Application of a new technology utilizing melt crystallization for the production of coated tablets

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1. Introduction

From between the widely known dosage forms considered by pharmaceutical industries, tablets are the most frequently used form. Advantages of administering active pharmaceutical ingredients through tablets include easiness of administration, accurate dosage delivery, convenience, portability and so much more [Lie89]. The production of coated tablets is also relied on within the confectionary industrial sector. This includes the production of candy, vitamins and minerals and many other applications. Despite being heavily conducted, the production of tablets is still a complicated process. This is because of the high number of steps involved in production that include milling, granulation, drying, compression, coating, further drying and packaging. Not only does this consume more machinery, power, and working force but it also results in more standard quality requirements that need to be reassured and tested within and after each of these steps of production. This is where melt crystallization makes an impact where its application in this specific field can substitute the previously mentioned conventional steps of tablet production with only four steps namely: melting, mixing, cooling and packaging. Melt crystallization is a widely employed industrial purification process that simply involves crystallization from the melt. At certain predetermined conditions, applying melt crystallization results in the purification of materials or in other words the separation of materials. As a clear advantage, in most cases, melt crystallization results in delivering a very high degree of purity with the lowest energy requirements possible. This advantage is further emphasized on when applying melt crystallization as a faster, reliable, money and energy saving method for tablet production through the crystallization of generated molten drops. Usually, the purification of materials through melt crystallization takes place within large crystallizers, however, in this case it takes place within a crystallizing molten drop. In this case, the drop is considered a very small crystallizer, and melt crystallization is tested for its ability to separate two different materials within this drop. One of them should be almost pure while the other one remains in a eutectic mixture. In theory, one material acts as the pure coat (of the produced tablet) while the other material is the active pharmaceutical ingredient to be incorporated within the eutectic core of the tablet. Therefore, within this presented application of melt crystallization it is clear that it does not just act as a simple tablet production method but is indeed a complete one that even involves the coating of tablets.

However, the great advantage of melt crystallization substituting the complex steps of tablet production involved in the conventional method of tabletting has its price. As previously mentioned, the drop is the crystallizer and controlling the crystallization at that small scale can present a tedious challenge. Therefore, careful studies including literature research and several experimentation trials have to be practiced to produce tablets by the proposed technology. This is the purpose of this study. Two binary mixture model systems (as case studies) **A** and **B**, are tested for their ability to produce coated tablets using melt crystallization; system **A** consists of a mixture between lauric acid and ibuprofen, and system **B** constitutes a mixture of lutrol and ibuprofen. As a purification process, melt crystallization is tested for its efficiency to produce purely coated tablets in this study.

2. State of the art

2.1 Melt crystallization

The consequent stages of nucleation and crystal growth can either take place from a supersaturated solution, a melt, or even vapor. As known, the process of nucleation can take place by either changing the composition, temperature, pressure or through a chemical reaction. Like the case with crystallization from suspension, in a process mainly dominated by heat transfer such as layer crystallization from the melt, changing the temperature seems the most straightforward method for nucleation, and later crystal growth, to proceed [Chi03]. In the process of purifying a product as a melt from a feed mixture, addition of an auxiliary agent like a solvent is not needed. As a result, the process of melt crystallization enjoys the presence of many major advantages. Firstly, providing much higher efficiency per separation stage compared to gas-liquid or liquid-liquid separation systems. Secondly, delivering a high degree of product purity (for many systems) in an absolutely efficient manner (≥99.9 %). In addition, the heat energy consumed to purify a mixture using melt crystallization is much lower than consumed by other physical means of separation (e.g. distillation). Therefore, crystallizing from the melt is more environmentally friendly and is actually cheaper as it leads to an overall lower energy consumption. Despite these profound industrial advantages of melt crystallization as a purification method, several limitations and/or challenges still exist when considering eutectic systems. Some of these challenges branch from the process thermodynamic and/or kinetic limitations specific to certain materials and/or systems. From the thermodynamic perspective, systems with a eutectic point very close to one side of the phase diagram (close to the melting point of the target to-be-purified material), renders the method un-applicable. Moreover, systems than need slower kinetics for a successful purification pose a challenge to applying the methodology, since how fast the process proceeds is important to consider within process engineering to ensure industrial productivity. In addition, as compared to other purification methods such as distillation, melt crystallization can be limited (with respect to multi-component systems) by the existing thermodynamic constraints. For instance, a binary eutectic mixture can never be separated as two individual pure compounds but rather be separated as a pure component and a mixture [Ark95].

However, using a process limitation can sometimes provide a useful way to realize a unique industrial application, such as the pastillation process from a molten mixture [Bül03].

2.2 Batch versus continuous process design

The operating vessel in which crystals are formed is termed, a crystallizer [Ark95]. Any crystallization process can be operated through batch or continuous modes of operation. The choice between batch and continuous crystallizers depends on the product specifications and the given budget of operation. Different batch processes usually operate within different conditions, different feed recipes, and processing instructions per batch. On the other hand, a continuous process enjoys operation within minimally changing conditions day by day [Per97]. There are specific advantages to every operational mode employed in industry. For instance, a batch crystallization setup enables the user to test new chemical candidates for their potential in future mass production in little amount of time as compared to the time consuming continuous processes. Also, the lack of continuous feed, recycling, and filtration loops in a batch process makes it more suitable when handling expensive materials since it results in minimized material losses. Also, batch crystallizations are favored in case the feed has larger temperature difference than the mother liquor operating within the crystallizer. On the other hand, the operating conditions within continuous processes can be finely tuned through the use of online PAT tools [Chi12] for a better and more consistent product quality. Since the operation is continuous in nature, the need to store feed is decreased (in case of continuous feed) and so are the costs of storage. In addition, more efficient energy utilization is apparent when a crystallizer operates continuously rather than in batch mode [Ben02]. Since both modes are advantageous in their own worlds, careful planning of the experimental operations must be considered. Factors such as operating at a small or a large scale should be analyzed. Moreover, target product quality and yield are relevant factors that play a role in choosing between the two operations.

2.3 Indirect cooling and the pastillation of melt

As no direct contact exists between the product and the cooling medium, indirect cooling, clarifies the mechanism with which a molten substance is solidified on a cooled surface. One of the mechanisms of this process explains the disintegration of the molten liquid into individual solidifying volumes, termed “pastillation of the melt”. This mechanism, in practice, is possible through the formation of melt drops on a cold plate. Key physical properties are therefore relevant and important to address, such as viscosity, density, surface tension, and crystallization kinetics of the drops. All of these properties, and some more, affect the drops’ shape which then affects the product geometry and quality. Despite the simplicity of this procedure, strict process control and analysis have to be employed for the production of reproducible quality product, pastilles or tablets. In addition to using melt crystallization with a major advantage in reduced costs and energy consumption as a purifying separation technique, the disintegration of a liquid directly into individual volumes is further interesting in that aspect. This is due to the additional energy savings of the process because the force needed to disintegrate a liquid is much lower than that necessary to mechanically granulate a solid [Bül03]. Other advantages of the pastillation process include no dust generation as a result of avoiding any, otherwise required, mechanical cutting or breakage. One of the drawbacks of the process, however, may include low productivity due to the free space needed to be left between the drops on the cooling surface. Since the nature of the pastillation process is an industrial application to melt crystallization, several industrial scale dropping units and cooling surfaces are introduced to the market. In Fig. 2.2, an example of a chrome-nickel steel belt is displayed. This moving belt is temperature controllable from the bottom by a cooling medium sprayed beneath it. Different dropping units can be installed to this belt such as the GS and the ZN injector systems where up to 15 mm diameter pastilles can be produced. Fig. 2.3 displays different dropping devices with different modes of operation to form drops from molten mixtures with various viscosity ranges for the production of a wide variety of customized products based on target specifications. All of these parts and units serve the simple pastillation process on a large industrial scale for mass production in a continuous operational mode [Bül03]. More information on the mechanisms of the different dropping devices and units can be found in [Bül03].

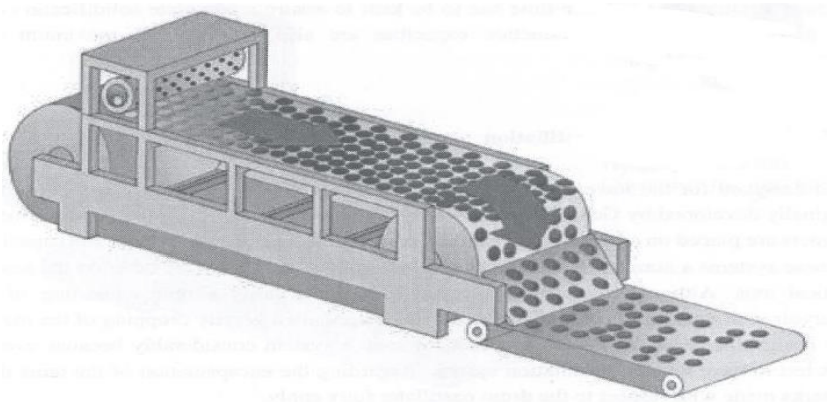
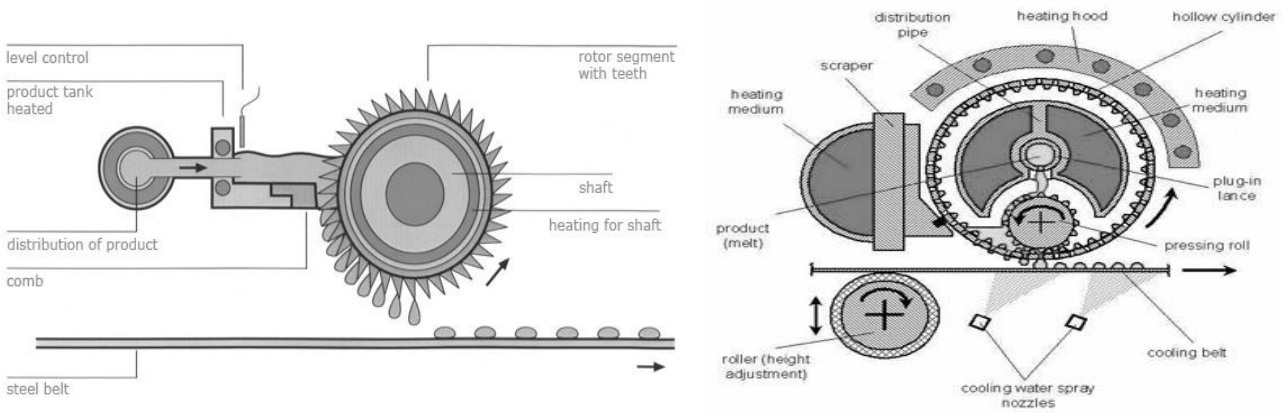


Fig. 2.2 Sketch of an industrial scale steel belt used for the pastillation process on a large scale [San88].



A **B**

Fig. 2.3 Different dropping devices can be used with the pastillation unit. A) Rolldrop system [Bül99], B) Rollomat system [Rob96].

2.4 Phase diagrams

A phase diagram is a graphical illustration that gives information about a system's phases from the thermodynamic perspective. A phase is a homogenous part of a system with uniform physical and chemical properties. Systems existing in thermodynamic equilibrium can consist of either a single phase (homogenous) or multi-phases (heterogeneous). Therefore, phase diagrams can be displayed as unary, binary, or even ternary [Cal07]. Thermodynamic equilibrium is best described in terms of the free energy of the system termed, the Gibbs free energy of change. In formula 2.1, Gibbs free energy is displayed as a function of the internal energy of the system (enthalpy), and the disorder of the system (entropy) [Atk02].

$$\Delta G = \Delta H - T\Delta S \quad \textbf{(2.1)}$$

Gibbs free energy of change	[ΔG]
Change in enthalpy	[ΔH]
Temperature of the system	[T]
Change in entropy	[ΔS]

A system can exist in nature at a thermodynamic equilibrium whenever the Gibbs free energy is at an absolute minimum with respect to predefined temperature, pressure, and composition. In some crystallization systems, pressure tends to be left as a constant non varied parameter. However, any change in those three parameters disrupts a system's equilibrium increasing the Gibbs free energy. This change often results in an increase or decrease in the number of phases in a trial of the system to attain a new equilibrium state. The processes of dissolution or crystallization are very good examples to demonstrate the reliability of the phase diagrams. Since phase diagrams are thermodynamic illustrations they only give information about the equilibrium characteristics of the system without the time period necessary to attain a new equilibrium. In other words, phase diagrams do not deal with the kinetics of the system. Though, kinetics of the system is very important to study since any process of change should be occurring at a specific adjustable rate [Cal07].

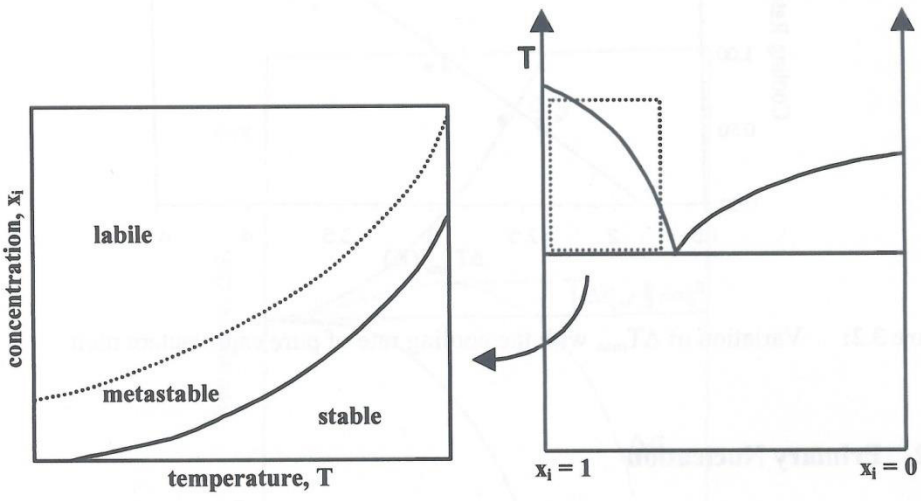


Fig. 2.4 The solubility curve (on the left) used to illustrate solution crystallization is only a part of the full binary phase diagram (on the right) [Chi03].

As to be seen in Fig. 2.4, a phase diagram familiar in explaining the solution crystallization thermodynamics is the same as the usual binary phase diagram. However, due to the difference in crystallization nature between solution and melt crystallization, a specific part of the full phase diagram is usually considered when crystallizing from a supersaturated solution. To realize crystallization, the concentration of the main component must be above the equilibrium value where the solution or the melt becomes supersaturated and then nucleation occurs. After this, the system moves from a labile to a stable condition through the temporary metastable state signifying the completion of crystallization [Chi03].

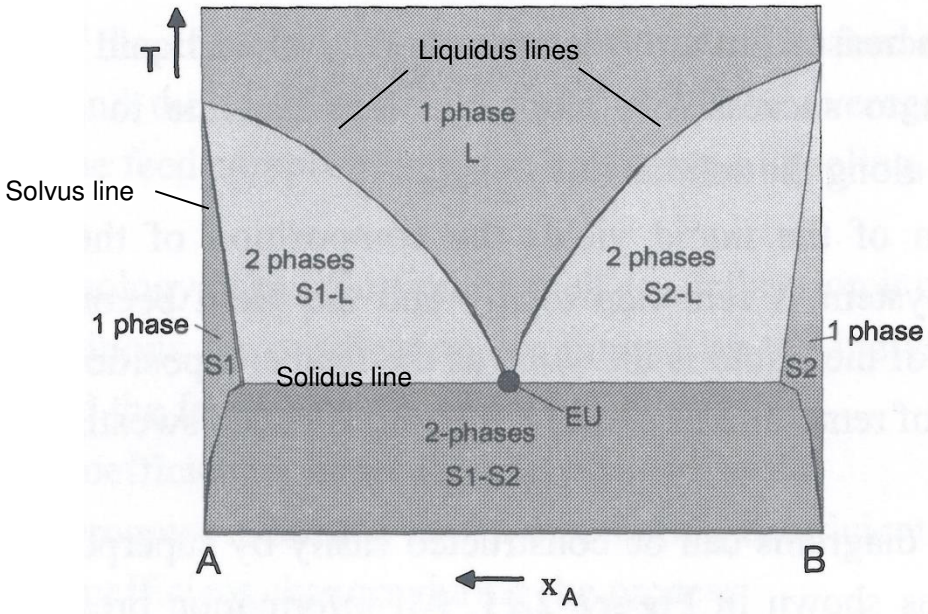


Fig. 2.5 Binary phase diagram showing the eutectic behavior or components A and B [Kön03].

With the help of a binary phase diagram (Fig. 2.5) a eutectic system can be explained where a two component system (A and B) may exhibit more than one phase consequently as temperature and/or composition are changed (in case of constant pressure). Three single phase regions can be identified as L (liquid), S1, and S2 (solid). The L phase is a molten component where both components A and B are intersoluble. The S1 and S2 phases are both in the solid state and they describe the occurrence of a solid solution where a little amount of solid B is soluble in solid A inside the S1 region. The same explanation goes for the S2 region on the other side of the phase diagram and these regions are confined within the so called, solid solubility limit or the solvus line [Cal07].

Usually these one solid phase areas are practically neglected since they are theoretically too small for a major experimental or any analytical influence. Moreover, three two phase regions can thermodynamically exist as S1-L, S2-L, and S1-S2. The S1-L and S2-L regions describe the coexistence of one solid phase of a certain component, respectively, A or B, with a specific composition of the molten liquid mixture formed of both components. Within the S1-S2 region, the S1 and S2 phase solid solutions coexist for all compositions and temperatures. Furthermore, as component B is added to A, the temperature at which the molten mixture is naturally liquid decreases. In other words, the addition of component B decreases the melting temperature of component A [Cal07], [Kön03]. This can be seen along the liquidus line A in Fig. 2.5. The same explanation is viable for liquidus line B. Both liquidus lines meet at the invariant point "EU" through which the solidus line "S1-EU-S2" also passes. The eutectic point (EU) designated by both a eutectic composition (C_E) and temperature (T_E). A eutectic composition passing through the eutectic temperature can be described through the following reaction [Cal07]:

$$L(C_E) \underset{\text{Heating}}{\overset{\text{Cooling}}{\rightleftharpoons}} S1\ (C_{s1E}) + S2\ (C_{s2E}) \qquad \textbf{(2.2)}$$

Liquid phase	[L]
Eutectic composition	[C_E]
Solid phase 1	[S1]
Solid phase 2	[S2]
Composition of S1 phase at the eutectic temperature	[C_{s1E}]
Composition of S2 phase at the eutectic temperature	[C_{s2E}]

At the eutectic composition the liquid phase is transformed by cooling into two solid phases, S1 and S2. The solid product of eutectic solidification is always two solid phases. A reversible path is also possible upon heating. The horizontal solidus line in Fig. 2.5 situated at the eutectic temperature is also called the eutectic isotherm or the "T" line. Because of the nature of this "eutectic reaction", a phase diagram as the one in Fig. 2.5 is termed a eutectic phase diagram [Cal07].

2.5 The solidification mechanism of a molten mixture drop

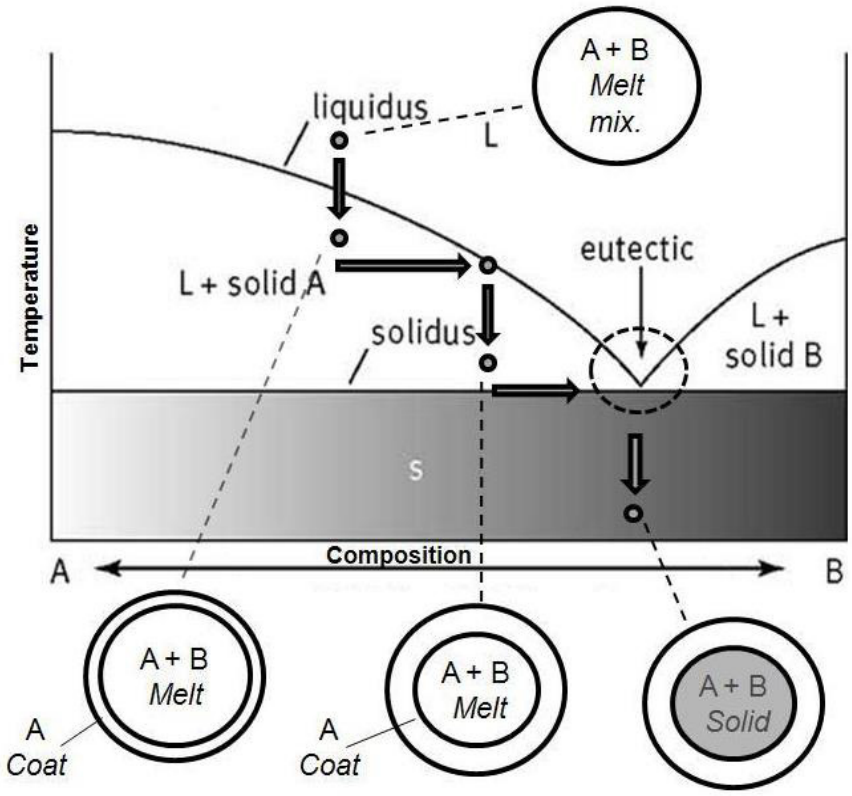


Fig. 2.6 Binary phase diagram showing the crystallization mechanism of a molten mixture drop [Abo14a].

In Fig. 2.6, a binary phase diagram describes the mechanism of solid phases' solidification taking place within a solidifying drop. Cooling down a drop produced from a molten mixture of two components, A and B, at a certain composition results in a phase separation process between the two solidifying phases. This phase separation, or in other words the purification, mechanism exclusive to the crystallization process can effectively be utilized to coat the molten drop with a pure coating substance A. Once cooling of that drop starts, the liquidus line of component A is crossed and therefore, component A starts crystallizing at the surface of the drop initially. This leads to an ongoing compositional shift of the molten mixture (towards the right) which has less of molten A than molten B in terms of concentration. Once this occurs and the liquidus line is again reached, further solidification of component A takes place at the drop's surface. This continuous mechanism results in the thickening of the component A coating layer.

As cooling continues, this mechanism repeats in a sequence of specific steps, the number of these steps depends on different factors related to the cooling rate, and the rising viscosity of the melt (mass transfer) [Chi03]. The end point of this process, of component A purification on the surface of the solidifying drop is the eutectic point. At this point, for the first time component B crystallizes as the eutectic temperature is reached within the core of the solidifying drop. Moreover, the rest of molten A also crystallizes at this specific point. Further cooling beyond this point (below the isotherm solidus line), leads to crystallization and the full solidification of the drop. This mechanism of molten drop layer specific solid phase separation during cooling can be utilized through the application of industrial pastillation process discussed in Chapter 2.3. In addition, if component A is a suitable coating material or an excipient and component B is a pharmaceutical active ingredient the pastillation process can be proven as an effective simpler method for the production of pharmaceutical tablets.

3. Aim of the project

The evaluation of an alternative tablet production has to be discussed. Here, the production of pharmaceutical tablets through in-situ coating is therefore the main aim of this study. This is due to the fact that it could act as a practical, easy replacement to the tedious conventional method of tablet production, which focuses on both, productivity and quality of the tablet manufacturing process. In-situ coating summarizes the ability to utilize the purification characteristic of melt crystallization for the production of coated tablets in just one step. This is possible through, first, understanding the process thermodynamics with respect to the system to be tested (composed of a binary mixture between the active pharmaceutical ingredient (API) and the coating material) and the consequent pastillation of the melt. Since the formation of coated tablets is realized in this study through solidifying molten drops, melt crystallization is a process that needs to be studied and understood from the respective application perspective as well. Only through this understanding, further necessary process optimization can be done. However, for this to be achieved, lab scale process design has to be implemented mimicking the real industrial procedure of pastillation of the melt. Moreover, gathering important analytical information on the to-be-used materials or mixtures makes sure that the lab scale designed experiments lead to an expected outcome related to the intended purpose of realizing the phase separation within a crystallizing drop. This step is also important to make sure that the existing mandatory process prerequisites of melting and forming drops out of a molten mixture can still frame the scope of the used materials from the thermodynamic and physical property point of views, respectively. In the next stage, and before production, it is important to determine the critical process parameters including careful choice of a starting solid mixture composition and choice of the molten drop cooling temperatures as well. Within the production stage, several analytical techniques should be employed to prove the critical phase separation process occurring within a molten mixture drop. Some techniques are operated inline within production using the lab scale designed experiment, and some others deal with evaluating the phase separation quality offline using the final product, in this case, a solidified tablet. Specifically, at this stage, it is also very important to learn about the critical quality attributes of the produced tablets that in the end are related to the phase separation quality.

Through this combined knowledge, further optimization of the experimental conditions is done through an ongoing series of key parameters' changes per experiment. Upon reaching an optimum result that is backed up by valid theoretical explanations, process transfer from the lab to industrial scale is done. Since this is the last major step that can actually prove the reproducibility of the employed method of lab scale experimentation, careful and accurate transfer of the experimental conditions is to be taken into full consideration. In the end, it is then possible to map a step by step guide to the complete process of tablet production using melt crystallization. This guide is most useful in displaying the major key parameters as well as the most sensitive process constraints that could otherwise limit the product quality if not taken into account. This guide also deals with ways to counteract such constraints to be able to successfully implement the production of tablets using melt crystallization.

4. Materials and methods

4.1 Materials

In Table 4.1 the materials used in experiments of the in-situ coating process are listed together with information from where they were purchased and their purity.

Table 4.1 Overview of the different substances used in the project experiments.

Substance name	Company	Location	Purity [%]
Lauric acid	Alfa Aesar	Karlsruhe, Germany	98
Lutrol	Sigma Aldrich	St. Louis, United States	≥99
Ibuprofen	Caelo	Hilden, Germany	99
Starch	Cargill	Krefeld, Germany	99
Cobalt (II) chloride	Alfa Aesar	Karlsruhe, Germany	97

4.1.1 Lauric acid

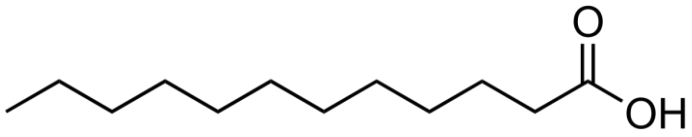


Fig. 4.1 Lauric acid chemical structure [Row09].

Systemically known as dodecanoic acid, lauric acid exists as white crystalline powder. As to be seen in Fig. 4.1 lauric acid is a 12-carbon atom (medium chain) carboxylic acid. It is isolated from coconut oil and palm kernel oil through a multi-phase extraction process ending with its hydrogenation to its known saturated acid form and distillation. There are many uses of decocanoic acid nowadays in industry. It is used as an emulsifying agent and a surfactant in pharmaceutical industries. In addition, it is a popular food additive in food industry and is used as a lubricant in chemical industries. Some notable physiochemical properties make lauric acid an ideal candidate for the use in the in-situ coating of drops. Firstly, it has a moderate melting point of 44 °C and therefore not much energy is needed to transform it into the molten state. It also has a moderate viscosity (η) of 7.3 mPa s at 50 °C [Row09]. This means that using this substance in its molten state will not hinder the required mass transfer for the phase separation to occur [Chi03] within a crystallizing droplet.

Moreover, since lauric acid is considered safe to handle as it is non-toxic and it has a long shelf life. It is, therefore, considered from the application point of view appropriate to use as a coating material for the production of coated tablets.

4.1.2 Lutrol

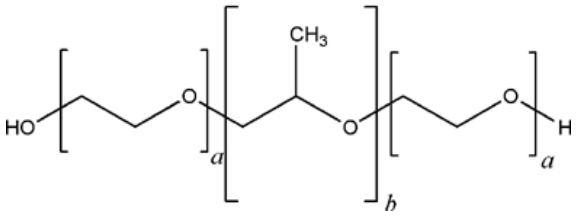


Fig. 4.2 A generalized chemical structure of the poloxamer family [Row09].

Related to the family of poloxamers, lutrol is also known by the name kolliphor p188. Lutrol is a synthetic block co-polymer produced by reacting propylene oxide with propylene glycol forming polyoxypropylene glycol (central hydrophobic chain) to which ethylene oxide is added (hydrophilic chains). It exists as a white, waxy, free flowing granular powder (non-sticky) which makes it an excellent material to be used in seeding, for instance, with regards to good handling. Poloxamers are stable, non-ionic and non-toxic making them popular in pharmaceutical industries as solubilizing and emulsifying agents. Lutrol also has a history of guaranteed therapeutic administration as it is given orally for the treatment of constipation. It has a moderate melting point as well in the range of 52 – 57 °C making it ideal for the melting procedure. Based on the above mentioned data lutrol is chosen as another coating substance candidate to be used with the in-situ coating process for production of tablets. The only drawback of lutrol is that it has a very high viscosity of, 1000 mPa·s (in comparison to lauric acid discussed in Chapter 4.1.1) [Row09]. This means that a significantly higher operating temperature during melting must be used for the ability to form drops.

4.1.3 Ibuprofen

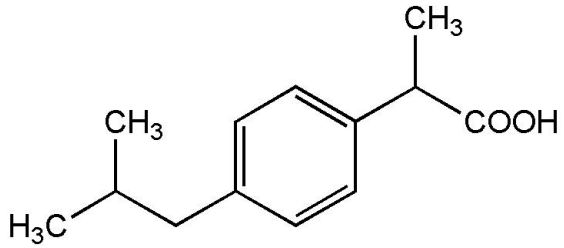


Fig. 4.2 Chemical structure of ibuprofen [Ler97].

Known chemically as 2-(4-isobutylphenyl) propionic acid, ibuprofen belongs to the class of non-steroidal anti-inflammatory drugs. It is marketed under several different trade names by pharmaceutical industries and is an effective treatment for many disorders such as rheumatoid arthritis, and osteoarthritis. It also acts as an analgesic for pain relief and alleviating symptoms of fever and many other conditions. Since it possesses a chiral center, ibuprofen exists as a racemic mixture of the R and S enantiomers where the S enantiomer is the pharmaceutically active form of the drug [Kho14]. The R form, however, undergoes an enzymatically catalyzed chiral inversion inside the body, into the active S form [Kum10]. Ibuprofen exists as a white crystalline fine powder with a melting point range of 75-77 °C [Ler97]. As a drug with a huge pharmaceutical market demand and a strong scientific experimental based history of forming eutectic mixtures with other substances [Sto98], a case study is presented here where ibuprofen is used here as an active pharmaceutical ingredient to be coated using the in-situ coating technology.

4.1.4 Starch

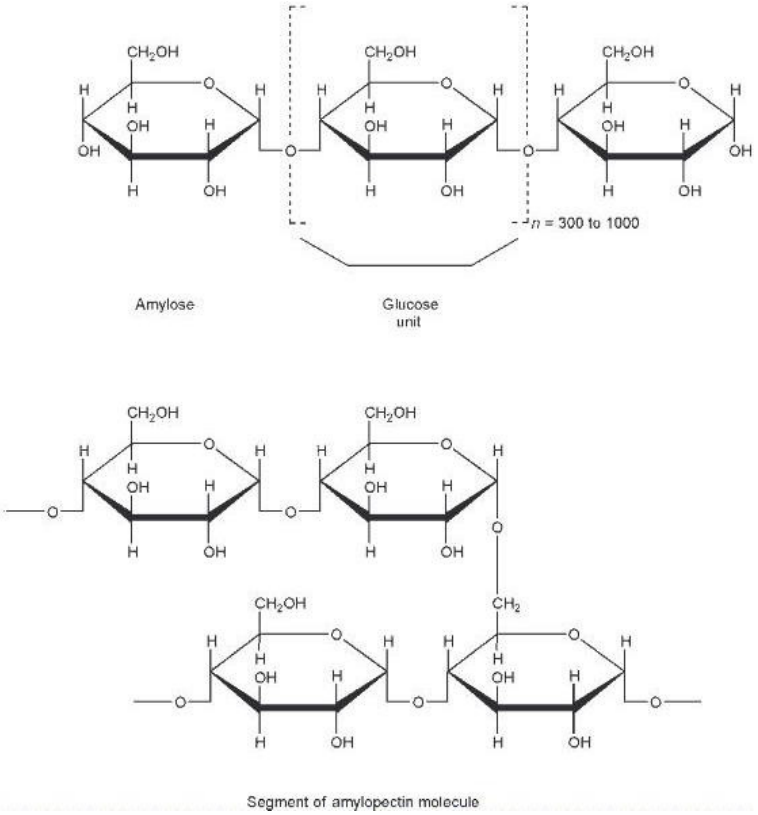


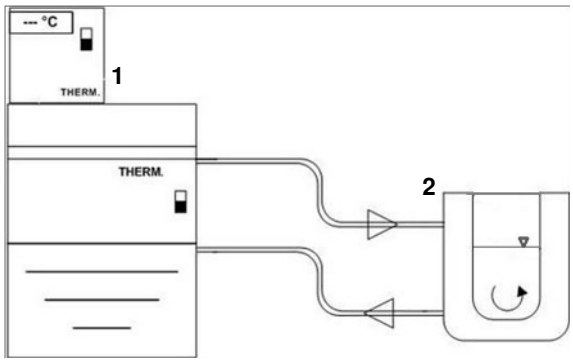
Fig. 4.3 Starch consists of linear amylose and branched amylopectin [Row09].

Starch is a polysaccharide that acts as the primary energy reserve stored in plants during the daily photosynthesis process [Feu14]. This is the main reason why starch can be isolated from many sources such as corn, potato, rice and wheat. Chemically, starch consists of two types of molecules, amylose and amylopectin. The ratio of both molecules is distinctive to the different sources from which starch is isolated. Starch is a widely used pharmaceutical excipient in oral dosage forms as a binder, diluent, and disintegrant. Corn starch occurs as a fine white powder consisting of very small spherical grains with a characteristic size (ranging from 10 to 100 µm) and shape that distinguishes itself from other starch kinds. Most noticeable characteristics of starch are its insolubility in water and its tendency to absorb humidity from the environment as a hygroscopic material [Row09]. These characteristics are useful if the nature of dropping surfaces need to be changed for the advantage of the pastillation process. Therefore starch is used as a material to form seeded bed on the dropping surfaces to facilitate and/or control the drops' geometry and crystallization.

4.2 Methods

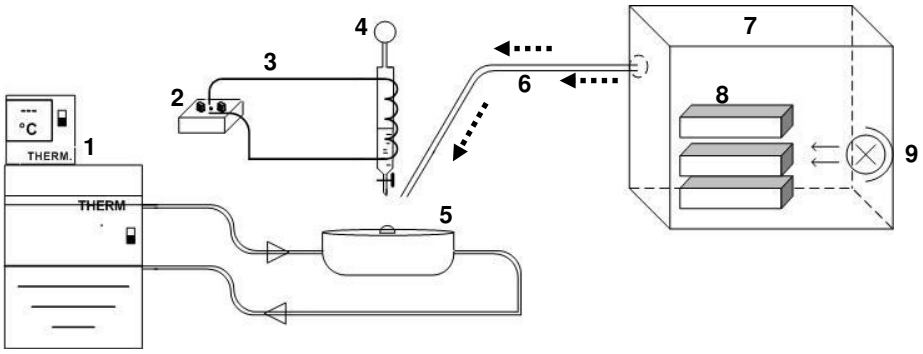
4.2.1 The general experiment of drop forming

The drop forming method is a batch operated lab scale simulation of the industrial pastillation process utilizing the same basic principles of melting, mixing, and cooling a binary solid mixture. However before the cooling step, a necessary step of forming drops out of the homogenous molten mixture is required, and this is where the drop forming method becomes beneficial. Also, this simple batch operated lab scale setup allows a quick and robust drop forming for testing different binary systems for their ability to melt, mix homogenously, and form drops as it is very easily operated, controlled, and cleaned [Bül99], [Ste09].



1. **Thermostat**
2. **Double walled beaker**

Fig. 4.4 Lab scale setup used to melt a binary solid mixture.



1. **Thermostat**
2. **Temperature controller**
3. **Heating wire**
4. **Dropping funnel**
5. **Cooling steel plate**
6. **Air**
7. **Cooling box**
8. **Ice packs**
9. **Fan**

Fig. 4.5 Drop forming and solidifying the molten mixture drops. Cooling from above using air acts as an extra optimization step in some cases [Abo14a].

As to be seen in Figs. 4.4 and 4.5, the drop forming method is composed of two consequent stages. The first step is melting and mixing a binary solid mixture at a specific wt% composition in a double walled beaker. This mixture is being molten at a predetermined temperature inside the beaker which is temperature controlled using a thermostat. Usually using a magnetic stirrer inside the beaker is sufficient for mixing the low volume (test) mixture. However, in some instances where the viscosity of materials is very high it is only possible to use a motorized overhead mixing device to be inserted inside the beaker. After the production of a homogenous molten mixture, the melt is transferred using a 10 mL syringe into the second stage, specifically into the dropping funnel. The temperature of the melt inside the dropping funnel is conserved using a heating wire wrapped around the funnel which is temperautre controlled with an external controller as to be seen in Fig. 4.5. The generation of drops from the funnel is controlled using a simple switch at the lower tip of the funnel, and a rubber bulb at the top of the dropper adds another layer of controlling the flow of the drops out of the dropper. The cooling plate is the platform on which the molten drops and laid, cooled, and crystallized into a tablet product. This is why it is temperature controlled using a thermostat. When the steel cooling plate is set at the desired cooling temperature, the drops are laid onto the cooling surface with the most minimum dropping distance of 0.5 cm. In some cases, cooling from above is a viable optimization step of providing uniform cooling of the drops from the top as it is being cooled from the bottom. In such cases a fan can be fitted in the cool box with ice plates as to be seen in Fig. 4.5 to provide cold air flowing at the upper surface of the cooling plate where the drops are crystallizing. After some time, the drops are fully crystallized into tablet form that can be easily removed from the cooling plate.

This process can be easily repeated to produce the required number of tablets collected for further testing and analysis. The geometry of the tablets is affected by the shape and size of the generated molten drops to a large extent. The drops' shape and size can be directly altered by the distance between the dropper tip and the cooling surface. Moreover, pressing differently on the fitted rubber bulb directly influences the size of the generated drops. For the sake of reproducibility these factors are usually fixed while the cooling temperature of the drops is usually changed unique for every experimental objective. The cooling temperature not only affects the drops' crystallization and the phase separation, but they also play an additional role of producing tablets with different geometries. These results and observations are analyzed, studied and explained in full details in the next respective sections of this thesis. Two model systems are being used in these experiments, namely; lauric acid-ibuprofen (system A), and lutrol-ibuprofen (system B) where lauric acid and lutrol both act as the coating material in their respective systems.

4.2.2 Preliminary analysis and materials' testing

Preliminary analysis is the type of collective analyses done in this project before commencing with the tablet production step using the drop forming method discussed in Chapter 4.2.1. It is a very useful step to gather important information on the to-be-used systems, A and B. There are too many different kinds of analyses that can be done to gather different sorts of information on these systems. For example, thermal gravimetric analysis can give information on the thermal stability of the systems and the absolute threshold of high temperature a system could withstand before its unfavored decomposition. Also XRPD (x-ray powder diffraction) can give additional information on the mixed, molten, and recrystallized components regarding their crystallinity. However, within the scope of this thesis two kinds of analysis were the given the privilege to start with as they are the pillars upon which further experiments will follow as well as they provide the key to understand more about the phase separation taking place within the drops. These analyses are discussed in full experimental details in the next two subsections, respectively.

4.2.2.1 Thermal analysis - Differential scanning calorimetry (DSC)

As known, DSC is useful for providing information on the exothermic and/or endothermic heat transfer occurring within a material that is chemically or physically changing [Atk02]. A thermogram (graphical representation of a DSC result) is mainly dominated by a series of endothermic and exothermic peaks denoting these changes at the respective temperatures. This is clearly tied with the purpose of this analysis in the scope of the project, which is the ability to monitor the change in melting point of the binary solid mixture, lutrol-ibuprofen, as the change in composition, C, (in wt%) proceeds. It is then possible to generate a binary phase diagram of the respective system, in order to study the system from the thermodynamic perspective and be able to choose the composition at which the molten mixture drops should be produced. The composition of ibuprofen in the mixture samples was changed as follows; 10, 20, 30, 45, 55, 70, 80, and 90 wt%. The respective solid samples used in the analysis were prepared via two stage milling process which included milling, mixing, melting, and re-crystallizing the mixtures, followed by another step of milling. This was done to ensure that the sample mixtures were totally mixed to eliminate any possible sources of analytical errors. The melting points of 10 mg of the respective samples were analyzed at a heating rate of 1 K/min using the Netzsch DSC 204 phoenix device. With such a slow heating rate, it is ensured that any minimal changes of heat transfer occurring within the melting sample are recorded resulting in high resolution thermograms. Every DSC measurement was run from 20 to 100 °C. The resulting thermograms of the different compositions were plotted on the same graph denoting the heat transfer (enthalpy of melting) peaks against the respective melting points. Using the melting peak offsets, a binary phase diagram was plotted to explain the eutectic change in melting points of the changing mixture compositions.

4.2.2.2 Viscosity measurements

Viscosity (η) of the molten mixtures is the second important parameter to check. As known from literature, high viscosity tends to impede the mass transfer. Mass transfer in this case is necessary for the solid phase separation to occur successfully within the solidifying molten drop mixture.

For the sake of comparative study, the viscosity of two binary molten mixtures; lauric acid (coupled with cobalt (II) ions – to be explained in Chapter 4.2.3.1) with ibuprofen (system A) and lutrol with ibuprofen (system B), is analyzed using the HAAKE Viscotester VT550 device. The mixture compositions were fixed to constitute 10 wt% of ibuprofen and 90 wt% of the other component for each system, respectively. In addition, the rotational speed used in measurements for both systems was fixed at 150 rps. However, for system A, the viscosity measurement was run from 48 to 90 °C at an increasing rate of 1 K/11 min step. While in system B, the measurement was run from 50 to 108 °C with an increasing rate of 2 K/11 min step. Since heating was mediated through an oil thermostat in the case of system B, the actual stable fixed temperatures at which viscosities were measured were not exactly as the set thermostat temperatures, however, the rate of temperature increase was the same as set. The viscosity in mPa·s was plotted against temperature and the viscosity change is observed in both systems.

4.2.3 Proving the phase separation at the drop scale

This section discusses the different ways to prove the phase separation mechanism taking place within the crystallizing drop of the binary molten mixtures, lauric acid-ibuprofen, and lutrol-ibuprofen. Providing this proof goes in hand with analyzing how effective the phase separation took place in every case and the different ways to improve such a result.

4.2.3.1 Phase separation analysis using colour

Visual analysis using microscopy is a simple straightforward method to prove the crystallization of different solid phases within the lauric acid-ibuprofen tablet. Since both of these materials are white in color it can be difficult to distinguish both solid phases within a tablet. Therefore coloring the coating material, lauric acid, is considered to be able to distinguish the separated solid phases within the tablet's cross section under the microscope. Coloring the lauric acid was done by reacting the lauric acid in a complexation reaction with the colored cobalt [II] chloride (purple in color) [Che11], [Abo14a].

$$[\text{Metal ion}]^{+} + [\text{Fatty acid}]^{-} \rightarrow [\text{Fatty acid – Metal ion complex}] \downarrow \qquad \textbf{(4.1)}$$

The dissolved cobalt [II] ions bind the exposed carboxylic group of the lauric acid, precipitating it in a colored complex. 14 g of lauric acid was dissolved in a 500 mL solvent mixture of distilled water and 99 % ethanol 50:50. The pH of this solution was also stabilized by adding 0.4 g of sodium hydroxide. The mixture was then left to stir giving it time to dissolve while preparation of the cobalt [II] chloride solution took place. 4.5 g of anhydrous cobalt [II] chloride was dissolved in 250 mL of distilled water. After its complete dissolution, the cobalt [II] chloride solution was added to the dissolved lauric acid drop wise using a 50 mL (refillable) dropping funnel while continuous stirring took place within the reaction flask. The mixture was then left to stir overnight and the colored lauric acid was then filtered using vacuum forced filtration, collected, and left to dry completely. The dried complexed lauric acid-$Co[II]^{+}$ was used to prepare the binary solid mixture with pure ibuprofen at the wt% ratio of 90-10 wt%, lauric acid-$Co[II]^{+}$ -ibuprofen. After weighing the solids, they were physically mixed and milled before melting. The drop forming method, discussed in Chapter 4.2.1, was applied to produce the tablets. The mixture was molten at a temperature (same temperature applied for the dropping funnel) of 60 °C for 10 min. The cooling plate temperature was set at 26.5 °C. In addition, cooling the drops from above was applied using a cool box as shown in Fig. 4.5 as soon as the drops were laid on the cooling surface. The air blown by the fan was cooled by passing over the ice placed in the box and the amount of ice was altered so that the air temperature was merely ranging from 15 to 17 °C. Cooling from above was chosen to be at a lower temperature than the actual cooling plate temperature since the contact of the drop with the metal surface results in better heat transfer from the bottom than air does from the top of the drop [Abo14a]. After the production of these colored tablets, two triple layer composites were produced. Triple layer composites are composed of three layers of individually dropped solidified molten components on top of each other. As to be seen in Fig. 4.6, the two triple layer composites were formed of two lauric acid-$Co[II]^{+}$ layers and a different middle layer. The middle layer of composite **A** was a solidified eutectic composition of lauric acid $Co[II]^{+}$ -ibuprofen, 70-30 wt%, while in composite **B** the middle layer was pure solidified ibuprofen, respectively.

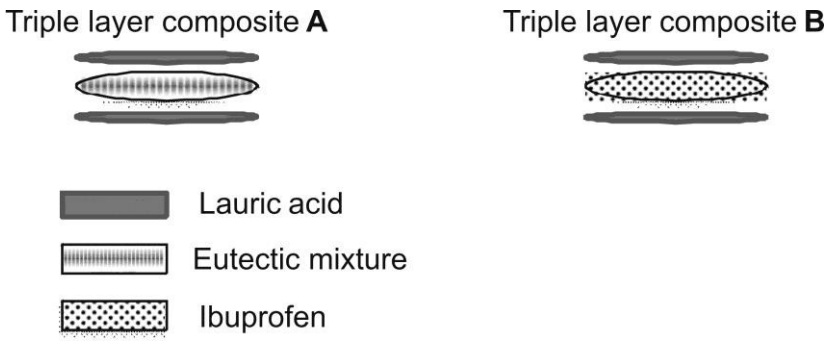


Fig. 4.6 Sketch showing the composition and the order of the dropped layers in both prepared composites [Abo14a].

The composites were simply prepared by dropping the components in their molten states using a preheated pipette tip (60 µL/drop) on the cooling plate, set at 26.5 °C, at the respective order presented in Fig. 4.6 for each composite. The produced colored tablets and the two triple layer composites were sampled to produce a comparable cross section analysis under the light microscope to check their respective cores.

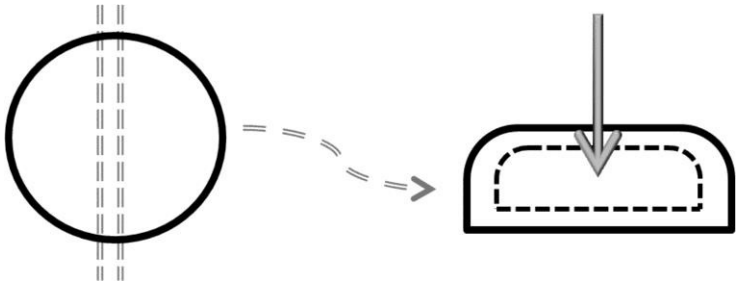


Fig. 4.7 The general microscopic sampling method employed to check the interior structure of the crystallized tablets and/or composites [Abo14c].

A thin cross section was cut from the middle of the tablets and the triple layer composites using a sharp blade. The sections were then checked using the VHX-500FD digital light microscope from Keyence at 100X magnification. This presented method of microscopic analysis in Fig. 4.7 is the general method applied for viewing the cross section of tablets through the frame of the whole project. Pictures of the samples were produced and compared to one another.

4.2.3.2 Online imaging analysis

Online analysis has an old history with monitoring the industrial crystallization processes. Imaging lies as a solid analytical technique within this history as it provides information for control in a direct manner free of the major complications other methods of analyses may suffer from. For example, imaging as an online analytical tool can provide reliable size information when the particles' shape deviates from the ideal spherical shape, which is not the case with most other analytical methods [Chi12]. In this project, online imaging is heavily relied on as a straightforward method to record the changes occurring within a crystallizing drop. As previously mentioned, the two model systems analyzed here are systems A and B, lauric acid-$Co[II]^{+}$ -ibuprofen and lutrol-ibuprofen, respectively. A low zoom ZEISS microscope with 2X magnification has been fitted with a PL-A662 PixeLINK recording camera. This setup was used on top of the small steel cooling plate so that the whole drop was incorporated within the microscopic scope. Different melting and cooling conditions, and different snapshot recording programs were applied for the two respective systems, A and B. This is summarized in Table 4.2.

Table 4.2 Summarizing the different conditions and recording programs for each system.

System A (Lauric acid-$Co[II]^{+}$-ibuprofen)			**System B** (Lutrol-ibuprofen)		
Experimental conditions					
Melt composition [wt%]	Melting temperature [°C]	Cooling temperature profile [°C]	Melt composition [wt%]	Melting temperature [°C]	Cooling temperature profile [°C]
90-10	60	26.5	90-10	90	45-32.5
Recording program					
Shot rate [shots/min]	Total time frame [min]		Shot rate [shots/min]	Total time frame [min]	
1	10		4	25	

The drop forming method was applied using the same binary mixture compositions for both systems, 90 wt% of the coating material and 10 wt% of ibuprofen. Snapshot recording was started once the molten mixture drop of each respective system has been placed on the temperature controlled cooling plate.

Cooling for system A was fixed at 26.5 °C while cooling for system B was started at 45 °C and lowered to 32.5 °C. After the respective experimental time frames depicted in Table 4.2, the experiment was stopped and the resulting images were analyzed using Windows Movie Maker to produce a video of the crystallizing drop. In addition, specific images for each system (for comparison) at defined time points were selected to denote the major changes a drop experiences in the crystallization process as it is being cooled down on the temperature controlled plate.

4.2.3.3 Active ingredient concentration measurement

Ibuprofen concentration measurement in the crystallized drops is very important to study since it acts as a direct way to detect and quantify the phase separation process taking place within the crystallizing layers of the lutrol-ibuprofen drops. Usually, a tablet coating layer is considered impure if it contains a certain percentage of the active ingredient being coated (ibuprofen in this case). Therefore, detecting a difference in ibuprofen concentration between the tablet layers is indeed a clear proof of an actual phase separation taking place at the drop scale. Using ultraviolet spectrometry is a direct way to attain such concentration measurements. However, three pillars are very important to consider demonstrating the efficacy of such a measurement technique in proving the phase separation. Firstly, the production of an ibuprofen calibration curve suited for directly calculating the ibuprofen concentration in the tablets' coat and core. Secondly, the development of a general method to sample the tablets (having a predefined geometry threshold) for the most reproducible concentration measurement results. Thirdly, the production of tablets under different conditions and linking the consequent concentration measurement results with microscopic analysis for the sake of experimental comparison.

4.2.3.3.1 Ibuprofen calibration

Four solid ibuprofen compositions with lutrol were prepared in four 25 mL volumetric flasks. Ibuprofen concentrations were as follows; 10, 20, 30, 45 wt%. Another 25 mL volumetric flask was used to include just lutrol acting as a blank measurement. Using a 50:50 mixture of 99 % ethanol and distilled water, the solids were dissolved in their respective 25 mL volumetric flasks.

The final concentration of sample in each flask was 0.18 %. In each measurement, a 1 mL sample was added to a UV-Cuvette which was placed in SPECORD 40 spectrometer, from analytikjena. The instrument was set to measure the samples at 265 nm to record the absorbance of ibuprofen. Before every measurement, the blank sample was used to set the reference according to which further samples (with ibuprofen) were measured. Every measurement was repeated three times and an average absorbance value was used to plot the calibration curve. Best fit was used to plot the calibration curve of ibuprofen concentration against the respective absorbance of the samples at 265 nm necessary to calculate the concentration of ibuprofen in the to-be-sampled tablets.

4.2.3.3.2 The general method of tablet sampling

Since this is the most sensitive part in the analysis according to which the viability of ultraviolet spectrometric measurement is determined, a universal tablet sampling method is presented in this section.

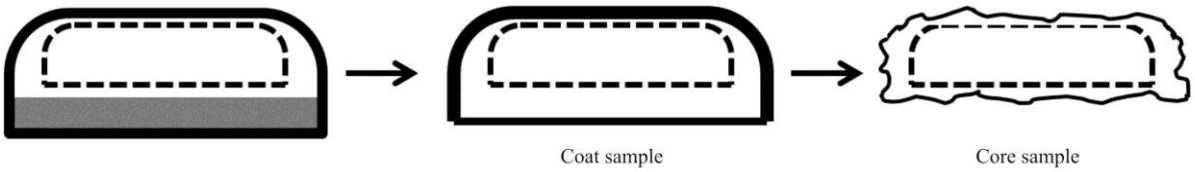


Fig. 4.8 Employing the same way of tablet sampling for the ultraviolet spectrometric measurements ensures reproducibility of the results [Abo14c].

The sampling was done using the appropriate cutting tools (blades) chosen according to the tablet texture and shape. According to the sketch in Fig. 4.8, the tablet is always considered as a thick structure with a specific roundness. Therefore, the final tablets suitable for analysis have to acquire minimal optimum geometry specifications (discussed in the next chapter). As to be seen in Fig. 4.8, the tablet sampling consists of three steps. First, in cases of the presence of a bottom seeds layer (to be discussed in the next chapter), it is removed from the bottom of the tablet as a single compact layer since its inclusion in the analysis may interfere with the ibuprofen concentration measurement giving a wrong conclusion of how successful the phase separation was. Moreover, the coat sample is separated by lightly scratching the tablets from the top and bottom parts. Five tablets were sampled to separate a sufficient amount of the measureable coat sample. The rest of the tablets are milled and mixed and a sufficient amount of the core sample is weighed.

The respective samples are then dissolved in 50:50 solvent mixture of 99 % ethanol and distilled water, to get a final UV sample concentration of 0.18 %. After this, a blank with just pure lutrol is measured with the UV spectrometer as discussed in Chapter 4.2.3.3.1 before measuring every coat and/or core sample.

4.2.3.3.3 Production of lutrol-ibuprofen tablets

The most important aspect in the step of producing tablets is the ability to reproducibly produce the most optimized tablets. Optimized tablets should have a specific geometry that ensures the successfulness of the in-situ coating necessary phase separation. Moreover, these minimal geometry requirements are in terms with the convenient application of the tablet sampling method discussed in Chapter 4.2.3.3.2. The final solidified tablet geometry is of course related to the molten drop geometry on the cooling plate which is related to the cooling surface properties. As a first trial, 90-10 wt% of lutrol-ibuprofen binary molten mixture drops were solidified on differently coated steel plate surfaces set at 40 °C. The different surfaces used were as follows: normal non-coated steel, 100 µm particle sized starch coated surface, lutrol coated surface, and 10 µm particle sized starch coated surface. The starch was treated in the oven at 90 °C for 3 hours to reduce its moisture content. The diameter and thickness of the produced tablets was measured using a digital caliper, and a ratio of diameter to thickness was plotted in a bar graphic representation. Furthermore, lutrol-ibuprofen tablets were produced at different conditions to study their effect on changing the phase separation efficacy in terms of ibuprofen concentration measurements using ultraviolet spectrometry. All drop batches were produced from a 90-10 wt%, lutrol-ibuprofen mixture molten at 90 °C. In addition, the cooling profile was always set to run from 40 to 20 °C at the moment the drops were laid on the cooling surface. Table 4.3 gives an overview on the different conditions employed within the production of every tablet batch.

Table 4.3 Different lutrol-ibuprofen tablet batches were produced using different conditions.

Batch	Starch bed	Power Ultrasound	Top cooling		Lutrol seeding	
		(10 %)	25 °C	40 °C	Top	Bottom
1	+	+	-	-	-	-
2	+	-	+	-	-	-
3	+	-	-	+	-	-
4	+	-	-	-	+	-
5	-	-	-	-	+	+

Power ultrasound (PUS) was used as energy input to initiate and/or control nucleation of the coating material, lutrol, at the drops' surface. This was done by allowing a SONOPULS Ultrasound Homogenizer HD 2070 sonotrode to touch the surface of the crystallizing drop for 2 seconds while on the cooling plate. As to be seen in Table 4.3, the PUS intensity was set at 10 % (out of 97 %). In the second and third batch, top cooling was applied (as shown in Chapter 4.2.1) without using ice. The air temperatures used for cooling the drops were 25 and 40 °C, respectively. The 40 °C temperature was realized by replacing the fan used in the setup with a drier. Moreover, in the fourth batch seeding the drops from the top was done by sprinkling sieved lutrol particles with average size of 0.71 mm on top of the drops. In the last, fifth, batch using a 10 µm starch bed was discontinued and was replaced with a lutrol coated surface which was also used as a top seeding material as in the fourth batch. Representative tablet samples from every batch were used for microscopic analysis and ultraviolet spectrometry that were prepared using the same methodologies discussed in Chapters 4.2.3.1 and 4.2.3.3.2, respectively. In addition, the difference between the tablets' core and coat ibuprofen concentration was calculated using the following formula.

$$C_{AI} = \frac{C_{core} - C_{coat}}{10} \times 100 \qquad \textbf{(4.2)}$$

Concentration of active ingredient [C_{AI}]
Active ingredient concentration in tablet's core [C_{core}]
Active ingredient concentration in tablet's coat [C_{coat}]

In Formula 4.2, the difference in ibuprofen concentration between the core and the coat is divided by the original ibuprofen wt% content in the molten mixture.

4.2.4 Scaling up the process

As a way to verify the results acquired using the lab scale methodology, the drop forming method, scaling up the process is a vital stage in the flow of this project. Since, the drop forming method was used to test new materials with preset conditions for every experiment, it is therefore necessary to make sure that these materials and these condition based experiments would work on an industrial scale using the pastillation device. The 3 meters steel belt was provided by Kaiser Steel Belt Systems, Germany. As to be seen in Fig. 4.9, the belt is temperature controlled with the help of two thermostats that spray water from underneath. In addition, its moving speed can be adjusted with a digital frequency controller connected to the two belt rotors. It is also noticeable that the setup is fitted with a motor operated dropping device which acts as a reliable replacement to the simple dropper used in the lab scale simulation. The dropping frequency and/or speed can therefore be easily adjusted as well. These adjustments or upgrades add a new layer of quality control in terms of producing an optimally fixed product shape by making it possible to simply control the size of the drop. The melt is placed in a temperature controlled reservoir which is not a direct part of the dropper, as was the case with the lab scale simulation.

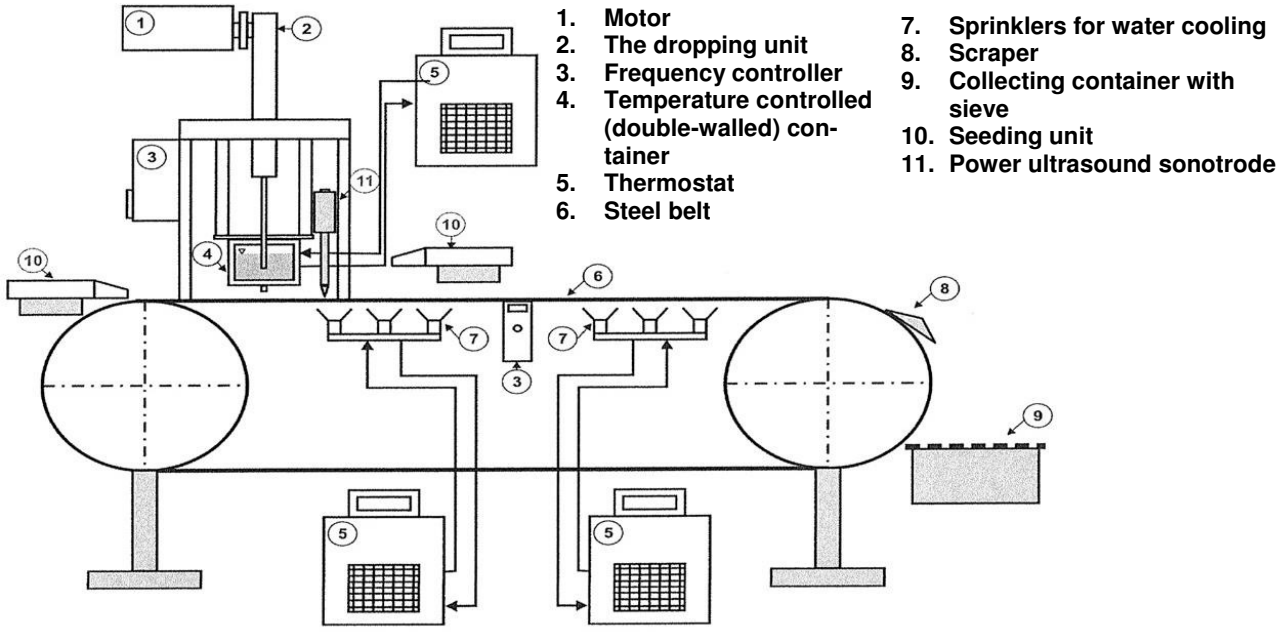


Fig. 4.9 A schematic representation of the industrial pastillation device used for scaling up the drop forming experiment [Ulr14], [Wen15].

Also, means of automated continuous product removal was made possible by simply adding a scraper at the end of the belt. Tools to control nucleation used before (separately) are added to this setup. This includes seeding which is possible by the addition of two automated seeding units (from the bottom and the top) controllable by adjusting their platforms' vibration frequency enabling the user to control the quantity of seeds used. These seeds can be easily recovered at the end of the belt for reuse. In addition, a power ultrasound (PUS) sonotrode has been fixed in position right after the melt reservoir with an adjustable height as to be seen in Fig. 4.9. This industrial pastillation device was operated using two modes of operation, continuous and batch modes. In both cases a 90-10 wt%, lutrol-ibuprofen, binary molten mixture was used to produce tablets. Moreover, 0.71 mm sieved lutrol powder was used for seeding the drops moving on the belt from the top and the bottom. In addition to preparing the temperature controlled steel belt by adjusting the respective cooling program for every mode of operation (see Table 4.4), a uniform lutrol seed layer was produced on the moving surface with the help of the bottom seeding device platform. After the drops are laid on the seeded bed temperature controlled surface, they are seeded from the top with lutrol as well through the aid of the other seeding platform. The cooling temperature used for the solidification of the molten drops in both modes was lowered from 40 to 20 °C. In the batch mode the steel belt was split into two segments according to the zone of effect produced by each of the two thermostats on the cooling belt. Once a sufficient amount of drops were placed after one another on the belt, the belt speed grade was reduced from 98 to 18 (as adjusted on the belt's frequency controller, see Table 4.4) and the dropping was terminated. In the first segment, cooling was set on the thermostat to be lowered from 40 to 20 °C. While the thermostat responsible for cooling the second segment of the steel belt was set at 20 °C directly. At belt speed grade of 18, the drops took a belt residence time of 32 min (16 min/cooling segment) until discharged at the scraper as solidified tablets. The belt residence is the total amount of time the drops were in contact with the steel belt. On the other hand, the continuous operation mode used a simpler approach of identifying the belt cooling temperature program. The thermostat in control of the first segment of the steel belt was set at 40 °C, while the second thermostat of the second segment was set at 20 °C.

Moreover, the belt speed grade was kept at a constant value of 31 (as adjusted on the belt's frequency controller) throughout the whole continuous dropping procedure. This resulted in lower belt residence time of the crystallizing drops of 14 min (for every produced batch).

Table 4.4 Two different modes of operation were applied on the industrial pastillation device.

Mode of operation									
Batch					**Continuous**				
Cooling program									
Gradient cooling					Non gradient cooling				
Belt speed grade	Seeding intensity		Dropping frequency	Total time on belt	Belt speed grade	Seeding intensity		Dropping frequency	Total time on belt
98-18	Bottom: 15	Top: 20	3.14 Hz	16 min/cooling segment	31	Bottom: 15	Top: 20	1.40 Hz	14 min

* Belt speed grade is a number that represents the belt speed as adjustable from the belt frequency controller.

* Seeding intensity is a value that is adjustable on the seeding device controller.

After solidification, the tablets produced from every mode of operation are collected and representative samples for ultraviolet spectrometric analysis and microscopy are studied to assess which mode works best for the most optimized phase separation.

5. Results and discussion

5.1 Results

5.1.1 Preliminary analysis - Differential scanning calorimetry

The change in melting point of the lutrol-ibuprofen successive compositions was investigated through performing a series of DSC measurements. Plotting the heat transfer peaks, represented by the “Offset Y values” against the temperature results in the following thermogram.

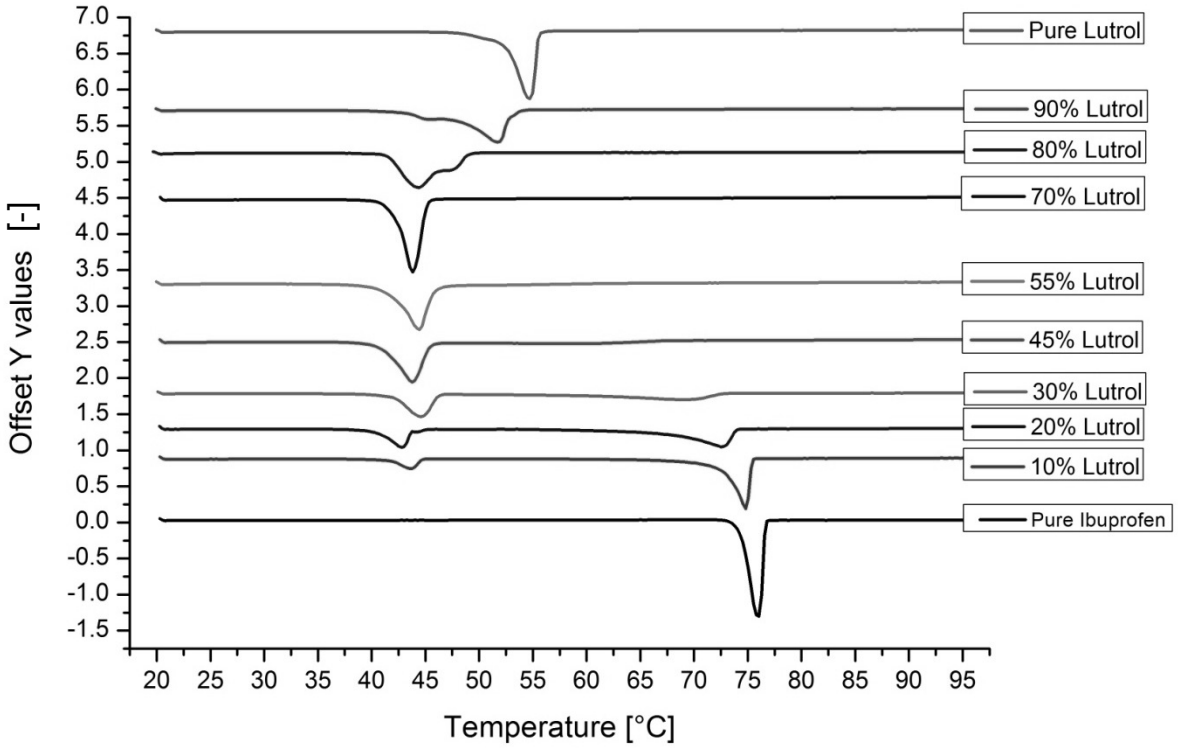


Fig. 5.1 A collective thermogram displaying the various melting point peaks of the different system compositions [Abo14b].

As seen from the graphical representation displayed in Fig. 5.1, the change in lutrol-ibuprofen composition leads to progressive noticeable changes in the melting points. Moreover, the emergence of a new melting point peak can be seen from 90 to 10 wt% lutrol compositions. This observed trend of change is a crucial requirement to plot a phase diagram, which is to be seen in the next chapter.

5.1.1.1 Phase diagrams - Lauric acid and lutrol systems with ibuprofen

In this chapter, phase diagrams of systems A and B, lauric acid-ibuprofen and lutrol-ibuprofen are shown, respectively. Using the melting point peaks' offset values with the respective compositions of lutrol-ibuprofen leads to the generation of binary phase diagrams, as to be seen in Figs. 5.2 and 5.3.

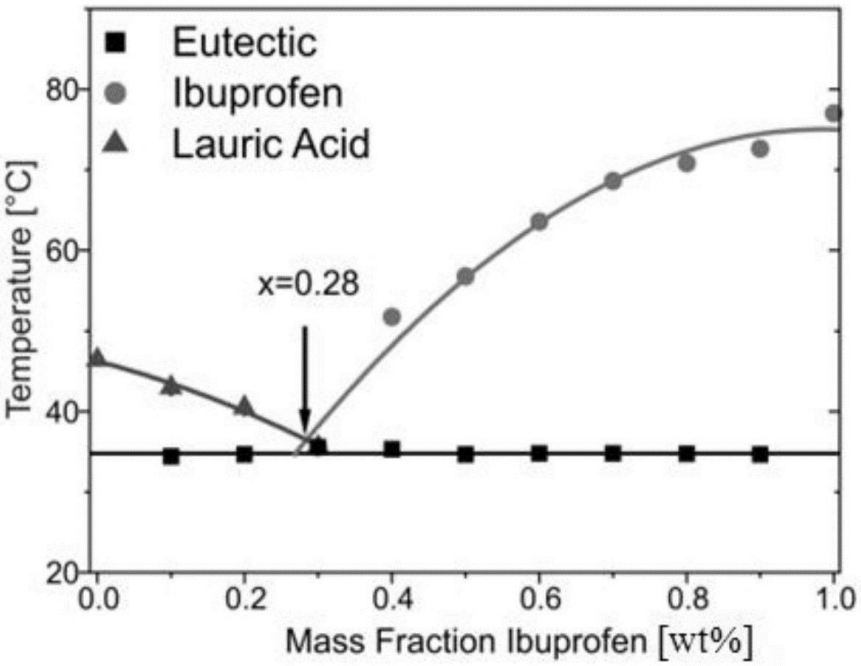


Fig. 5.2 Binary phase diagram for system A, composed of lauric acid-ibuprofen [Ulr12].

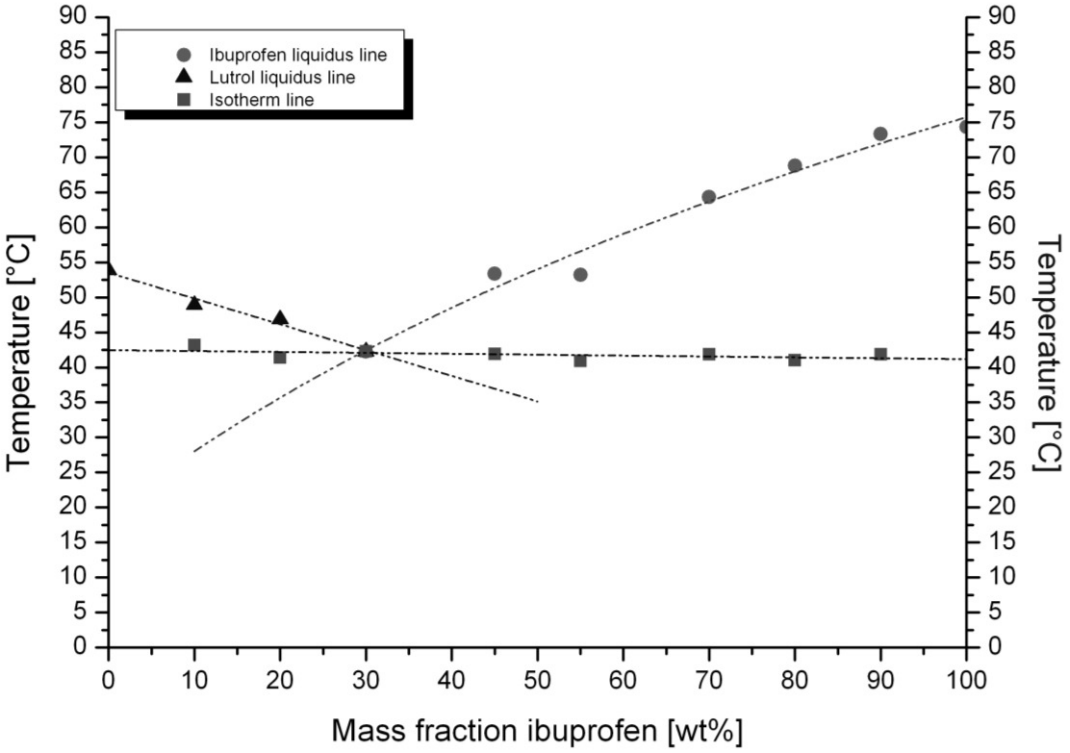


Fig. 5.3 Binary phase diagram for system B, composed of lutrol-ibuprofen [Abo14b].

The continuous change in melting points seen in the thermograms is best represented with the aid of the binary phase diagrams displayed for systems A and B in Figs. 5.2 and 5.3, respectively. As the mass fraction of ibuprofen changes, for both systems, (along with the lauric acid and lutrol mass fractions' change) in the binary mixture, the depression of melting point of pure lauric acid and pure lutrol, at 0 wt% ibuprofen, can be seen. The same description is also viable for the pure, 100 wt%, ibuprofen. In Fig. 5.2, the two liquidus lines for system A, intersect at ibuprofen wt% of 28. While the same can be seen for system B (Fig. 5.3), where this intersection occurs at ibuprofen wt% of 30.

5.1.2 Preliminary analysis - Viscosity measurements

Using the functions displayed in Figs. 5.4 and 5.5, the viscosities of system A and system B, lauric acid-Co[II]$^{+}$ -ibuprofen and lutrol-ibuprofen respectively, are plotted against temperature.

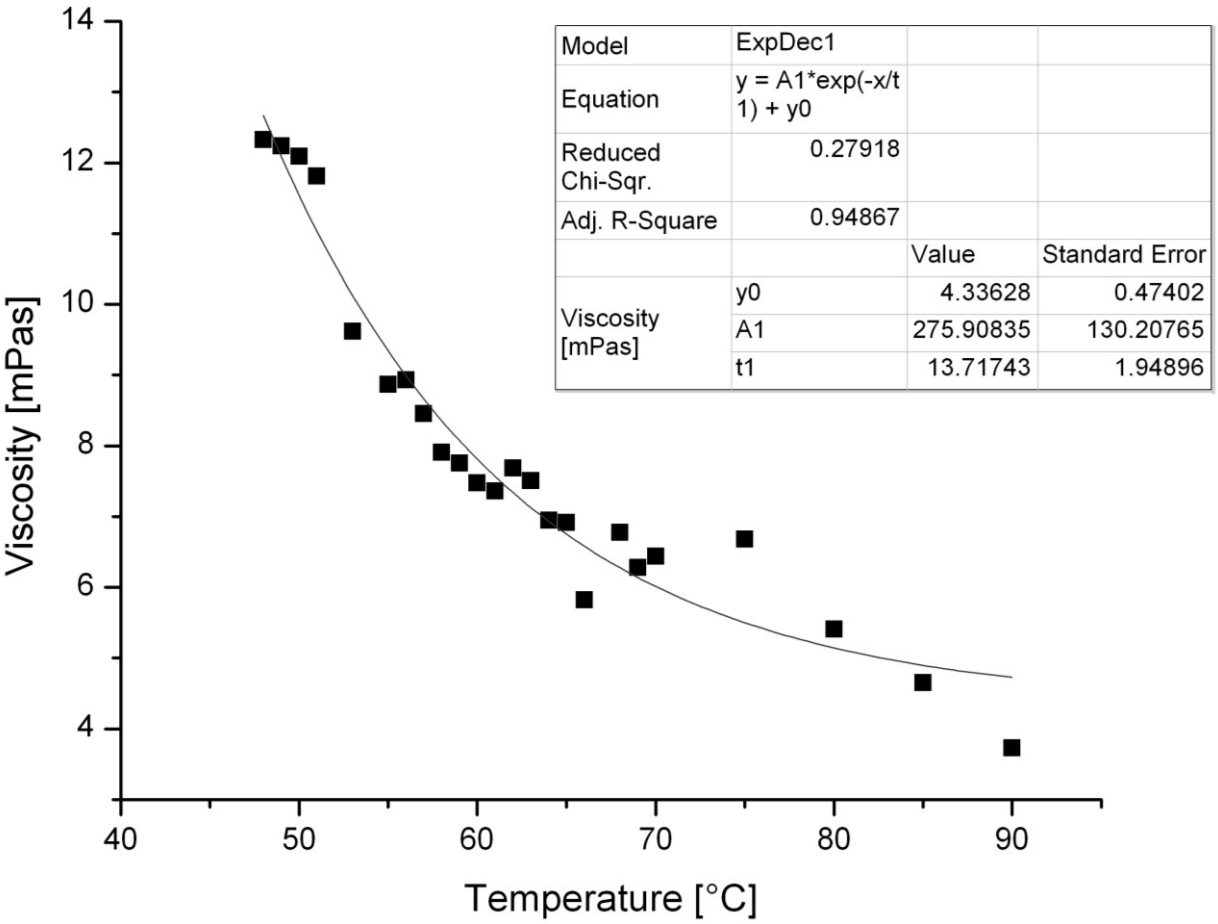


Fig. 5.4 Monitoring the change in viscosity against the temperature for system A [Abo14a].

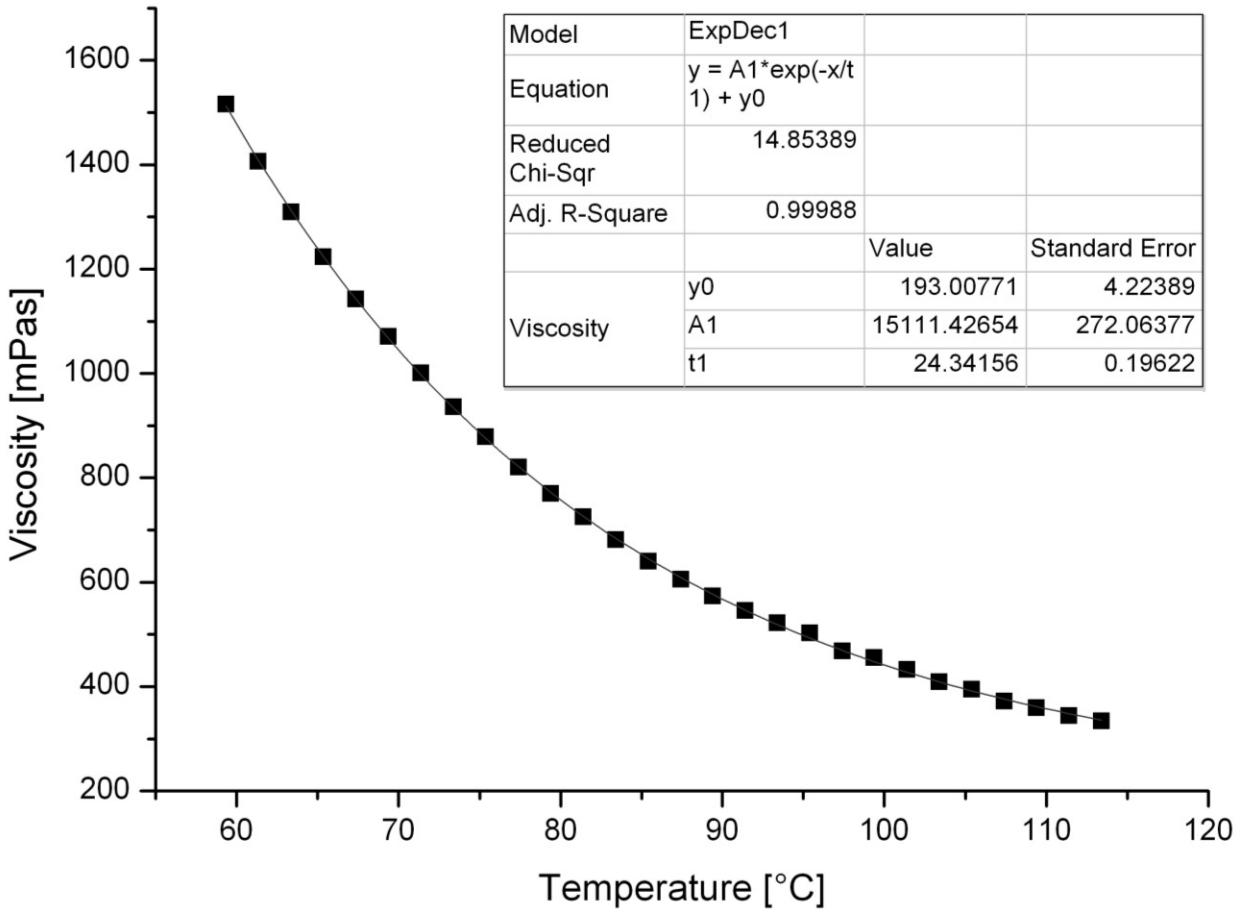


Fig. 5.5 Changes in system B viscosity plotted against the rising temperature.

Despite the large difference in viscosity between both systems, it still decreases exponentially as a physical term when the temperature is increased. In both cases a best fit was acquired using these functions. However, the viscosity measurement for the lutrol-ibuprofen system (system B) in Fig. 5.5 was much smoother than for the lauric acid-$Co[II]^{+}$ -ibuprofen system (system A) in Fig. 5.4, which has much more scattered data points. Upon this measurement, information on the recommended experimental mixing and/or melting temperature can be extrapolated with ease. Moreover, the expected mass transfer within a crystallizing drop can be directly explained and related to when performing the drop forming experiments using both systems.

5.1.3 Phase separation analysis using color

Chemically coupling the lauric acid with cobalt [II]$^{+}$ was successful in the production of colored lauric acid.

Fig. 5.6 Lauric acid after its reaction with cobalt [II] chloride.

As to be seen in Fig. 5.6, the lauric acid coupled with Co[II]$^{+}$ is vividly colored in pink. Mixing the colored lauric acid with ibuprofen as a binary mixture, results in the production of colored tablets.

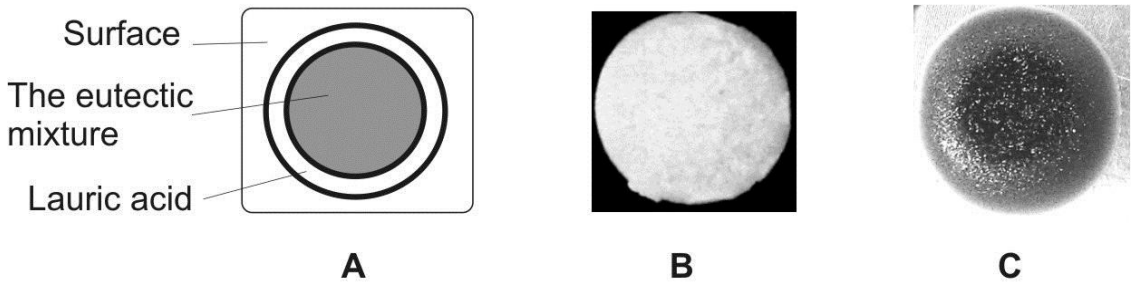


Fig. 5.7 Comparison between how theoretically a tablet should be [A], and how it actually looks [B] and [C] [Abo14a].

In Fig. 5.7, a comparison is done between how theoretically a tablet should crystallize [A] and how an actual produced tablet is using the lauric acid-ibuprofen system [B] and [C]. The difference between the presence of colored lauric acid in the binary mixture and its absence is expressed in the production of colored lauric acid-ibuprofen tablets in [C] as opposed to the completely white tablet in [B]. Moreover, even cooling the produced tablets from above (as they are from below) leads to the production of a significant internal tablet structure.

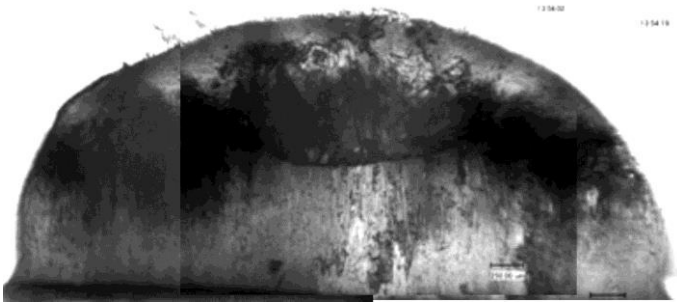


Fig. 5.8 Crystallized lauric acid-Co[II]$^{+}$ -ibuprofen tablet after cooling it from above [Abo14a].

As to be seen in Fig. 5.8, microscopic investigation proves the production of a double layered lauric acid-Co[II]$^{+}$ -ibuprofen tablet. Distinctive colors can be seen within the tablet's cross section. Microscopic analysis comparison between these normally produced tablets with the two triple layer composites **A** and **B** can be seen in Fig. 5.9.

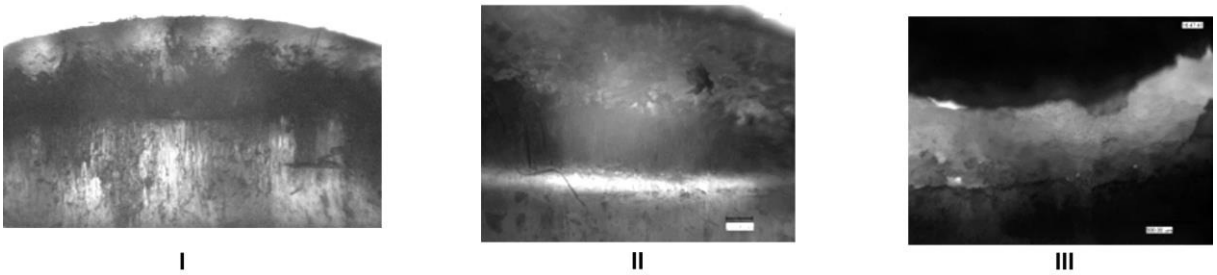


Fig. 5.9 The cross section of a normally produced tablet cooled from above [I], composite **A** [II], and composite **B** [III] [Abo14a].

As to be seen in Fig. 5.9, a dark color dominates the center of cross sections I and II, normal tablet and composite **A**. Cross section III, composite **B** however, possesses a bright white center to be clearly distinguished from the other two investigated cross sections.

5.1.4 Online imaging analysis

Through the procedures discussed in Chapter 4.2.3.2, online sequential imaging was possible during the actual crystallization of the droplets from systems A (lauric acid-Co[II]$^{+}$ -ibuprofen) and B (lutrol-ibuprofen), respectively. Selected images denoting the major changes occurring within a crystallizing droplet are to be seen in this chapter.

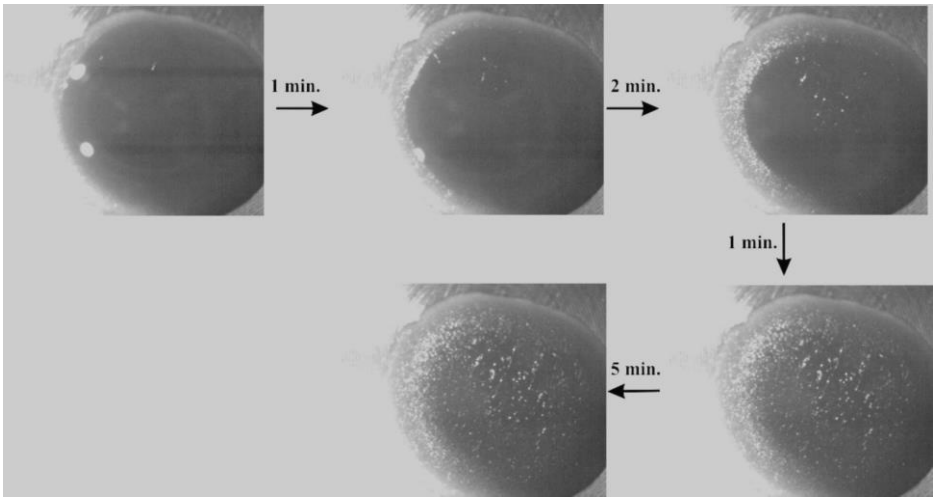


Fig. 5.10 A crystallizing lauric acid-Co[II]$^{+}$ -ibuprofen tablet while on the cooling plate [Abo14b].

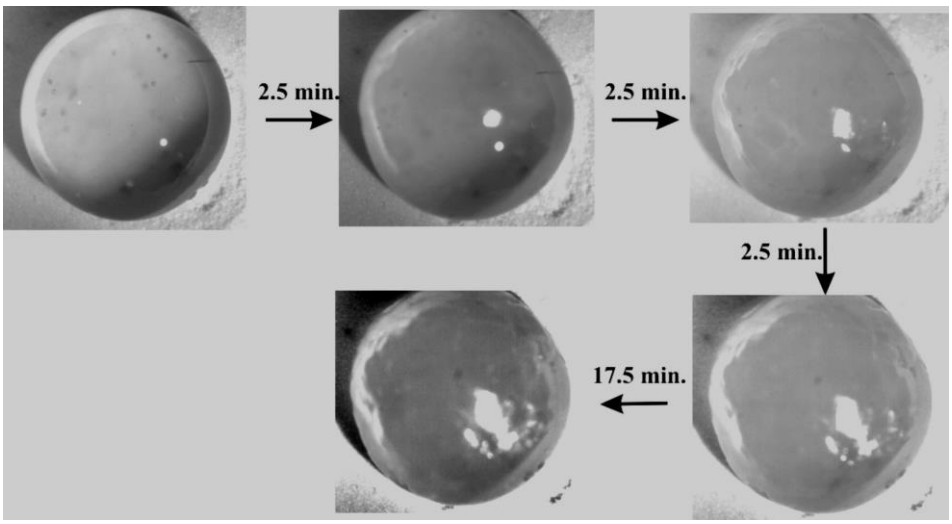


Fig. 5.11 A crystallizing molten droplet from the lutrol-ibuprofen binary mixture [Abo14b].

As can be seen from Figs. 5.10 and 5.11, a concentric circle is starting from the edges of the droplet as it is being cooled down on the plate, towards the center of the crystallizing droplet. The total time after which the drops completely solidify into tablets is different with every system.

5.1.5 Production and UV analysis of lutrol-ibuprofen tablets

Plotting the UV absorbance of successive ibuprofen concentrations, measured at 265 nm, lead to the development of the calibration curve.

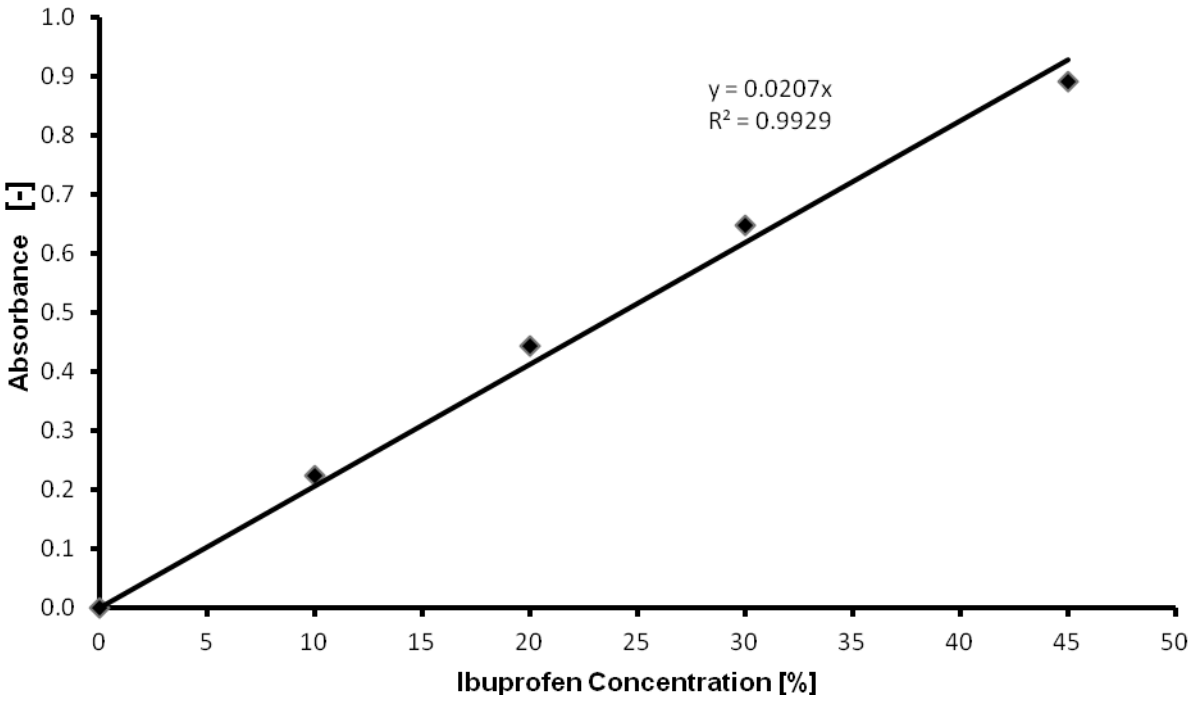


Fig. 5.12 Best fit of ibuprofen concentration calibration data points.

As seen in Fig. 5.12, the calibration of increasing ibuprofen concentrations lead to a directly proportional linear relation with the UV absorbance. Commencing with the first trials of lutrol-ibuprofen tablets production on different coated surfaces and analyzing their geometry resulted in the following bar graph representation.

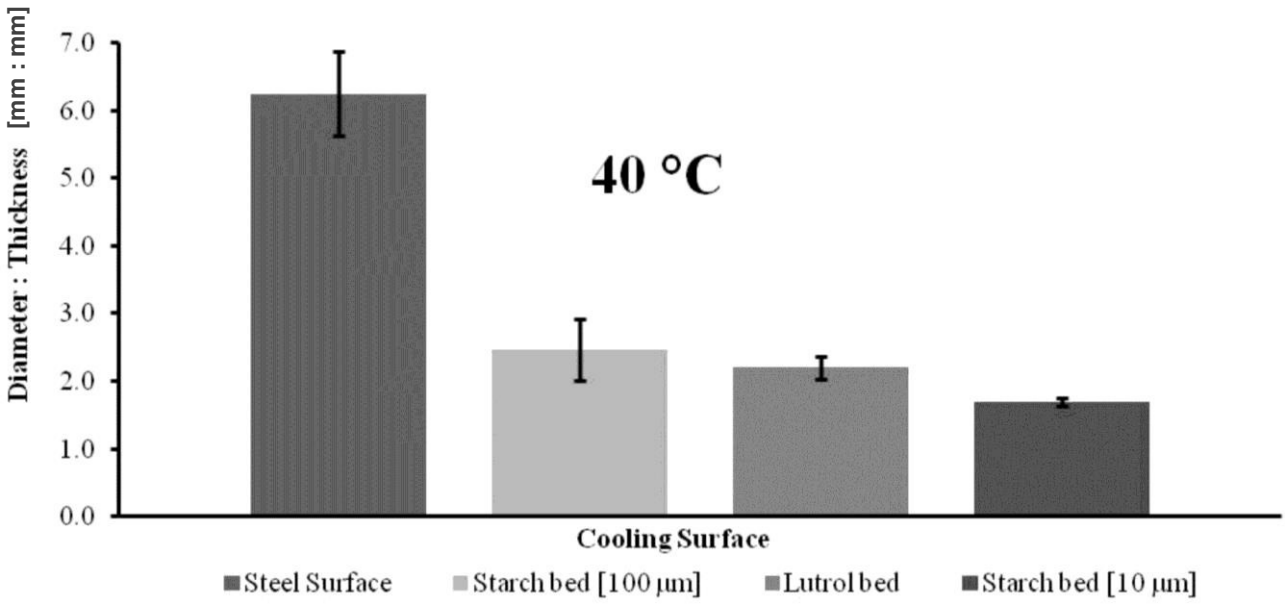
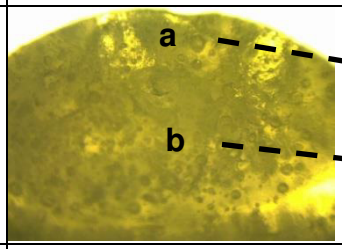
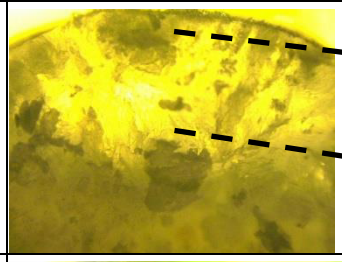
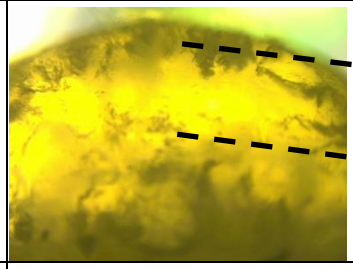
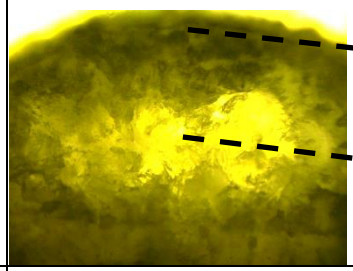
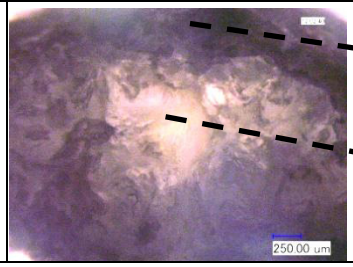


Fig. 5.13 The relation between "Diameter : Thickness" and the production of lutrol-ibuprofen tablets on differently coated surfaces [Abo14c].

As shown in Fig. 5.13, the production of tablets on different surfaces lead to changed geometry settings at a fixed temperature of 40 °C. Moreover, after producing the lutrol-ibuprofen tablets at different conditions (according to Chapter 4.2.3.3.3), and sampling them for microscopic and UV analysis (as done in Chapters 4.2.3.1 and 4.2.3.3.2, respectively), the results generated are as follows.

Table 5.1 Tablet samples from different batches displaying their internal structure along with the UV analysis results [Abo14c].

Batch	**Tablet's core structure** (labeled with ibuprofen concentration) **a**: tablet's coat **b**: tablet's core		**Ibuprofen concentration difference**
1		13.83 % 12.61 %	≈ 0 %
2		14.16 % 14.17 %	0.1 %
3		12.01 % 14.53 %	25.2 %
4		7.80 % 12.25 %	44.5 %
5		7.89 % 10.05 %	21.6 %

After sampling the produced lutrol-ibuprofen tablets from every batch respectively, the ibuprofen concentrations for both the coat and the core were determined. As to be seen in Table 5.1, these concentrations are matched with their microscopic section counterparts. Furthermore, the difference between the ibuprofen concentration in the core and the coat is displayed in the table. This gives a deeper and straightforward understanding to the efficacy of the phase separation.

5.1.6 Scaling up the process

Scaling up the process was done using a uniformly lutrol coated steel belt as to be seen in Fig. 5.14a.

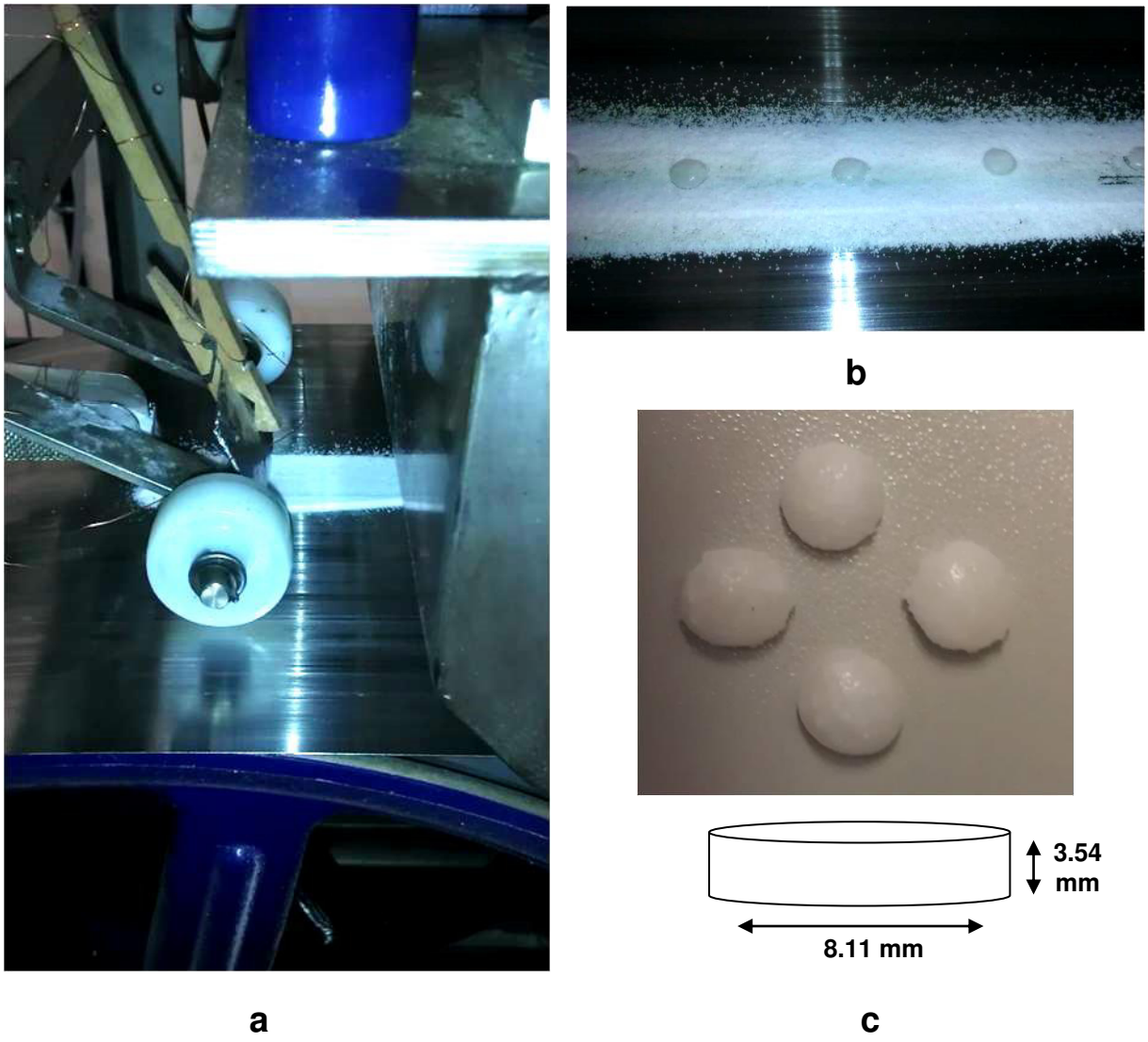
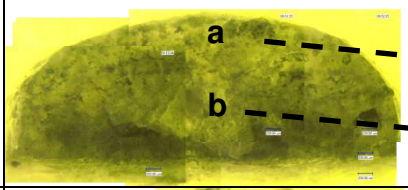
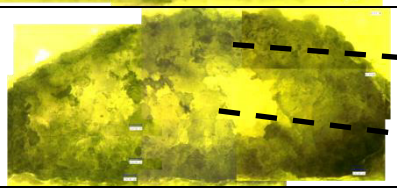


Fig. 5.14 The most remarkable stages in the scale up process (continuous operation) including **a)** compact lutrol coated surface, **b)** controlled dropping of the melt, and **c)** recovery of lutrol-ibuprofen tablets.

Moreover, as to be seen in Figs. 5.14b and c the drop forming device was set to produce uniform looking tablets whose geometry was determined as well. The following results were obtained after investigating samples from the batch and continuous modes of operation.

Table 5.2 Microscopic cross sections from tablet samples from the scaled up operations are displayed with the respective coat and core ibuprofen concentrations.

Batch	**Tablet's core structure** (labeled with ibuprofen concentration)		**Ibuprofen concentration difference**
	a: tablet's coat **b**: tablet's core		
Batch mode		8.89 % 10.02 %	11.3 %
Continuous mode		6.10 % 10.04 %	39.4 %

As to be seen in Table 5.2, a lower concentration of ibuprofen resides in the coating of tablets produced with the continuous mode. Moreover, a higher ibuprofen concentration difference is observed in these tablets as compared to the tablets produced from the batch mode.

5.2 Discussion

5.2.1 Preliminary analysis - Differential scanning calorimetry

The collective thermogram displayed in Fig. 5.1, records the presence of three distinctive peaks. The first peak is that of the pure lutrol, whose intensity starts declining as the mass fraction (wt%) of lutrol starts to decrease within the binary mixture. In addition, starting at lutrol composition of 90 wt% a new peak situated between 40 and 45 °C emerges. That peak starts to increase in intensity as the lutrol composition is decreased, reaching the highest intensity at mixture composition of 70 wt% lutrol. At that specific composition line there is only one melting peak (between 40 and 45 °C). Therefore, 70 wt% lutrol (30 wt% ibuprofen) is the eutectic composition of the lutrol-ibuprofen system. Moreover, this peak is common through lutrol compositions from 90 to 10 wt% which all share the eutectic part of the mixture.

As the amount of lutrol and the eutectic part in the binary mixture continues to decrease while the mass fraction of ibuprofen increases, a third peak emerges starting at 55 wt%, which is distinctive of the melting point of ibuprofen. The energy of melting of that part of the binary mixture (pure ibuprofen) continues to increase recording a maximum at the pure ibuprofen composition. Due to the collective fitting of all thermograms in one graphical representation, the resolution of each curve/composition line limits the ability to view the ibuprofen peaks that emerge at lutrol compositions of 55 and 45 wt%, respectively, from Fig. 5.1. The relation between these melting point peaks and the confirmation of the eutectic nature of such a system is best described with the generation of a binary phase diagram. This is to be discussed in the next chapter.

5.2.1.1 Phase diagrams - Lauric acid and lutrol systems with ibuprofen

As to be seen from Figs. 5.2 and 5.3, the two binary phase diagrams of the lauric acid-ibuprofen and lutrol-ibuprofen systems, generated from the DSC data, share many similarities. Firstly, the two liquidus lines of the two component systems intersect at a specific point. By referring to the phase diagrams, and from the thermodynamic point of view, this point refers to both a specific temperature and a specific composition. At this specific composition the most minimum (specific) melting temperature of the binary mixture is achieved and this is why it is called the eutectic point. At that specific (eutectic) composition, the solid mixture melts in a homogenous manner within the only one and/or same thermodynamic step. All of the other compositions show two melting peaks, yet still, the eutectic melting temperature is one of these peaks. These eutectic temperatures form what is so called, the isotherm line or the solidus line (mentioned in Chapter 2.4). Secondly, within both systems the eutectic composition is very similar to one another. For system A, (Fig. 5.2), the eutectic composition is at 28 wt% ibuprofen, while for system B, the eutectic composition is at 30 wt% ibuprofen. According to the purpose of coating the active ingredient, ibuprofen, with the other component in each system, and according to the nature of the eutectic composition seen in the generated phase diagrams, a small limitation arises. This limitation is based on the little difference of melting points between that of the pure coating material, lauric acid in system A and lutrol in system B, and the to-be-coated eutectic composition having the active ingredient ibuprofen.

For the ease of reference and/or description, this difference is to be called the gap of separation. That specific gap of separation is of great concern, in comparison to the other gap situated at the other side of the phase diagram, in Figs. 5.2 and 5.3, because the choice of the mixture composition from which the coating procedure is applied should be based on two characteristics. First, it should be a composition formed mostly of the coating substance (i.e. < 30 wt% ibuprofen), to be chosen from the left hand side of the eutectic point, since coating should be started from the outside of the molten drop to the inside as heat transfer proceeds starting with the crystallization of the coating material (as described in Chapter 2.5). Second, the mixture composition should be chosen as the farthest point away from the eutectic point for an increased gap of separation. This results in the realization of more purification steps (according to the description in Chapter 2.5) before the crystallization of the eutectic composition within the crystallizing drop's core starts, leading to the production of coatings with higher purity (in case of optimal crystallization conditions). This is why, in both systems, a binary mixture composition formed of 90 wt% coating material and as little as 10 wt% ibuprofen is chosen to be the starting mixture from which molten drops are formed. The low included amount of ibuprofen is of an issue from the practical and/or applicable point of view, but since these are just starting model systems to test the primary viability of the technology, it is not of a big concern in this study. All in all, the eutectic properties proven through the generated phase diagrams respective of each system, makes these two systems suitable for applying the drop forming method for the production of coated tablets.

5.2.2 Preliminary analysis - Viscosity measurements

By comparing the viscosity measurements of both systems, A and B from Figs. 5.4 and 5.5, respectively, two conclusions can be deduced. Firstly, as viscosity is a physical term that is dependent on the applied temperature, it decreases when the temperature of the melt for each system increases. Secondly, that the viscosity of system A (lauric acid-$Co[II]^{+}$ -ibuprofen) is much lower than the viscosity of system B (lutrol-ibuprofen) at the respective coating material to ibuprofen wt% ratio of 90:10.

This results in a lower melting temperature necessary to prepare the molten system A appropriate for dropping (60 °C as mentioned in Chapters 4.2.3.1 and 4.2.3.2), which in turn means lower energy consumption than system B which demonstrates drop forming applicability at 90 °C. Moreover, the risk of reaching extremely high temperatures that could result in the decomposition of the active ingredient is always lowered when working at lower melting temperatures as in system A. In addition, the lower viscosity of the melt, in theory, aids the molecular mass transfer whilst the crystallization process is taking place within the drop, resulting in a better phase separation. Furthermore, the difference between both Figs. 5.4 and 5.5 is also reflected in the increased scattering of the data points that is noticeable in Fig. 5.4. This is because the instances where the temperature was unstable (changing) were much more frequent using the oil thermostat for system B (in Fig. 5.5) than for system A (in Fig. 5.4). Therefore, these non-equilibrated temperature and viscosity data points were excluded when developing the viscosity plot of system B for a clearer representation.

5.2.3 Phase separation analysis using colour

Fig. 5.6 shows the result of the complexing reaction that took place between the white lauric acid and the colored cobalt [II] chloride. The produced colored lauric acid when dried exists in the form of fine colored powder. The colored lauric acid is of great significance to the success of the visual analysis as proven through Fig. 5.7. Theoretically a crystallized drop undergoing the successful phase separation process should have a crystallized outer layer of the coating material, here lauric acid, and the eutectic composition residing in its core. By mixing lauric acid with ibuprofen in a 90:10 wt% ratio and applying the drop forming method the resulting tablets are plain white in color, as seen in Fig. 5.7B. Therefore, no resemblance can be seen with Fig. 5.7A. However, applying the drop forming method using a binary mixture between the lauric acid-$Co[II]^{+}$ and ibuprofen with the same wt% ratio results in the formation of colored tablets with two distinctive colors. In Fig. 5.7C, the outer layer is lightly colored, while the core of the crystallized drop is much darker. Differentiation between the respective layers of the outer coating and the inner core can therefore take place.

By comparing the theoretical sketch of the crystallized drop (A) with the actual colored tablet (C) it is clear that the composition of the tablet's outer layer is different from the composition within its core. This is a clear sign that phase separation has taken place during the crystallization of the drop according to the phase diagram discussed in Chapter 5.2.1.1. However, the result displayed in Fig. 5.7C needs reconsideration during further production since it is unexpected to be able to view the tablet's core simply from above if the tablet should be coated evenly from the top as the bottom. The reason the coat was only crystallized within the tablet's bottom is that the bottom of the drop is the only part that is in direct contact with the temperature controlled cooling plate. This is a clear indication that non-uniform drop cooling was the cause behind that. In order to directly tackle this problem, cooling the drops from above was done as soon as the drops were placed on the cooling plate. This was done through the setup and methodology described in Chapters 4.2.1 and 4.2.3.1, respectively, where a cooling box was used. As to be seen from the microscopic cross-section of a drop cooled from above, a lightly colored solid phase has crystallized within the two opposite sides of the tablet (the top and the bottom), while the darker solid phase (also seen in Fig. 5.7 C) has crystallized within the inner core of the tablet. However, through a closer look at the tablet's cross-section displayed in Fig. 5.8, it is clearly observed that the tablet's lightly colored phase from above is much thinner than from below. This is expected, since as mentioned in Chapter 4.2.3.1 the heat transfer through air is less efficient than from the direct contact with the temperature controlled cooling plate from the crystallizing drop's bottom. However, at this point, how is it possible to make sure that the lightly colored phase consists of lauric acid-$Co[II]^{+}$ while the dark phase consists of the eutectic mixture? To prove the identity of the tablet's different layers and since this chapter mainly deals with visual microscopic analysis, the triple layer test is considered. This test mainly deals with differentiating and identifying the different layers of the lauric acid-$Co[II]^{+}$ -ibuprofen tablet that was cooled from above as well. For that to be done, two triple layer composites were produced as described in Chapter 4.2.3.1. By comparing the normally produced tablet with the two triple layer composites through Fig. 5.9, the identity of the tablet's layers can be deduced. Purely dropped molten ibuprofen (middle layer) in composite B looks as a bright white crystalline material after cooling the composite.

This is to be easily differentiated from the structure and color of the dropped eutectic mixture, 70:30 wt% of lauric acid-Co[II]$^{+}$ -ibuprofen, (middle layer) in composite A which is observed as a dark phase under the microscope. However, the produced composite A looks identical to the normal tablet produced using a 90:10 wt% molten mixture of lauric acid-Co[II]$^{+}$ -ibuprofen. This proves two major facts about this specific solid phase separation. Firstly, that the lightly colored phases seen in Fig. 5.8 consist mostly if not entirely of lauric acid-Co[II]$^{+}$, the coating material. Secondly, that the darker phase residing in the tablet's core, in Fig. 5.8, consists of the eutectic composition (according to the phase diagram displayed in Fig. 5.2) that shares the same microscopic crystalline structure and color with the actual eutectic mixture dropped in the middle layer of composite A.

5.2.4 Online imaging analysis

Analyzing the produced tablets' layers and relating them to the eutectic compositions according to the phase diagrams displayed in Figs. 5.2 and 5.3 is solid proof of the success of the phase separation, the whole process, and methodologies related. But, what is even more important is proving the theory behind the phase separation process. This is done in this chapter using the theoretical phase diagram discussed in Chapter 2.5. The step wise growth of the outer coating layer on the crystallizing drop described in Chapter 2.5 can be seen in Figs. 5.10 and 5.11. As to be seen from both figures, an outer circle forms at the boundary of the crystallizing drop and as cooling continues this circle constricts towards the middle of the drop. The constriction is due to the growth of the outer coating layer (lauric acid-Co[II]$^{+}$ in Fig. 5.10 and lutrol in Fig. 5.11) on the drop's surface as the cooling takes place. As heat transfer continues, finally reaching the inner core of the drop (situated in the middle) the drop's inner core crystallizes with a different solidified structure and/or color than the growing (constricting) outer layer. The different structure in the middle of the crystallized tablet is due to the crystallization of the eutectic composition in the tablet's core (proven for the lauric acid-Co[II]$^{+}$ -ibuprofen tablets in Chapter 5.2.3). Thus, the phase separation mechanism is not only studied and understood with the aid of the phase diagram, but it can also be seen and described with the aid of visual analysis. Moreover, additional useful information exclusive for every system can be extracted from the online imaging analysis done in this section.

For instance, the total time needed to obtain fully crystallized drops for the two systems is different. The lauric acid-Co[II]$^{+}$ -ibuprofen drop took around 5 minutes while the lutrol-ibuprofen molten drop took around 17.5 minutes to fully crystallize into a final product. This information is particularly useful to consider if the tablet production is to be done on an industrial large scale to predetermine the time needed for the production of different tablet batches. By looking at Figs. 5.10 and 5.11 it is also important to note that the constriction of the outer layer from the boundaries of each respective drop is noticeably different. This constriction or the growth of the outer coating layer towards the center of the drop is much more restricted in the case of the lutrol-ibuprofen system (Fig. 5.11). As mentioned in Chapter 4.1.2, lutrol is a synthetic co-polymer, and this results in giving an overall significantly higher system viscosity than the other system of lauric acid at the same melting temperature. This high viscosity becomes even higher as the drop is being cooled down into a tablet (on the cooling plate) thus restricting the mass transfer necessary to achieve the phase separation between the respective solid phases of the system. This finding is clearly in agreement with an already developed theory [Ger09]. Nevertheless, this system will be used as a model to produce tablets using the drop forming method in a trial to prove the phase separation process in the next chapter.

5.2.5 Production and UV analysis of lutrol-ibuprofen tablets

The best fit plotted in Fig. 5.12 aids in calculating the ibuprofen concentration in the produced lutrol-ibuprofen tablets. This can be done by direct extrapolation of the to-be-known absorbance of the prepared tablet sample at UV wavelength of 265 nm. The significance of using the ibuprofen concentration measurement as indicative of the phase separation is understood from Chapters 2.5 and 5.2.4 where the highlights of these chapters mainly revolves around the formula of, a successful phase separation equals crystallization of a pure outer coating on the whole outer surface of the drop ending with crystallization of the eutectic composition within the drop's core constituting the eutectic composition and the crystallization of the active ingredient, ibuprofen, for the first time. Therefore this chapter mainly discusses the possibility to produce a pure lutrol coating, with lowest ibuprofen concentration, on the crystallizing drop's surface and a significantly higher ibuprofen concentration within the drop's core.

The better this formula is realized, the better is the quality of the phase separation. However, for this to happen drops with minimum geometry requirements have to be studied and produced. It can be even seen according to Chapter 2.5, that the perfect theoretical phase separation is described on the basis of having a perfectly round crystallizing structure. But due to the nature of the drop forming method and the involvement of laying the drops from a minimized dropping distance on a cooling plate, a certain degree of non-favored drop spreading has to occur. The extent according to which the drop starts spreading as it is laid on the cooling plate (in its molten state) till the point where crystallization takes over depends on the nature and/or material properties of the cooling plate. To determine the best surface that offers the lowest drop spreading, a trial of dropping lutrol-ibuprofen tablets on differently coated surfaces (at the same cooling plate temperature, 40 °C) is discussed here. In Fig. 5.13 the lower the diameter to thickness ratio is, the less is the drops' spreading and the more round the crystallized tablets are. As to be seen from Fig. 5.13, laying the lutrol-ibuprofen molten drops on the bare steel surface results in the highest diameter to thickness ratio, >6, indicating maximal spreading of the drops. By forming a compact bed of starch (with mean particle size 100 µm) on the same surface and using it for laying the drops, the ratio marked a significant decrease from >6 to >2. Replacing, however, the 100 µm particle sized starch bed with a rough lutrol bed marked only a slight improvement of tablet geometry. Finally, by coating the surface with lower particle sized dried starch of 10 µm, the diameter to thickness ratio of the produced tablets has dropped to the lower range between 1 and 2, as shown in Fig. 5.13. This marks a big improvement in comparison with all other surfaces on which tablets were produced. It can be concluded from Fig. 5.13 that starch is a perfect material to produce the lutrol-ibuprofen drops on for providing less drop spreading, yet still slight differences exist. The higher spreading of the drops on the larger particle sized starch bed in comparison to the drops on the smaller particle sized starch bed, was due to the ability to obtain a more compact coated bed with the case of the smaller particle sized starch which offered lower amount of spaces or grooves on the dropping surface where spreading could otherwise occur. Moreover, despite it not being the best for geometry, the roughness of lutrol also makes it a very good material to produce well round tablets on. Lutrol can also be considered an alternative surface coating material since it gives an exclusive advantage of seeding the drop's surface with the same coating material used in the melt.

As a general conclusion from this test low particle sized starch of 10 µm offers the lowest spreading of the drops on the surface, and the highest produced tablet roundness, therefore it is used for further experiments involving the production of lutrol-ibuprofen tablets. As to be seen in Table 5.1, microscopic cross-sections of lutrol-ibuprofen tablets produced at the respective conditions listed in Table 4.3 are displayed. Also, the measured ibuprofen concentration from the different sampled tablet layers are labeled on the microscopic cross-sections. This gives a direct proof that the different layers of the tablets seen under the microscope constitute different ibuprofen concentrations which indicates that a phase separation is taking place. Different optimization conditions are tried with every tablet batch to analyze the direct effect on the phase separation. Batch 1 drops were treated with power ultrasound (PUS) to deliver an extra energy input capable of forcing the crystallization of the coating material, lutrol, to kick start on the drop's surface. In Table 5.1, the representative sample displayed from Batch 1, does not show any distinctive layers under the microscope. However, the whole cross section is a single crystallized structure. This is because treating the crystallizing molten drop by immersing the PUS sonotrode on the surface at the lowest intensity of 10 % resulted in extra mixing of the drop contents while its crystallization was taking place. This is reflected in the UV analysis where the percentage of ibuprofen in the coat and the core is almost the same indicating no separation taking place. Cooling the drops from the top to achieve even drop cooling from all sides is always considered a viable straightforward option to optimizing the separation (as proven in Chapter 5.2.3). Cooling the lutrol-ibuprofen drops was done from the top at two different temperatures, 25 and 40 °C, for Batches 2 and 3, respectively. Cooling the drops from the top, at 25 °C, results in a faster crystallization of the drops into full tablets which is against providing the most optimum kinetics necessary for the phase separation to be successful. This can be seen as a very thin dark coating layer is formed on the top while the crystallized eutectic phase dominates the mid top cross section of the tablet. Also nearly, no phase separation was observed in this case with ibuprofen concentration difference between the core and the coat of 0.1 %. However, proceeding with the process at a higher cooling temperature (40 °C) from the top satisfies the prerequisite of providing more optimized kinetics, for the crystallization of the two solid phases to proceed in a separate manner.

This results in a thicker top layer in comparison to Batch 2, and an outer coating ibuprofen concentration of 12.01 % which is lower than the core concentration of 14.53 %. Phase separation is therefore detectable here with an ibuprofen concentration difference of 25.2 %. As cooling from the top was tried with two different temperatures, seeding the molten lutrol-ibuprofen drops from the top has been tried using two different strategies in Batches 4 and 5. In Batch 4, lutrol was sprinkled on top of the crystallizing drops as soon as they were laid on the starch coated surface. The result is an extensive proof of the phase separation process that took place within the crystallizing drop, proven by microscopic analysis and UV analysis. It is clear from the microscopic cross-section displayed at Batch 4 in Table 5.1, that two dark layers from the top and the bottom of the tablet surround a brighter core. To explain the reason behind these differences in crystalline structures between the coat and the core, the composition of these layers should be studied. The coat UV analysis recorded the presence of ibuprofen impurities in the tablet's coat of 7.80 %. While the core ibuprofen concentration was 12.25 %, and a difference in ibuprofen concentration between the respective layers of 44.5 % was calculated. Substituting the starch seeded bed with a lutrol bed in Batch 5, however, did not yield any significant improvement regarding the concentration values as seen in Table 5.1. Yet, tablets with similar coat ibuprofen impurities were produced. The lower difference in ibuprofen concentration calculated for Batch 5 was, however, due to the lower ibuprofen concentration detected in the core of tablets from Batch 5. This was due to the inclusion of external lutrol seeds (from the seeded bed) that were sticking to the bottom side of the tablets during sampling of the tablets' cores for the UV analysis and concentration measurement. This resulted in a dilution of the ibuprofen concentration measured within the tablets' cores. Since using starch and lutrol seeded beds in the process of tablet production yielded similar results, lutrol is to be considered as the favored bottom seeding material for the production of lutrol-ibuprofen tablets on a large scale (during scaling up the process), and this is due a variety of reasons. Firstly, as mentioned in Chapter 4.1.4, starch is a very hygroscopic material that absorbs humidity from the environment and this fact results in two consequent limitations. Firstly, the need to dry starch in the oven for long periods of time at a high temperature will result in a higher overall energy consumption of the process which is economically unfavored.

Secondly, the production of consistent product quality (regarding geometry and phase separation) will be of a question when working with the process for longer periods of time where starch will continuously be in contact with the surrounding air absorbing humidity and deteriorating in quality over time. Moreover, the granular nature of lutrol (even after sieving it to a smaller particle size) gives it excellent flow properties when using it for forming an evenly compact seeded bed layer on the moving steel belt.

5.2.6 Scaling up the process

Simply put, tablets are solid preparations that contain a single dose of one or more active ingredients [Swa07]. Other sources stress on the compression step of tabletting where tablets are defined as solid unit dosage forms made by compaction of a formulation containing the drug and certain fillers or excipients [Lie89]. Excluding the compaction step that is exclusive to the conventional tabletting methodology, the resulting product of this study, in fact, fits the previously mentioned tablet descriptions. Since the crystallization of drops through the drop forming method results in the production of tablets, it is only a direct implication to consider applying such method of tablet production on an industrial scale. Also, utilizing the exclusive property of phase separation through crystallizing a binary eutectic melt results in an added advantage of coating and producing the tablets in one step. This gives many reasons to transfer the process of the simple drop forming complete with the full set of predetermined melting, cooling and seeding conditions onto an industrial scaled up process which can be considered in the future for serious application within the pharmaceutical industries. Scaling up the process enjoys many advantages over the lab scale simulation. Most importantly is gaining tight control over the dropping process through changing the steel belt speed, and changing the rate of dropping which in turn gives control over the size and the shape of the drop. This gives consistency in production which can be seen from Figs. 5.14a and b that shows lutrol-ibuprofen drops placed on the lutrol coated moving steel belt with equal distances from one another. In addition, the consistency carries on through the final product quality in terms of geometry where in Fig. 5.14c, the produced tablets are shown to be similar in size and shape.

The tablets therefore enjoy very acceptable roundness where the average diameter to thickness ratio is a little above 2, which matches the previous geometry result displayed in Fig. 5.13 (producing the lutrol-ibuprofen tablets on a seeded lutrol bed, lab scale). The need to operate the industrial scale steel belt in continuous operation mode is evident. By looking at Table 5.2, it can be noticed that tablets produced by the continuous mode gave a higher separation of ibuprofen concentration between the tablets' core and coat (39.4 % for continuous mode, and 11.3 % for batch mode). As explained in Chapter 5.2.5, this means a better phase separation efficiency operating the device within a continuous operation. Moreover, it is further proven by the microscopic pictures, in Table 5.2, that show a clear separation of layers in comparison to the microscopic cross-section displayed for the batch mode. The main reason for this is that operating the steel belt in continuous mode ensures that all of the crystallizing drops face the same exact cooling and seeding conditions. Difficulties during operating in batch mode include: some drops (the last few) were crystallized even before reaching the top seeding platform when the belt was slowed down as explained in Chapter 4.2.4. In addition to this non-uniform seeding, non-uniform cooling as well was another implication to changing the belt speed as another set of drops was transferred faster to the second cold segment of the belt (fixed at 20 °C), as compared to another set that stayed longer within the gradually cooling 40-20 °C belt segment. These difficulties give a large variation in the produced tablets regarding geometry as well as the efficiency of the phase separation. This is against one of the main purposes of this scale up which is to improve the final product overall quality and assure reproducibility of the pastillation process for tablet production using melt crystallization.

5.2.7 The general process flow scheme

After the several experimental trials performed within the process of application of melt crystallization (through the pastillation process), combined with literature research to form coated tablets using different systems, different conditions and consequent results explanation, a sequential process specific flow scheme was developed just for that purpose. This flow scheme is generalized to deal with the main challenges that will be commonly faced during application of such a technology to produce coated tablets.

Since this flow scheme was produced with all aspects of production challenges in consideration, it can be used to kick start the process from the start or can also be a useful tool if process optimization is required to enhance the product quality. However, since the progression of this study was done with just pharmaceutical substances in consideration many further exceptions and subsequent pieces of determinative process specific knowledge can be acquired and added to update such a scheme when a broader range of substances are considered (for other types of applications) as well. Moreover, since the process knowledge was simply acquired through literature research in combination with usage of limited types of analysis, this flow scheme can definitely benefit from some important additions as well. The more substances tested for their ability to produce purely coated tablets, the more understanding and process specific knowledge about the respective systems can be acquired. This can subsequently result in development of a “systems appropriate for process application” database to be generated. Such database can include an updated process flow scheme (s) (also suited for different applications) as well as key systems’ properties that determine the eligibility of application.

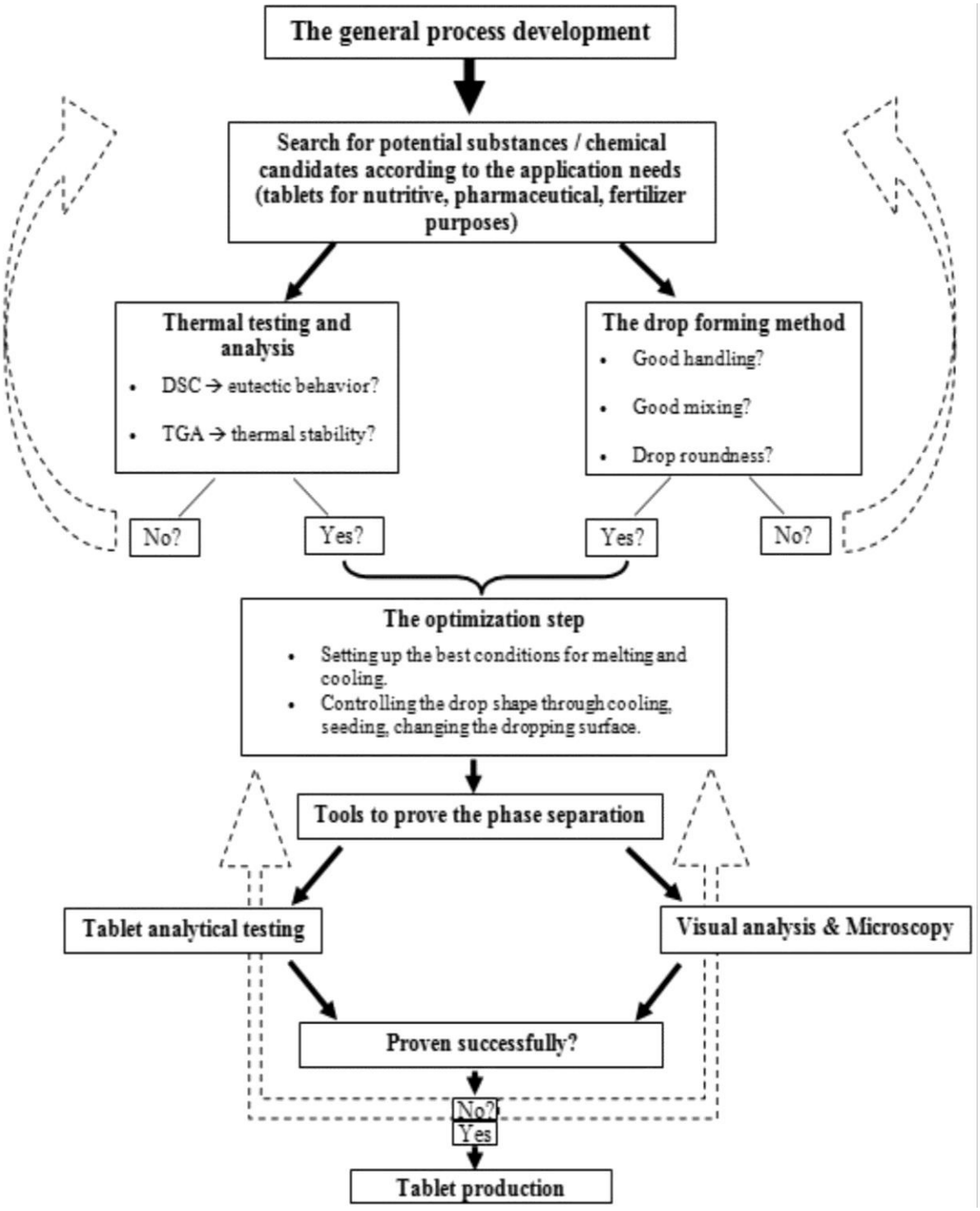


Fig. 5.15 Flow scheme of the development of the pastillation process to produce coated tablets utilizing melt crystallization, marking the primary and final stages of production [Abo14b].

As shown in Fig. 5.15, the very first stage of coating tablets using melt crystallization is searching for appropriate chemical candidates for application. This is the most important stage as it includes two important aspects. First, defining an appropriate application sector for the process according to the type of industry (food, chemical, or pharmaceutical), and the current market needs and/or trends, especially if a profitable end result is given priority. The second aspect is primary literature research to gain as much already developed knowledge about the substances under scope (and their properties) as possible. This will not only speed up the process development but will also be beneficial for providing a positive feedback loop to enrich the long term process understanding (through updating the process scheme). After finding the appropriate substances, two different steps are of simultaneous importance. One step involves doing preliminary analyses with the system to determine if it has a eutectic nature through DSC measurements, and phase diagram generation. The types of analyses are not just restricted to the ones presented before in this study (Chapter 4.2.2), but generation of the phase diagram is of crucial importance to identify the appropriate working conditions that are most likely to yield results. Variety of analysis can be very useful as well, for example, TGA can be used to ascertain the system's thermal stability and XRPD to test the crystallinity of the recrystallized materials. The other important simultaneous step, as to be seen from Fig. 5.15, involves doing primary trials (even with varied heating and cooling conditions) with the drop forming method using the system in question. This enables the user to get a primary feel if the system's materials are appropriate in terms of handling, flowability, mixing (in solid and molten states), and the resulting drop roundness. This is crucial because even a perfectly eutectic melt mixture (proven by thermal analysis) has to be forced through a drop former onto a cooling platform in an acceptable drop shape/form. In other words, knowledge of a system's thermodynamics is not a guarantee that the system would fit the proposed methodology and/or process technology. If both simultaneous steps yield a negative feedback, then it would be necessary to reconsider the system in question in terms of choice. However, giving a positive result means proceeding onto the next step of process optimization. At first, literature research as well as the preliminary analyses done earlier can guide the user to trying primary heating and drop cooling conditions. A part of the optimization can be done with the aid of further analysis (after production) but another part can be done earlier during the production itself.

For example, producing tablets with appropriate geometry which is necessary to achieve the phase separation (as seen in Chapter 5.2.5) is one aspect according to which early optimization of the cooling temperature and/or type of the cooling platform can take place. The other part of the optimization step has to be done with choosing the appropriate tools that are able to prove the phase separation. The direct feedback on phase separation quality provided by these tools, such as but not limited to microscopic analysis and UV spectrometry, results in reconsideration of the production key conditions. The more trials that are done based on preliminary (primary experimental) and literature research, the better becomes the overall process understanding which further adds to the long term success of the whole technology application (in-situ coating) of producing coated tablets using melt crystallization. Other tools can be utilized to gain more information on the questionable phase separation phenomenon at this stage, such as SEM and RAMAN spectroscopy. The optimization step, seen in Fig. 5.15, is in fact a necessary loop through which the “proof of separation” always tends to direct the process progression back towards the optimization step. However, providing evident information on the quality threshold of the tablets produced (system dependent) in terms of coat purity together with an acceptable geometry fixes the process conditions that can be easily scaled up and/or transferred onto a larger setup to proceed with the final stage of industrial production.

5.2.7.1 The working formula

In the last chapter, a detailed description of the developed general process flow scheme, in Fig. 5.15, was the main objective. This sub-chapter is, however, a straightforward simplified description of the same flow scheme with emphasis on the direct working formula that is to be applied just to get the final result. The working formula proceeds as follows:

1. The active pharmaceutical ingredient (API) that needs to be coated needs to be characterized with its specific physiochemical properties.

2. Search for an appropriate chemical substance that can be used as the coating material for the appropriate API. Key criteria to be researched upon may include, but not restricted to:

a) A known famous excipient used in pharmaceutical industries for the production of tablets.

b) The coating material should be non toxic, edible and generally safe for human consumption.

c) The coating material's melting point should not be higher than that of the to-be-coated API.

d) The coating material's viscosity should not be higher than 1000 mPa·s.

3. Using the potential substances that form the system, a series of simultaneous steps are:

a) The production of a phase diagram of the system through DSC analysis.

➔ If system is not eutectic, repeat step 2.
➔ If the system is eutectic, proceed onwards.

b) Test the materials' thermal stability through TGA analysis.

➔ If the system decomposes at its melting point, repeat step 2.
➔ If the system is stable, proceed onwards.

c) Design a batch lab scale process to apply the drop forming fundamentals for production of tablets using melt crystallization.

➔ This step is crucial to the development of the whole procedure, otherwise the process is not possible to proceed with.
➔ Upon completion, proceed onwards.

d) Using the designed setup, primary lab scale drop forming trials are done to check the handling, mixing of the materials and the produced drop roundness (i.e. testing the applicability of the drop forming method using the respective system).

➔ If the system cannot be molten, mixed or be used to form drops, repeat step 2.
➔ If the method is applicable with the system, proceed onwards.

4. Perform several lab scale drop forming trials in order to:

   a) Setup the best experimental conditions of melting and cooling.

   ➔ Best melting means the least temperature at which the system is molten, mixed and can be dropped conveniently.
   ➔ Best cooling is reflected in the highest cooling temperature possible without sacrificing the tablet form or leading to tablet sticking on the cooling surface.
   ➔ When best preliminary experimental conditions are determined, proceed.

   b) Optimize the process in terms of involving seeding and/or power ultrasound (PUS) application (or a mixture of both) to gain control on the crystallization of the mixed materials within the drop.

   ➔ Performing this step (as an additional form of control) depends on the system's responsiveness to yield solidifying round drops on the cooling surface at a controlled (reproducible) total crystallization time in the range of 5 - 17.5 min, without affecting the final tablet form.
   ➔ Seeding is done from the bottom of the laid drops by coating the cooling surface with sieved coating material powder. It is also done from the top of the drops by sprinkling a small amount of the sieved coating material powder.
   ➔ PUS can be applied by touching the surface of the solidifying drop with the sonotrode.
   ➔ If the system cannot yield an acceptable tablet form using these optimizations, repeat step 4a or step 2.
   ➔ If normal tablets can be produced, proceed onwards.

   c) Determine the optimal tablet geometry through controlling the drops' shape through changing the cooling and seeding from the bottom (changing the cooling surface properties).

   ➔ If the tablets' diameter to thickness ratio is more than 6, repeat steps 4a and/or 4b.
   ➔ If the tablets' diameter to thickness ratio is less than 6, proceed onwards (the closer this ratio is to 1, the better is the process).

5. Prove the tablets' quality in terms of phase separation through:

   a) Tablet sampling by separating the coat and core sections of the tablets. Consequent active pharmaceutical ingredient (API) concentration measurement testing for each separated section is to be done through ultraviolet spectrometry (UV).

   b) Visual analysis possible through light microscopy.

   ➔ If the solid phase separation cannot be proven by both of these analyses (represented by a low API content in the coat and a high API content in the core with an additional color and/or structural difference between the tablets' layers), repeat step 4.

   ➔ If the solid phase separation can be proven by these analyses, proceed onwards.

6. Fix and transfer the optimized experimental conditions, mentioned in step 4, onto a scaled up process for tablet production, the steel belt. These conditions include:

   ➔ Mixture melting and cooling programs.

   ➔ Optimized seeding and/or PUS application.

7. During operation with the steel belt, several conditions should be tested and accounted for, such as:

   ➔ Adjusting the belt speed to match the time for complete droplet crystallization.

   ➔ Adjusting the vibration intensity of the seeding platforms to produce an appropriate seeding layer for the drops.

   ➔ Being able to collect and reuse the seeding material in a timely manner so as not to disrupt the continuous operation of the steel belt.

   ➔ Adjusting the water level within the thermostats responsible for controlling the temperature of the steel belt.

6. Conclusion

Since in-situ coating as an alternative tablet manufacturing procedure is being tested, several crucial steps to the process development were considered in this study. Through the aid of materials' preliminary analysis two important pieces of information were extracted. Thermal analysis through performing DSC measurements helped in determining the eutectic nature of the binary systems, lauric acid-ibuprofen and lutrol-ibuprofen, namely systems **A** and **B**. This was possible through the generation of binary phase diagrams, Figs. 5.2 and 5.3, for each system. The phase diagrams proved useful in determining a starting point from which the experimental conditions of the drop forming method were further optimized. The second segment of preliminary analysis provided information on the systems' viscosities, where system **B** (because of the incorporation of lutrol) has shown a much higher viscosity than system **A**. This was reflected in the online imaging analysis results where mass transfer was impeded in system **B** showing a slow crystallization of the lutrol-ibuprofen drop, as compared to system **A**, in Figs. 5.10 and 5.11. Furthermore, as a way to prove the phase separation, colouring the coating material, lauric acid (by coupling it with cobalt [II] ions), has provided a useful key to visually analyze the separation process during tablet coating. This could be seen in Fig. 5.7 where separation has resulted in the production of a tablet with a dark core and a lightly coloured coating. Such result was optimized by cooling the solidifying drop of system **A** from above, which resulted in coating the produced tablet from the top as well, as to be seen in the microscopic sample displayed in Fig. 5.8. In order to check the identity of the coloured layers within the shown microscopic sample, the triple layer test provided a strong foundation to prove such identity. As expected, the top and bottom lightly coloured layers in Fig. 5.8 were proven to constitute mostly (if not entirely) of the coating material lauric acid. In addition, the dark core was proven to constitute the eutectic mixture between lauric acid and ibuprofen, as to be seen through the comparative result displayed in Fig. 5.9. The strategy of colouring the coating material has therefore provided a successful primary proof of the ongoing phase separation process within a crystallizing binary molten drop. As for system **B**, trials for tablet production using the drop forming method with differently coated cooling surfaces were done to identify the best cooling surface material that produces tablets with the best geometry.

As a result, the 10 µm particle size starch seeded surface was found to be the best for the drop roundness and the consequent tablet geometry. Lutrol seeded bed came at the second place for providing the best produced tablet geometry. Moreover, further lab scale drop forming experiments with different conditions were carried out using system **B** to optimize the phase separation. A relation between microscopic investigation and the measured ibuprofen concentration per tablet layer (which quantifies the phase separation) using ultraviolet spectrometry was shown in Table 5.1. As conditions were optimized from Batches 1 to 4 the difference in ibuprofen concentration between the tablets' core and coat was increasing. This was the expected relation as the conditions were optimized, since the high difference is an indication to more ibuprofen crystallizing in the core (within the eutectic composition) and less within the coat. Optimization in this case is therefore equivalent to producing tablets with the least amount of ibuprofen residing in the coat as much as possible, indicating coats of best purity. This ongoing trend of ibuprofen concentration difference increase from Batches 1 to 4 is supported by the respective microscopic images as well. For instance, in Batch 1 where the tablets were treated with power ultrasound (PUS) from the top, there is no significant layer separation seen through the microscopic image. However, due to the additional mechanical drop mixing provided by the PUS within the drop, the separation was never possible in this case. Replacing the PUS with cooling from above in Batches 2 and 3, however, has resulted in the formation of a thin top coating layer and a differently looking core within the investigated tablet cross sections. Seeding with lutrol from the top on the other hand, when introduced in Batch 4, resulted in the formation of the thickest lutrol coating possible where the top layer of the tablet is clearly comparable with the bottom layer. This is of course accompanied with a leap increase of ibuprofen concentration difference marking the least ibuprofen concentration of 7.80 % residing in the lutrol coating. Replacing the starch coated bed with lutrol bed in Batch 5 lead to a similar coating purity despite the little deterioration that took place concerning the tablet geometry. At this stage the optimum conditions for producing tablets with best phase separation quality and geometry were identified.

These conditions were transferred onto an industrial scale set up to produce larger tablet batches testing the efficiency of the continuous industrial machinery in attaining a product of even quality. In order to test this efficiency, the industrial steel belt was operated through continuous and batch modes of operation. By comparing both modes, the continuous mode has proven to be the best in terms of producing tablets with the best phase separation (also proven by microscopic investigation and UV analysis). In addition, lutrol-ibuprofen tablets with overall acceptable and reproducible dimensions were produced resulting in a successful scale up process. Combining key conclusions from the different trials done to apply the technology of coating tablets through melt crystallization, together with the challenges faced during the optimization, an overall general process development scheme was produced. This scheme is a simplified guide that shows how to coat tablets with this technology step by step starting with the stage of literature research, going through the analysis and optimization cycles and ending with scaling up the process for mass tablet production. However, since this scheme was produced with just pharmaceutical tablets in consideration it could be further updated in a more generalized manner that fits more diverse types of applications that suits different industrial sectors when other kinds of materials are tested. The generalized scheme can also benefit from, testing different types of analysis besides the visual microscopy and UV analysis, such as RAMAN that could give more decisive information on the separation. Other tools such as XRPD may be of great importance in giving additional information on the crystallinity of recrystallized materials as well. In addition to the need for performing different kinds of analysis, several experimental additions and/or modifications can also be considered. For instance, knowledge of the metastable zone width of the systems under investigation can be very important in optimizing the cooling strategy of the drops for more efficient phase separation. It can be also useful to determine at which cooling temperature is it the most effective to start seeding the top of the crystallizing drop with the coating material. Moreover, studying the effect of different coating material seed sizes on the phase separation can play as a simple, yet, a very effective optimization tool. All these experimental tests that involve more diverse analytical tools and concluding further observations are very important to consider if this process is to be taken on a next stage of further development in the future.

7. Summary

The term “In-situ coating” refers to coating in place which is possible through the crystallization of binary eutectic molten drops and the formation of complete tablets in one step at the place of production, e.g. a steel belt. Compared to the conventional methods of tabletting, in-situ coating, is in fact a faster, easier and cheaper tablet coating method that enjoys fewer number of production steps. But in order to realize this objective, a series of consequent steps have to be considered. A pre-requisite for the process to work, that is tied with the nature of melt crystallization (as a purification method) is the establishment of solid phase separation during crystallization of the drops in order to form a separate tablet coat and a core with the active pharmaceutical ingredient, ibuprofen. Special coating materials were used in two separate systems with ibuprofen as the active ingredient. System **A** used lauric acid, while system **B** used lutrol. A lab scale drop forming method which acts as a simulation of the real dropping process was the method of choice to produce tablets out of each system. Moreover, preliminary analyses in the form of DSC and viscosity measurements were necessary to construct a phase diagram, and being able to choose the right experimental conditions, respectively. Constructing a phase diagram was mandatory to understand the system and choose the starting mixture composition ratio which was 90:10 wt% (coating material to ibuprofen ratio), for each system. Proven eutectic in nature, both systems were used through a series of drop forming trials to realize the solid phase separation necessary to coat tablets. Ways to control and/or to enforce the phase separation were successfully applied. In addition, analytical techniques that have proven the phase separation was actually taking place were identified. One of those ways experimented with system **A**, dealt with colouring the coating material, lauric acid, and sampling the produced tablets through a devised general way of tablet sampling and performing microscopic analysis. Colouring, therefore, was proven useful through microscopic analysis by comparing the crystallized drop cross section with triple layer composites (with different cores) cross sections. The difference in the crystallized structure and colour between the tablets and composites has proven that the phase separation was taking place.

In addition to microscopic analysis, online imaging analysis done for both systems **A** and **B** has not only provided an additional proof to the phase separation but has also displayed the expected theoretical mechanism of a crystallizing drop undergoing the solid phase separation on actual crystallizing drops. Furthermore, another way that helped to quantify the phase separation process was to measure the ibuprofen concentration within the different tablet layers through UV analysis. In this case too, another general tablet sampling procedure was employed to ensure the reproducibility of results. Moreover, system **B** tablets were produced at different experimental optimizations and/or conditions to check quantitatively (through UV analysis) which experiment results in the best phase separation for coating the drops into tablets. The best optimization, that was proven was seeding of the crystallizing drops with lutrol from the top and the bottom, was transferred onto an industrial steel belt to scale up the process of tablet production. Through the continuous operation of the industrial set up, together with fixing the experimental conditions, the tablet scaled up production was proven efficient to produce lutrol coated tablets of system **B**. Through literature research, the several experimental trials and the gathered key conclusions, a general flow scheme of tablet production through melt crystallization was devised. This scheme provides simplified information on the different stages and challenges faced during application of such a technology for coating tablets. Moreover, a simplified step-wise explanation of the production flow scheme was provided for a more straight forward applicable setting. This flow scheme also provides basis for the proof of concept that was clearly shown in this study through the production of tablets using the melt crystallization technology.

8. Zusammenfassung

Der Begriff "In-situ Beschichtung" bezieht sich auf den Überzug von Tabletten durch Kristallisation von binären eutektischen Schmelztropfen und der Bildung von ganzen Tabletten in einem Schritt am Ort der Produktion, z.B einem Stahlband. Verglichen mit den herkömmlichen Methoden der Tablettierung, ist die in-situ Beschichtung tatsächlich eine schnellere, leichtere und preiswertere Tablettenbeschichtungmethode, die weniger Produktionsschritte benötigt. Aber um dieses Ziel zu erreichen, muss eine Reihe von Maßnahmen betrachtet werden. Eine Voraussetzung für den Prozess der mit der Schmelzkristallisierung (als eine Reinigungsmethode) arbeitet, ist das Erreichen der Festphasentrennung während der Kristallisation der Tropfen, um einen getrennten Tablettenmantel und Kern mit dem aktiven pharmazeutischen Stoff, hier Ibuprofen zu erhalten. Spezielle Überzug-Materialien wurden in zwei getrennten Systemen mit Ibuprofen als die aktiver Substanze verwendet. System **A** verwendete Laurinsäure, während System **B** Lutrol nutzt. Eine Tropfbildungmethode im Labormaßstab, die als eine Simulation der echten Vertropfung fungiert, war die Wahl, um Tabletten aus jedem System zu produzieren. Außerdem waren vorläufige Analysen in der Form von DSC und Viskositätsmessungen notwendig, um ein Phasen-Diagramm zu erstellen, und die richtigen experimentellen Bedingungen zu wählen. Das Konstruieren eines Phasen-Diagramms war obligatorisch, um das System zu verstehen und das Startmischungs-verhältnis so wählen, dass für jedes System das richtige Verhältnis Beschichtungmaterial zu Ibuprofen zu finden, hier 90:10 wt% war. Beide Systeme sind nachweislich eutektisch. Durch eine Reihe der Tropfbildungversuchen die Festphasentrennung herausgefunden, die notwendig ist, um Tabletten zu beschichten. Maßnahmen der Steuerung und/oder Durchsetzung der Phasentrennung wurden erfolgreich angewandt. Außerdem wurden analytische Techniken, die den Erfolg der Phasentrennung bewiesen haben identifiziert. Eine diese Methoden hier mit dem System **A** befasste sich mit der Färbung des Überzug-Materials Laurinsäure und dem Sampling der produzierte Tabletten durch mikroskopische Analysen. Der Unterschied in der kristallisierten Struktur und Farbe zwischen den Tabletten und dem Komposit hat bewiesen, dass die Phasentrennung stattfand.

Zusätzlich zur mikroskopischen Analyse, wurde online Bildverarbeitungs Analyse für beide Systeme **A** und **B** genutzt, was einen zusätzlichen Beweis zur Phasentrennung zur Verfügung gestellt hat, aber auch den erwarteten theoretischen Mechanismus eines realen kristallisierenden Tropfens gezeigt hat, der die feste Phasentrennung durch laufen hat. Eine andere Weise den Phasentrennungsprozess zu messen, war die Ibuprofen-Konzentration innerhalb der verschiedenen Schichten durch die UV Analyse zumessen. In diesem Fall wurde ein anderes allgemeines Tablettensampling verfahren verwendet, um die Reproduzierbarkeit von Ergebnissen zu sichern. Außerdem wurden mit dem System **B** Tabletten unter verschiedenen experimentellen Bedingungen produziert, um quantitativ zu überprüfen (durch die UV Analyse), welches Experiment auf die beste Phasentrennung hinausläuft, um die Tropfen zu beschichteten Tabletten zu verwandeln. Die beste Optimierung, die wurde, ist das Seeding von den kristallisierenden Tropfen mit Lutrol von oben und unten. Diese Methode wurde auf ein Stahlband übertragen, um den Prozess auf das Niveau einer Produktion hochzuschrauben. Durch die Verwendung des Industriellen Aufbaus, zusammen mit dem Optimieren der experimentellen Bedingungen, wurde die größere Produktion der Tabletten als effizient nachgewiesen, um mit Lutrol beschichte Tabletten des Systems **B** zu produzieren. Ein allgemeines Schema der Tabletten-Produktion durch Schmelzkristallisierung wurde erstellt. Dieses Schema gibt vereinfachte Auskunfte über die verschiedenen Stufen und Herausforderungen während der Anwendung solch einer Technologie zur Beschichtung von Tabletten. Außerdem wurde eine vereinfachte schrittweise Einweisung des Produktionsablauf-Schemas für eine besser anwendbare Einstellung zur Verfügung gestellt. Dieses Fluss-Schema schafft auch die Grundlage für den Nachweis des Konzepts, was in dieser Studie durch die Produktion von Tabletten durch Schmelzkristallisierungstechnologie deutlich gezeigt wurde.

9. Symbols and abbreviations lists

Symbols list		
Symbols	**Description**	**Units**
ΔG	Gibbs free energy of change	kJ/mol
ΔH	Change in enthalpy	kJ/mol
T	Temperature of the system	°C
ΔS	Change in entropy	J/molK
η	Viscosity	mPa s
C	Composition	wt%
C_{AI}	Concentration of active ingredient	%
C_{core}	Core active ingredient concentration	%
C_{coat}	Coat active ingredient concentration	%

Abbreviations list			
Abbreviation	**Description**	**Abbreviation**	**Description**
API	Active pharmaceutical ingredient	PUS	Power ultra-sound
C_E	Eutectic composition	RAMAN	Raman spec-troscopy
C_{s1E}, C_{s2E}	S1, S2 phase compositions at the eu-tectic temperature	S1	1st solid phase
DSC	Differential scanning calorimetry	S2	2nd solid phase
EU	Eutectic point	SEM	Scanning elec-tron microscopy
L	Liquid phase	TGA	Thermal gravi-metric analysis
PAT	Process analytical technologies	UV	Ultraviolet spec-trometry
p188	Poloxamer 188	XRPD	X-ray powder diffraction

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11. Appendix

11.1 Lutrol-ibuprofen phase diagram

Mass fraction ibuprofen [wt%]	Temperature [°C]	
	Offset	**Isotherm**
0	53.9	--
10	49	43.2
20	46.9	41.4
30	42.3	42.3
45	53.4	42
55	53.3	41
70	64.4	41.9
80	68.8	41.05
90	73.35	41.9
100	74.35	--

11.2 Viscosity measurements

11.2.1 Lauric acid-Co[II]$^{+}$ -ibuprofen system

Temperature [°C]	Viscosity [mPa·s]
48	12.33
49	12.24
50	12.09
51	11.81
53	9.62
55	8.87
56	8.93

57	8.46
58	7.91
59	7.76
60	7.48
61	7.36
62	7.69
63	7.51
64	6.95
65	6.92
66	5.82
68	6.78
69	6.28
70	6.44
75	6.68
80	5.41
85	4.65
90	3.73

11.2.2 Lutrol -ibuprofen system

Temperature [°C]	**Viscosity [mPa·s]**
55.34	1745.76
57.34	1628.14
59.34	1516.00
61.33	1406.80
63.35	1309.80
65.34	1224.00
67.35	1142.36

69.36	1070.93
71.37	1000.86
73.37	936.38
75.37	878.87
77.39	820.52
79.39	769.76
81.40	725.12
83.40	681.33
85.41	639.84
87.41	605.80
89.40	573.35
91.40	545.83
93.40	522.44
95.40	502.77
97.39	468.01
99.38	455.33
101.39	432.84
103.39	408.86
105.39	395.03
107.39	372.41
109.39	359.66
111.40	344.01
113.40	334.40

11.3 Lutrol-ibuprofen tablets' geometry

Condition	Tablet geometry									
	Tablet thickness [mm]					Tablet diameter [mm]				
	T_1	T_2	T_3	T_4	T_5	D_1	D_2	D_3	D_4	D_5
Steel surface	1.51	1.33	1.21	1.55	1.37	9.00	9.00	8.50	8.50	8.20
Starch bed [100 µm]	2.22	2.65	2.45	2.36	2.98	7.00	6.50	5.20	6.20	6.00
Lutrol bed	2.70	2.80	2.65	2.75	2.75	5.80	6.20	6.50	6.00	5.50
Starch bed [10 µm]	2.83	2.71	3.00	2.57	2.75	4.80	4.80	5.00	4.20	4.70
	Diameter : Thickness ratio									
	R_1	R_2	R_3	R_4	R_5	R_{Av}	Standard deviation			
Steel surface	5.97	6.76	7.00	5.50	6.00	6.20	0.62			
Starch bed [100 µm]	3.16	2.45	2.12	2.62	2.01	2.5	0.46			
Lutrol bed	2.14	2.21	2.46	2.18	2.00	2.2	0.17			
Starch bed [10 µm]	1.69	1.77	1.66	1.63	1.71	1.7	0.05			

11.4 Lutrol-ibuprofen tablets ultraviolet spectrometric analysis

11.4.1 Ibuprofen calibration line

Ibuprofen concentration [%]	Absorbance at 265 nm			
	1	2	3	Average
0	0	0	0	0
10	0.2161	0.2170	0.2385	0.2239
20	0.4540	0.4645	0.4136	0.4440
30	0.6487	0.6423	0.6554	0.6488
45	0.8805	0.9293	0.8675	0.8924

11.4.2 Lutrol-ibuprofen tablet layers' ibuprofen concentration

Calibration line equation			*Y = 0.0207x*	
Batch	**Absorbance at 265 nm**		**Ibuprofen concentration [%]**	
	Core	Coat	Core	Coat
1	0.2610	0.2864	12.61	13.83
2	0.2934	0.2931	14.17	14.16
3	0.3007	0.2486	14.53	12.01
4	0.2535	0.1614	12.25	7.80
5	0.2081	0.1633	10.05	7.89
Scale up				
Batch mode	0.2075	0.1840	10.02	8.89
Continuous mode	0.2077	0.1264	10.04	6.10

Declaration under Oath

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

Date: 16.02.2015 Signature

List of publications

- Abouzeid, S. Petersen, J. Ulrich: The effect of seeding on the phase separation phenomenon in a solidifying molten drop, Advanced Powder Technology, 26 (2015), 309-314.

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- Actively took part in the *19th International Symposium On Industrial Crystallization* (ISIC *2014*) conference held in France, Toulousse. My participation in the conference was in the form of presenting a scientific poster.

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J. Ulrich, S. Petersen, K. Wendt, T. Stelzer, A. Hartwig, A. Abouzeid: Verfahren und Vorrichtung zur Herstellung von beschichteten Granalien, Pastillen oder Tabletten mittels In-situ Beschichtung / Method and apparatus for preparing coated granules, lozenges, or tablets by means of in-situ coating German Patent Application 10,2014,006,502.2, filed May 6, 2014.

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