓		-
Latent heat of freezing, J*g^{-1}	-127 ÷ - 220	↑↑↑	↑↑		-
Freezing point, °C	-14 ÷ -22	↓↓	↓↓↓, xylitol < isomalt ~ sucrose		-
Melting point, °C	-3 ÷ -7	↓	↓↓↓, xylitol < isomalt ~ sucrose		-

1.3 Characteration of freeze casted tablets										
Property	General		Critical factors							
			Freezing conditions				↑ Additive content, 0 - 0.40 g*mL^{-1}			↑ Solid loading, 25 ÷ 33 wt%
		↑ Freezing temperature	1 side, -24 °C		2 sides, -24 °C		isomalt	sucrose	xylitol	
		-24 ÷ -34 °C	Instant	1 K*min^{-1}	Instant	1 K*min^{-1}				
Tablet	- Without additive: + 1-side freezing: good looking, denser in bottom area and more porous in the middle and top + 2-side freezing: compacted structure, good looking - With additive: more porous	More porous, less organized	good, porous	good, dense + porous	fail, brittle in middle	good, dense	good, porous	good, porous	too porous	denser
Pore morphology	- strongly influenced by freezing mode and freezing rate - totally changed when additives are used	No change in kind of structure	needle-like, columnar, directional channel	needle-like, columnar + planar-lamellar	needle-like, separated in middle	planar-lamellar	undetermined shape, sphere-like pore, multidirectional channel			No change in kind of structure but denser
Porosity	58 ÷ 75 %	↑	Similar value				↓			↓↓↓
Pore size	2.8 ÷ 9 µm - strongly depend on the freezing mode, the additive content and solid loading	↓↓ 6.3 ÷ 3.4 µm	4 ÷ 7 µm	5 ÷ 9 µm	-	~ 3 µm	↑↑↑	↑↑↑	↑↑↑	↓↓↓
Tensile strength	- extremely low in case of without additives - two-side freezing mode results in better hardness of produced tablets - significantly improved by binding effect of additives	- ↓↓ in vertical direction - negligible decrease in horizontal direction	0 ÷15 N	-	-	16 ÷ 19 N	↑↑↑ - 1-side*: up to 24 N - 2-side**: up to 45 N	↑↑↑ - 1-side*: up to 25 N - 2-side**: up to 34.5 N	↑↑ - 1-side*: up to 19 N - 2-side**: up to 22 N - reach maximum value at $C_{xylitol}$ = 0.15 g/mL^{-1}	↑↑↑
Dissolution / Dispersal time	- without additive: strongly depend on and in proportion to the hardness of tablet - with additive: significantly decrease	> 1 ÷ 7 mins ↓↓	> 2.5 ÷ 4.5 mins	-	-	2 ÷ 6 mins	↓↓↓ down to 45.5 s	↓↓↓ down to 58.5 s	↓↓↓ down to 40 s	↑↑↑

2. Case study 2: High tensile strength paracetamol tablets

2.1 Composition and general condition

Composition:

In suspension:
- Solid: Paracetamol : 20 ÷ 65 wt% (based on weight of mixture with water)
- Modified starch: 0 ÷ 0.40 g*mL^{-1} (based on water)
- Sugar: 0 ÷ 40 g*mL^{-1} (based on water)

In tablet:
- Paracetamol: 29.4 ÷ 100 wt%
- Modified starch: 0 ÷ 61.53 wt%
- Sugar (sucrose): 0 ÷ 47.06 wt %

Conditions:
- Freezing mode: instant one-side freezing
- Freezing temperature (T_f): -24 °C
- Freezing time (t_f): 2 h
- Drying temperature (T_d): -8.1 °C
- Drying time (t_d): 24 h
- Tablet size: Ø = 16 mm, h = 5 mm

2.2 Suspension properties

Property	General	Effect of critical factors			
		↑ Solid loading 30 ÷ 65 wt%	↑ Additive content: 0 ÷ 0.40 g*mL^{-1}		↑ Temperature, 5 ÷ 35 °C
			Modified starch	sucrose	
Density, g*cm^{-3}	1.1 ÷ 1.2	↑↑	↑, sucrose < modified starch		↓↓
Surface tension, mN*m^{-1}	38 ÷ 58	↑↑↑	↓↓	-	not applicable
Viscosity, mPa*s	< 20 ÷ ~ 1400, at D = 50 s^{-1} - non-Newtonian liquids - thixotropy phenomenon when solid loading ≥ 33.3 wt % - strongly increase with increasing solid loading - rapidly decrease with shearing time, solid is easily setle down to the bottom - strongly dependent on temperature	↑↑↑	↑↑↑	-	↓↓↓
Latent heat of melting, J*g^{-1}	860 ÷ 213	↓↓↓	almost constant	↓↓	-
Latent heat of freezing, J*g^{-1}	-90 ÷ - 218	↑↑↑	almost constant	↑↑	-
Freezing point, °C	-15 ÷ -21	almost constant	↓	↓↓↓	-
Melting point, °C	-1 ÷ -5	almost constant	↓	↓↓↓	-

2.3 Characteration of freeze casted tablets					
Property	General	Effect of critical factors			
		↑ Solid loading 40 ÷ 65 wt%	With out additive	↑ modified starch content 10 ÷ 0.40 g*mL^{-1}	↑ sugar (sucrose) content 0 ÷ 0.40 g*mL^{-1}
Tablet	- with out additive: could not keep the tablet form - with modified starch as additive: good looking, high tensile strength and enhancing dissolving tablet	- denser, harder but slower dissolving behavior	no tablet	- denser, harder slower dissolving behavior - occur cracks on the surface when modified starch content > 0.25 g*mL^{-1}	more porous, softer and dissolve faster
Pore morphology	- with modified starch: needle-like channel - with sucrose: honey-comb-like structure	- no change in type of morphology - more embattled	-	- no change in type of morphology - more embattled	- honey-comb-like structure - more porous
Porosity	40 ÷ 65 %	↓↓↓, from 65 to 40 %	-	↓↓, from ~ 64 to ~ 57 %	not defined but look more porous
Pore size	4 - 6 µm	-	-	↓↓, from 6 - 4 µm	↑↑↑, not measured but visible in SEM images
Tensile strength	0.6 ÷ 2.5 N*mm^{-2} - with modified starch: significantly increase - with sucrose: remarkably decrease - strong dependence on the solid loading	↑↑↑ from to 0.6 ÷ 2.5 N*mm^{-2}	-	from 0.6 to 2.5 N*mm^{-2} - ↑↑↑ when modified starch content lower than 0.2 g*mL^{-1} - almost stable when modified starch content > 0.2 g*mL^{-1}	fluctuated but strongly decreased in general from 1.1 to 0.3 N.mm^{-2}
Dissolution/ Dispersal time	from 1.5 to > 20 mins - strongly dependent on the solid loading and modified starch content - with sucrose: remarkably decrease	↑↑↑ from < 2 to > 20 mins - faster than commercially compressed tablet when solid loading ≤ 60 wt%	-	↑↑↑, from < 2 to 15 mins - faster than commercially compressed tablets when modified starch content lower than 0.40 g*mL^{-1}	- fluctuated but strongly decreased in range of 1.5 - 6 mins - considerly shorter in comparison to commercially compressed tablets

Tab. 6-4: Optimized conditions and products

Case study 1: Fast dissolving cocoa tablets	Case study 2: High tensile strength paracetamol tablets
Composition: ✓ *In suspension:* - Cocoa : 28 wt% (based on weight of mixture with water) - Additive: isomalt or sucrose, 0.20 g*mL^{-1} (based on water) ✓ *In tablet:* - Cocoa: 66 wt% - Additive (isomalt or sucrose): 34 wt% **Condition:** - Freezing mode: instant 1-side or 2-side freezing with cooling rate of 1 K*min^{-1} - Freezing temperature (T_f): -24 °C - Freezing time (t_f): 4 h - Drying temperature (T_d): -8.1 °C - Drying time (t_d): 24 h **Product:** - Fast dissolving cocoa tablet: Ø = 16 mm, h = 10 mm - Dissolving/dispersal time: 45 ÷ 60 s - Tensile strength: 25 ÷ 45 N 	**Composition:** ✓ *In suspension:* - Paracetamol : 50 wt% (based on weight of mixture with water) - Additive: modified starch, 0.20 g*mL^{-1} (based on water) ✓ *In tablet:* - Paracetamol: 83.33 wt% - Modified starch: 16.67 wt% **Condition:** - Freezing mode: instant 1-side freezing - Freezing temperature (T_f): -24 °C - Freezing time (t_f): 2 h - Drying temperature (T_d): -8.1 °C - Drying time (t_d): 24 h **Product:** - High tensile strength 500 mg paracetamol tablet: Ø = 16 mm, h = 5 mm - Dissolving/dispersal time: 3 mins (more than 3 time faster in comparison to commercially compressed tablets) - Tensile strength: 1.05 N*mm^{-2} (better than commercially compressed tablets) 

6.4 Outlook

This work demonstrates that the freeze casting can be applied to produce the fast dissolving tablets in case studies of foods and pharmaceuticals.

For the cocoa system, due to the limitation of time, in this work, a simple optimization was carried out based on an in turn alternating of each element which affects the freezing step. The parameters of the drying step are also not considered. In further studies, an optimization based on multifactors is recommended to investigate. The geometry and the size of produced tablets need to be considered more in depth in order to get the optimized hardness. Furthermore, a scaling up is also needed to be investigated.

For the paracetamol system, the work focused on the role of additives. For example, modified starch is proven to be potentially applicable for the freeze casting in the pharmaceutical field. Here, the optimization of the parameters in the freeze casting process was not fully carried out. It is suggested to investigate the desired release profile further with respect to the active ingredient.

The results of different case studies prove that this technique works well for various systems with a requirement of a few modifications. Application with other new foodstuff such as instant foods (coffee, milk, protein, coconut powder, etc.) or pharmaceuticals are recommended. It is noted that it is also possible to try the technique of freeze casting in other new fields such as fertilizer, chemical or bio industry.

Moreover, discovering new potential additives is also a challenging task in this field of study.

7. Summary

Fast dissolving tablets or instant products are of high interest in the modern pharmaceutical and foods fields. The conventional compression is considered as the most common tableting method, however, it often accompanies with high pressure and high temperature in several local points. Because of these reasons, solid powders which are heat and pressure sensitive or have a low flowability are not able to be compressed into tablets by direct compression techniques. Thus, alternative tableting methods using low temperatures and low or non pressures are necessary.

For fast dissolving tablets, to obtain a rapid diffusion of the liquids into solid bodies, it is necessary that the porosity of tablets and the pore size should be as high as possible. However, the tablets also need to be hard enough to be handled and stable under processing, storage and transportation processes. Freeze casting is a cold molding technique which can produce a solid body with a designable (either dense or very porous) microstructure at low temperature and pressure free. The open or closed pores and the pore sizes can also be tailored. Thus, this technique is a promising method which can be applied to produce fast dissolving tablets of the above-mentioned substances.

In the pharmaceutical field, freeze casted tablets often achieve the required fast dissolution rates, but their poor tensile strength is the remaining limitation which hinders their application in the drug field. Thus, an optimized porosity and pore size as well as structure to keep the balance between dissolution/dispersal rate and mechanical strength of tablets are very important and need to be clearly determined.

This work demonstrates the strong applicability of the freeze casting process in the food and pharmaceutical field. It is found that water-soluble additives can play a role as multifunctional agents which can enhance the connection between solid particles without a marked decrease of the porosity and the pore size. This is an excellent way to improve both the dispersal rate and the tensile strength of tablets. Thus, by means of a freeze casting process the fast dissolving cocoa tablet and the high tensile strength paracetamol tablet with a significantly enhanced dispersal/dissolution rate were successfully produced from aqueous suspensions containing multifunctional additives.

A proof of concept of the freeze casting process applied to produce fast dissolving cocoa tablet was presented. Here it could be shown that:

- The metastable zone width was determined. The temperatures of -24 °C and -8 °C are proven to be suitable temperatures for the freezing and the drying process respectively.
- By controlling the freezing conditions, the morphology of pores and the physical properties of produced tablets are able to be modified:

  - Two pore morphologies are found according to different freezing modes and cooling profiles. By the two-side freezing mode at a cooling rate of 1 $K*min^{-1}$ a dense and lamellar structure of pores was found. In case of an instant freezing a porous needle-like channel structure was found. The instant freezing was not able to be applied for the two-side freezing mode, tablets produced in that way are always splitted in the middle (they fall apart).
  - With a denser structure the use of a two-side freezing mode can enhance the tensile strength of produced tablets, however, slower dispersal or dissolution rates are accompanied, too.

- Sugar (sucrose) and sugar alcohols, i.e. isomalt and xylitol depress the freezing and melting point as well as the latent heat of suspensions. Consequently, an addition of the sugar and the sugar alcohols reduces the supercooling or the driving force of the nucleation and the growth of ice crystals. It leads to a slower nucleation and growth rate, as results, the morphology of ice crystals or pores are changed. The needle-like or lamellar structures were replaced by the sphere-like porous structure with bigger pores. Multidirectional connections between the solid particles were created by sugar and sugar alcohols. Thus, the tensile strength of tablets was promoted without prolong the dispersal/dissolution time.
- A flow chart for the development of a freeze casting process of foods/APIs could be presented. The optimized freeze casting process used to produce fast dissolving cocoa tablet is determined.
- As results, cocoa tablets with a fast dissolving/dispersal time (less than 1 minute) and an acceptable tensile strength (35 to 45 N) which is considered strong enough to be handled and meeting the requirements of soft tablets was achieved. The freeze casted cocoa tablets fulfilled the requirements for instant foods.

Subsequently, the production of high tension strength paracetamol tablets was also successfully generated with the assistance of modified starch.

- Optimized parameters of the freeze casting process to produce fast dissolving cocoa tablets were modified to be applied for the paracetamol system. Changing studied solid substance in suspensions does not cause a pronounced change in the appearance of the ice crystallization.
- Modified starch is found to be a powerful multifunctional agent for a high tensile strength tablet. Modified starch is able to be rapidly dissolved in water and to be well distributed between solid particles. During freezing, it solidifies and functions as glue connecting solid particles together. At the same weight concentration, the modified starch does not cause a pronounced affect on the thermodynamic properties of the suspensions in comparison to sugar and sugar alcohols, here, i.e. sucrose. As being different to sugar

and sugar alcohols using the modified starch as additive maintains the needle-like structure of the pores.

- The higher the modified starch content is the harder is a tablet, however, a slower dispersal or dissolution behavior is followed. By adjustment of the modified starch content the balance between the tensile strength and dispersal behavior of the freeze casted tablets can be generated.

  As a result, freeze casted paracetamol tablets with an equal tensile strength and a faster dissolving time in comparison to the commercially compressed product were achieved.

- With the binding effect of the sugar or sugar alcohols, here, i.e. sucrose can enhance the tensile strength of tablets. With a big size of pores and a very porous structure the tablets containing sugar and sugar alcohols can only reach a moderate hardness which allows them being stable under handling. However, a further higher tensile strength can hardly be achieved.

In both case studies, not only the multifunctional agents but also the solid loadings are key factors in controlling the balance of dispersal/dissolution rate and tensile strength of a tablet. The highest solid loading which does not highly depress the porosity of a tablet and does not significantly slow down the dispersal/dissolution rate of a tablet is recommended.

Furthermore, rheological properties of suspensions were investigated. A non-Newtonian liquid behavior was found for both cocoa and paracetamol suspensions in the used composition. The viscosity of suspensions is time and temperature dependent. A reasonable re-mixing is required to prevent a sedimentation of solid particles and to rebuilt the homogeneous structure of suspensions. In case of paracetamol using modified starch as an additive, the suspensions show a thioxotropic phenomenon when the solid loadings are moderately high. For processing a paracetamol content equal or lower than 60 wt% of the mixture of paracetamol and water is recommended.

This work proves the significant role of multifunctional water soluble additive and the strong power of the freeze casting technique in the food and the pharmaceutical field. It opens a new challenge of the freeze casting technique in production of fast dissolving tablets in pharmaceuticals as well as instant food products. With the achievement of the instant drink cocoa and high tensile strength paracetamol tablets demonstrated in this work, further new products produced by the freeze casting technique in various fields such as foods, pharmaceuticals, fertilizers as well as chemicals could be promised to be produced in future.

8. Zusammenfassung

Schnell auflösende Tabletten oder Instant-Produkte sind von großem Interesse in der modernen Pharmazie und Nahrungsmittelindustrie. Die konventionelle Pressung ist die häufigste Methode zur Herstellung von Tabletten, diese ist jedoch häufig mit hohem Druck und hohen Temperaturen verbunden. Aus diesen Gründen sind feste Pulver, die Hitze und Druck empfindlich sind oder eine geringe Fließfähigkeit aufweisen nicht für die Kompaktierung zu Tabletten geeignet. Deshalb sind alternative Methoden bei niedrigen Temperaturen und mit niedrigen oder keinen Drücken erforderlich.

Für sich schnell auf lösliche Tabletten, die eine schnelle Diffusion der Flüssigkeiten in den Festkörper ermöglichen, ist es erforderlich, dass die Porosität und die Porengröße so groß wie möglich sind. Jedoch müssen die Tabletten trotzdem fest genug sein, um gehandhabt werden zu können und stabil genug für eine Verarbeitung, Lagerung und einen Transportprozesse. Der Gefrierguss ist eine Kaltformtechnik, die den Festkörper mit einer gestaltbaren (entweder dichten oder sehr porösen) Mikrostruktur bei niedriger Temperatur und ohne Druck produzieren kann. Die offenen oder geschlossenen Poren und die Porengrößen können ebenfalls angepasst werden. Somit ist diese Technik ein mögliches Verfahren, das angewendet werden kann, um schnell auflösende Tabletten aus den oben genannten Substanzen zu erzeugen.

Im pharmazeutischen Bereich, erreichen Gefrierguss-Tabletten oft die geforderten schnelleren Auflösungsraten, aber ihre schlechte Bruchfestigkeit behindert ihre Anwendung im Arzneimittelbereich. Sowohl eine optimierte Porosität und Porengröße als auch die Struktur müssen stimmen, um die Balance zwischen Auflösung / Ausbringungsrate und der mechanischen Festigkeit von Tabletten zu erhalten, dies ist sehr wichtig und muss klar festgelegt werden.

Diese Arbeit zeigt die gute Anwendbarkeit des Gefriergussverfahrens im Lebensmittel- und Pharmaziebereich. Es wurde festgestellt, dass wasserlösliche Zusätze als multifunktionelle Mittel eine Rolle spielen können, welche die Verbindung zwischen festen Teilchen, ohne bemerkbare Abnahme der Porosität und Porengröße, beeinflussen. Dies ist eine ausgezeichnete Möglichkeit, sowohl die Ausbreitungsrate als auch die Bruchfestigkeit der Tabletten zu verbessern. Somit konnten mittels des Gefriergießens eine schnell lösliche Kakaotablette und eine bruchfestere Paracetamoltablette mit einer deutlich verbesserten Dispergierung / Auflösungsrate erfolgreich aus wässrigen Suspensionen mit multifunktionellen Additiven hergestellt werden.

Eine Machbarkeitsstudie des Gefriergussverfahrens wurde umgesetzt, um eine schnell lösliche Kakao Tablet zu produzieren. Hier konnte folgendes gezeigt werden:

- Die metastabile Zonenbreite ist determiniert. Die abwechselnden Temperaturen von -24 °C und -8 °C wurden als geeignete Temperaturen für den Gefrier- und den Trocknungsprozess nachgewiesen.

- Durch die Steuerung der Gefrierbedingungen, konnten die Morphologie der Poren und die physikalischen Eigenschaften der hergestellten Tabletten wie folgt geändert werden:
    - Zwei Porenmorphologien wurden, bei der Nutzung von unterschiedlichen Gefriermodi und Kühlprofilen gefunden. Durch den zweiseitigen Gefriermodus bei einer Kühlrate von 1 $K*min^{-1}$, wurde eine dichte Lamellenstruktur der Poren gefunden. Im Falle eines sofortigen Gefrierens wurde eine poröse nadelartige Kanalstruktur gefunden. Das Instant-Gefrieren konnte nicht für den Zweiseitengefriermodus angewendet werden, da auf diese Weise hergestellte Tabletten immer in der Mitte auf gespaltzt sind.
    - Mit einer dichteren Struktur kann durch die Verwendung von einem zweiseitigen Gefriermodus die Bruchfestigkeit der hergestellten Tabletten verbessert werden, dies wird aber begleitet von einem langsameren Auflösungen.
- Zucker (Saccharose) und Zuckeralkohole, z.B. Isomalt und Xylit setzen den Gefrier- und Schmelzpunkt als auch die latente Wärme von Suspensionen herab. Folglich reduziert eine Zugabe von Zucker und Zuckeralkoholen die Unterkühlung oder die Antriebskraft der Keimbildung und das Wachstums von Eiskristallen. Sie führt zu einer langsameren Keimbildungs- und Wachstumsrate mit dem Ergebnisse, dass sich die Morphologie von Eiskristallen oder Poren verändert. Die nadelförmigen oder plättchenförmigen Strukturen wurden zu einer kugelartigen porösen Struktur mit größeren Poren. Multidirektionales Verbindungen zwischen den festen Teilchen wurden durch Zucker und Zuckeralkohole hergestellt. Somit wurde die Bruchfestigkeit von Tabletten ohne Verlängerung der Auflösungszeit begünstigt.
- Ein Fießdiagramm für die Entwicklung eines Gefriergießprozess von Lebensmitteln / APIs konnte vorgelegt werden. Das optimierte Gefriergussverfahren wurde eingesetzt, um schnell auflösende Kakaotabletten herzustellen.
- Als Ergebnisse, konnten Kakaotabletten mit einer schnellen Auflösungszeit (weniger als 1 Minute) und einer akzeptablen Festigkeit (35 bis 45 N), welche als stark genug angesehen wird, um gehandhabt werden zu können die Anforderungen von Weichtabletten erfüllen, erreicht werden. Die Gefrierguss Kakaotabletten erfüllen die Anforderungen für Instant-Nahrungsmittel.

Anschließend war die Herstellung von bruchfesten Paracetamoltabletten ebenfalls erfolgreich und konnten mit Hilfe von modifizierter Stärke erzeugt werden.

- Die optimierten Parameter des Gefriergussverfahrens für sich schnell auflösende Kakaotabletten wurde modifiziert, um auf das Paracetamol-System angewendet werden zu können. Andere untersuchte Feststoffe in der Suspension führten zu keiner Änderung im Aussehen der Eiskristallbildung.
- Modifizierte Stärke ist ein leistungsfähiges Multifunktionsmittel für bruchfeste Tabletten. Modifizierte Stärke ist in der Lage, sich schnell im Wasser aufzulösen und sich zwischen den Feststoffpartikeln zu verteilen. Beim Einfrieren kristallisiert sie und funktioniert als „Kleber“ zwischen den Feststoffpartikeln. Bei gleicher Gewichtskonzentration, hat

modifizierte Stärke keine ausprägende Wirkung auf die thermodynamischen Eigenschaften der Suspensionen im Gegensatz zu den Zuckeralkoholen, wie z.B. Saccharose. Im Unterschied zu den Zuckeralkoholen blieb mit modifizierter Stärke als Additiv die nadelförmige Struktur der Poren erhalten.

- Je höher der modifizierte Stärkegehalt ist, desto härter ist die Tablette, jedoch hat dies eine langsameres Auflösungsverhalten zur Folge. Durch die Einstellung des modifizierten Stärkegehaltes kann die Balance zwischen Bruchfestigkeit und Auflöseverhalten der Gefrierguss Tabletten erzeugt werden.

Als Ergebnis konnten Paracetamoltabletten mit der gleichen Bruchfestigkeit und einer schnelleren Auflösezeit im Vergleich zu den kommerziellen komprimierten Produkten erzeugt werden.

- Mit der Bindewirkung von Zucker oder Zuckeralkoholen, in diesem Fall Saccharose kann die Bruchfestigkeit der Tabletten verbessert werden. Mit einer großen Größe und sehr poröser Struktur erreichen die Tabletten mit Zuckeralkoholen nur eine moderate Härte, welche jedoch eine Handhabung ermöglicht. Jedoch kann eine noch höhere Bruchfestigkeit kaum erreicht werden.

In beiden Fallbeispielen sind nicht nur multifunktionellen Substanzen, sondern auch die Feststoffbelastung wichtige Faktoren bei der Steuerung des Gleichgewichts der Auflösungsgeschwindigkeit und der Bruchfestigkeit einer Tablette. Die höchste Feststoffbeladung, die nicht die Porosität einer Tablette herabsetzt und nicht signifikant die Auflösungsrate einer Tablette verlangsamen, wird empfohlen.

Weiterhin wurden die rheologischen Eigenschaften von Suspensionen untersucht. Ein nicht-Newtonschenes-Flüssigkeits Verhalten wurde sowohl für Kakao- und Paracetamol Suspensionen in der verwendeten Zusammensetzung gefunden. Die Viskosität von Suspensionen ist zeit- und temperaturabhängig. Ein regelmäßiges Neumischen ist erforderlich, um ein Sediment von Feststoffpartikeln zu verhindern und die homogene Struktur der Suspensionen wieder herzustellen bzw. aufrecht zu erhalten. Im Falle von Paracetamol mit modifizierter Stärke als Zusatzstoff, zeigen die Suspensionen ein thixotropes Phänomen und die Feststoffbelastbarkeit ist mäßig hoch. Für die Verarbeitung wird ein Paracetamol-Gehalt gleich oder niedriger als 60 Gew% empfohlen.

Diese Arbeit belegt die bedeutende Rolle von multifunktionellen wasserlöslichen Zusatzstoff und die starke Kraft der Gefriergusstechnik im Lebensmittel- und pharmazeutischen Bereich. Es öffnet sich eine neue Herausforderung für die Gefriergusstechnik in der Produktion von schnelleren (oder besser) auflösende Tabletten in der Pharmazie sowie Instant Lebensmittelprodukten. Mit dem Erreichen vom Instant-Getränk Kakao und bruchfesteren Paracetamoltabletten in dieser Arbeit könnten weitere neue Produkte durch die Gefriergusstechnik in verschiedenen Bereichen wie z.B. Lebensmittel, Pharmazeutika, Düngemittel sowie Chemikalien hergestellt werden und zeigen an, was in Zukunft noch erreicht werden kann.

9. List of symbols and abbreviation

Latin symbols

A	-	pre-exponential factor
A	[mm^2]	area where the force F applied
A_n	[-]	absorbance value of the sampled solution at the sampling step n
$A_{paracetamol,\ 242\ nm}$	[-]	absorbance of paracetamol at wave length of 242 nm
c	[$\mu g*mL^{-1}$]	concentration
c_w	[wt%]	weight concentration of solid in suspension
D	[mm]	tablet diameter
D	[s^{-1}]	share rate
D_n	[%]	dissolution rate at sampling step n
F	[N]	applied force
h	[mm]	tablet thickness
ΔH	[J]	heat of fusion
M	[-]	molecule weight
m	[g]	mass of substance
m	[$mol*kg^{-1}$]	molality
m_0	[g]	total mass of paracetamol in initial tablet
$m_{additive}$	[g]	mass of additive
$m_{p,n}$	[g]	mass of total dissolved paracetamol in solution at the sampling step n
$m_{ps,i}$	[g]	mass of paracetamol in the taken-out sampled solution at the sampling step i
$m_{pv,n}$	[g]	mass of dissolved paracetamol in solution remaining in vessel after n sampling steps
m_{solid}	[g]	mass of solid
m_{water}	[g]	mass of water

n	[-]	number of sampling steps
P	[N]	applied crushing force
p	[atm, bar, Pa]	pressure
S	-	supersaturation
T	[K, °C]	temperature
$T_{(pure\ solvent)}$	[K]	freezing point of pure solvent
$T_{(solution)}$	[K]	freezing point of solution
T_d	[h]	drying temperature
t_d	[h]	drying time
T_f	[h]	freezing temperature
t_f	[h]	freezing time
V	[cm^3]	volume of substance
V_s	[mL]	volume of taken-out sampled solution used for dilution step
V_d	[mL]	volume of HCl 0.1 N solution added to dilute the sampled solution
$V_{v,n}$	[mL]	volume of solution in the vessel after n sampling steps
V_{water}	[mL]	volume of water
wt%	[%]	weight percent
ΔT	[K]	freezing point depression
J		nucleation rate

Greek symbols

ρ_s	[$g*cm^{-3}$]	apparent density of the solid
ρ	[$g*cm^{-3}$]	density
ρ_l	[$g*cm^{-3}$]	density of liquid
τ	[mPa]	shear stress
ν	-	molecular volume
η	[mPa*s]	dynamic viscosity

γ	-	specific surface energy
λ	[nm]	wavelength
σ_t	[N*mm^{-2}]	maximum diametral tensile strength

Other symbols

ϕ	-	factor of homogeneous or heterogeneous nucleation
Ø	[mm]	diameter

Indices

0	initial
f	freezing
m	melting

Constants

π	[-]	Pi constant
i	[-]	Van 't Hoff factor
k	[-]	Boltzmann constant
K	[K*kg*mol^{-1}]	cryoscopic constant

Abbreviations

DSC	Differential Scanning Calorimetry
Par.	Paracetamol
RD	relative density

10. List of figures and tables

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Statement of authorship

I declare that I have written this document on my own. It is a compilation of the results of work carried out by my own or by students under my supervision. The used resources and tools or previously cited information have been distinguished by quotation marks.

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Publication list

[1] 2008 **T. N. P. Nguyen**, K. J. Kim: *Kinetic study on hemi penta hydrate Risedronate Monosodium in batch crystallization by cooling mode*, Int. J. Pharm., 364 (2008) 1, 1-8.

[2] 09/2008 **T. N. P. Nguyen**, K. J. Kim: *Transformation of mono hydrate to anhydrous phase of risedronate monosodium,* in Proc. of 17th ISIC, eds. J.P. Jansens, J. Ulrich, Maastricht – Netherlands 2008, Vol. 3, 1709-1716 (ISBN: 9789076019277).

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[11] 09/2014 **P. T. N, Nguyen**, J. Ulrich, *Sugar alcohols - multifunctional agents in the freeze casting process of foods,* in Proc. of 19th, eds. Biscans B. and Mazzotti M., ISIC19 Sekretariat, INPT -SAIC "ISIC"19, France 2014, 178-220..

[12] 05/2015 **P. T. N, Nguyen**, J. Ulrich, *Sugar alcohols - multifunctional agents in the freeze casting process of foods,* J. Food Eng., 153 (2015), 1-7.

[13] 05/2015 **P. T. N, Nguyen**, J. Ulrich, *Production of High-Tensile-Strength Paracetamol Tablets Using the Freeze-Casting Process,* Chem. Eng. Technol., 38 (2015) 6, 991-998.

[14] 09/2015 **P. T. N, Nguyen**, J. Ulrich, *A primary reference for designing a freeze casting process of drugs - Rheological properties of suspensions,* in Proc. of 22th BIWIC, eds. K. J. Kim, K. Lee, Hanbat National University, Deajeon, Korea 2015, 68-76 (ISBN: 978-89-97590-15-5).

List of attended conferences

No	Authors, paper titles, conference name	Range	Holding place	Time	Presentation
[1]	H. J. Kim, H. S. Lee, **T. N. P. Nguyen**, Kwang-Joo Kim; *Mechanism analysis of the polymorph change of API*, Korea Institute of chemical Engineering Spring Meeting.	National	Ulsan, Korea	20th – 21st April 2007	Poster
[2]	H. J. Kim, H. S. Lee, **T. N. P. Nguyen**, Kwang-Joo Kim: *Mechanism analysis of the polymorph change of API*, 35th KSIEC Meeting.	National	Keimyung University (Seongseo Campus), Daegu, Korea	11st – 12nd May 2007	Poster
[3]	**N.T.N. Phuong**, Kwang-Joo Kim: *A study on the mechanism and hydrated behavior of an API (active pharmaceutical ingredient) in crystallization as monitored in-situ by liquisonic, FBRM and PVM*, Korea Institute of chemical Engineering Fall Meeting.	National	Kaist Institute, Daejeon, Korea	26th – 27th Oct 2007	Poster
[4]	**N.T.N. Phuong**, Kwang-Joo Kim: *The mechanism and hydrated behavior in crystallization of an API*, 36th KSIEC Meeting.	National	Korea	2nd – 3rd Nov 2007	Poster
[5]	**N.T.N. Phuong**, Kwang-Joo Kim: *The mechanism and hydrated behavior in crystallization of an API*, the 20th International Symposium on Chemical Engineering, Chung nam (Korea) Kyushu (Janpan).	International	Hanbat National University, Daejeon, Korea	30th Nov – 2nd Dec 2007	Poster
[6]	**N.T.N. Phuong**, Kwang-Joo Kim: *A study on phase trasnformation of an active pharmaceutical ingredient (API) in hydrate form*; 2008 Institute of Chemical Engineering Spring Meeting.	National	Jeju ICC, Korea	23rd – 25th April 2008	Poster
[7]	**N.T.N. Phuong**, Kwang-Joo Kim: *The phase transformation of hydrate forms of an active pharmaceutical ingredient (API),* 37th KSIEC Meeting.	National	Hanyang University, Asan, Korea	9th -10th May 2008	Poster
[8]	**N.T.N. Phuong**, Kwang-Joo Ki: *Monitoring the phase transformation of hydrates in crystallization solution*, ICSST08 - International Conference on Separation Science and Technology.	International	Karuizawa, Nagano, Japan	02nd -04th Oct 2008	Poster
[9]	**Nguyen Thi Nhat Phuong**, Kwang-Joo Kim: *Transformation of mono hydrate to anhydrous phase of risedronate monosodium*, ISIC17 - *17th International* Symposium on Industrial *Crystallization.*	International	MECC center, Maastricht, Holland	14th – 17th Sep 2008	Poster

[10]	**Nguyen Thi Nhat Phuong**, Kwang-Joo Kim: *A study on phase transformation between hydrate forms of an active pharmaceutical ingredient*, BIWIC2008 - 15th International Workshop on Industrial Crystallization	International	Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany	10th – 12nd Sep 2008	Oral
[11]	**N.T.N. Phuong**, Kwang-Joo Kim: *A study on phase transformation between hydrate forms of an active pharmaceutical ingredient*; 2008 Institute of Chemical Engineering Fall Meeting	National	Busan BEXCO, Korea	22nd -24th Oct 2008	Poster
[12]	**N.T.N. Phuong**, Kwang-Joo Kim*: Kinetic Study of An Active Pharmaceutical Ingredient in Batch Crystallization by Cooling Mode*; 38th KSIEC Meeting	National	Jeju ICC, Korea	12nd -14th Nov 2008	Poster
[13]	**Nguyen Thi Nhat Phuong**, Kwang-Joo Kim; *A study on phase transformation between hydrate forms of an active pharmaceutical ingredient using ultrasonic velocity measurement*; The 2nd Regional Conference on Chemical Engineering **-** Chemical Engineering for Sustainable Development and Collaboration in the ASEAN Region.	International	Rex Hotel, HCM city, Vietnam	23rd – 24th Oct 2009	Poster
[14]	**P. Nguyen,** J. Ulrich: *Fast dissolving tablet - a new dosage form of food produced by freeze casting*, Jahrestreffen der Fachgruppen Kristallisation und Mischvorgänge 2013.	National	Magdeburg	14th – 15th Mar. 2013	Poster
[15]	**P. T. N, Nguyen**, J. Ulrich: *Fast dispersible cocoa tablets - A case study of freeze casting applied on food industry,* in proceeding of BIWIC 2013 (20th International Workshop on Industrial Crystallization).	International	Odense, Denmark	18th – 20th Sept. 2013	Poster
[16]	**P. T. N, Nguyen**, J. Ulrich: *Production of High Tensile Strengh Paracetamol Tablets Using the Freeze Casting Process*, BIWIC 2014 (21th International Workshop on Industrial Crystallization).	International	Rouen, France	10th – 12th, Sept. 2014	Poster
[17]	**P. T. N, Nguyen**, J. Ulrich: *Sugar alcohols - multifunctional agents in the freeze casting process of foods,* ISIC19 (19th International Symposium on Industrial Crystallization).	International	Toulouse, France	16th - 19th, Sept. 2014	Oral
[18]	**P. Nguyen,** Ulrich: *Fast dissolving tablets - a new application trend of freeze casting in food and pharmaceutical industry*, ACHEMA 2015.	International	Frankfurt, Germany	15th – 19th Jun. 2015	Oral
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