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DEVELOPMENT OF DIRECTLY COMPRESSIBLE AMBROXOL HYDROCHLORIDE SPHERICAL CRYSTALS

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1. INTRODUCTION

One of the most common pharmaceutical forms of active pharmaceutical ingredients (APIs) is the solid one. From an industrial point of view, it is enough to know the exact characteristics of the tablet, for example, composition and physicochemical properties. However, the simplest parameters of the tablets could affect the adherence of the patient to the medicine such as its size. The bigger the tablet is, the more unlikely that the patient is willing to swallow it. Decreasing the size of a tablet via omitting most of the adjuvants from it is one option that can improve patient compliance and thus, the potential recruitment.

Direct compression is a well-usable method for the production of small-size tablets because it is quicker, more economical and often cheaper than the well-known tableting methods that start with wet or dry granulation. However its application is promising, it is also necessary, that the starting material possesses appropriate parameters, for example, increased flow rate generated by spherical or nearly spherical crystals or crystal agglomerates.

Spherical crystallization (Chatterjee et al. 2017) can happen via typical and non-typical methods. In the course of my work, both of them have been applied. In the case of non-typical methods, like antisolvent crystallization (O'Ciardha et al. 2012; Kaialy et al. 2014; Lamesic et al. 2017), cooling crystallization (Simon et al. 2009; Pataki et al. 2013) or combined (Szabo-Revesz et al. 2001; Nagy et al. 2008) we can adjust morphology via changing the physicochemical parameters for example temperature, solvent system composition, saturation. For example, cooling crystallization can be implemented with an alternating temperature profile. For the on-line observation of the counts and chord length values, real-time methods like FBRM can be used and useful inferences can be drawn. Typical spherical crystallization methods (like quasi emulsion solvent diffusion method (Morishima et al. 1993; Espitalier et al. 1997)) use three solvents, one which is a good solvent for the active agent, an antisolvent and a bridging liquid which is miscible with both and it wets the active agent. This way, different crystal morphologies can be achieved by changing the solvent system itself or by adding different types of emulsifiers.

In industrial production, parameter optimization is always necessary to advance product and process quality. For these reasons, Quality by Design (QbD) concept (Juran 1986) can be applied, which always starts and ends with the customer. The focus of this concept is that quality should be built into the pharmaceutical (or other) product with an understanding of the product itself and also the process by which it is developed. The knowledge of the risks should be involved in the manufacturing process and for this, quality tools – such as Pareto

analysis and Ishikawa diagram – can be applied. Once the predominant causes are identified, tools like the Ishikawa diagram can be applied to determine the root causes of a problem. (Hartung et al. 2012; Reddy et al. 2015; Casian et al. 2017; Iurian et al. 2017) The Pareto analysis represents the correlations between CPPs and CQAs and it can show us the most critical parameters which have to be paid attention to during development (Vilfredo Pareto 1971; Litten 2010; Hartung et al. 2012; O'Ciardha et al. 2012; Power et al. 2015). In the end, it is more likely that a product with the desired parameters are obtained.

2. AIMS

Our research can be divided into three larger sections.

A. In the first section, typical and non-typical spherical crystallization methods were applied to the model API, AMB HCl. The particles of the products were investigated from the aspects of morphology (light microscopy), polymorphism (DSC, XRPD), surface smoothness (SEM) and thermoanalytical (DSC, TG) properties. The products of the different procedures were compared and the best methods were chosen for further research.

B. In the second section of the work, we investigated the non-typical spherical crystallization methods. On the basis of the QbD principles, a risk assessment was carried out with the help of quality tools and a factorial design was built. After the crystallization processes under different circumstances, the dependent variables of the products were evaluated by means of statistical analysis.

C. Finally, we wanted to collect more information on the agglomeration mechanisms of the non-typical methods. For this reason, we used the FBR measurement to track particle number and chord length changes along the crystallization and draw the final conclusions.

3. MATERIALS AND METHODS

3.1 Materials

AMB HCl was generously supplied by Teva Pharmaceutical Industries Ltd. (Hungary). Dimethyl sulfoxide (DMSO) and n-hexane were purchased from Scharlau Concept Co., Ltd. (Hungary). Ethyl acetate, isopropyl alcohol (IPA), *n*-pentane *n*-heptane and *n*-dodecane were purchased from Molar Chemicals Ltd. (Hungary), methanol (MeOH) and ethanol (EtOH) were purchased from VWR Hungary. Isopropyl acetate was purchased from Brenntag Hungary Ltd. Purified water (W) of Ph. Eur. quality was used for the experiments. Span 80, Tween 20 and Span 20 were Sigma-Aldrich (Germany) products. Purified water and methanol

for the FBR measurements were supplied by EGIS Pharmaceuticals Plc. All the applied solvents were of analytical grade.

3.2. Methods

General information

A Julabo F32-ED Refrigerated/Heating Circulator® was used for setting and keeping the required temperature during the crystallization processes and the solubility measurements. Drying of the crystals was carried out with a Memmert dry heat sterilizator at 40 °C for 24 hours. Determination of the MSZW and the on-line observations were carried out with a Mettler Toledo FBRM D600R probe and the temperature was controlled with a Huber Petite Fleur Pilot ONE thermostat. The average number of particles (for each size range) was followed by the iContol FBRM 4.3.377 controller software.

Determination of solubility

It was determined by the gravimetric method (Nordstrom and Rasmuson 2006) in pure MeOH, EtOH, IPA, purified water and in mixtures of different volume ratios of W/MeOH, W/EtOH and W/IPA (1:1, 1:3, 3:1 each). The temperature range was 25–65 °C.

Crystallization utilizing typical methods

Quasi-emulsion solvent diffusion technique (QESD)

The W/MeOH = 1:3 mixture, and the W/EtOH = 1:3 and 1:1 mixtures were applied as good solvents. The bridging liquid was MeOH and EtOH, respectively. As antisolvents ethyl acetate, isopropyl acetate, *n*-pentane, *n*-hexane, *n*-heptane, and *n*-dodecane were used. A solvent/antisolvent ratio of 1:5 was applied based on literature data (Toldy et al. 2012). The effects of different types and amounts of emulsifiers were also investigated using mixtures of Span 80/Tween 20 and Span 80/Span 20, setting an HLB (hydrophilic-lipophilic balance (Griffin 1949)) value that contributes to the most stable emulsion and gives the highest yield.

$$HLB_{total} = Weight\%_1 \cdot HLB_1 + Weight\%_2 \cdot HLB_2$$

A 150 ml jacketed crystallization vessel was applied with a total solvent volume of 60 ml.

Crystallization utilizing non-typical methods

Spherical agglomeration (SA)

Nearly-saturated solutions of AMB HCl were prepared using MeOH, W/EtOH = 1:1 and 1:3 mixtures and DMSO as good solvents, respectively. Ethyl acetate, isopropyl acetate, *n*-pentane, *n*-hexane, and *n*-heptane were applied as antisolvents. The applied ratios were 1:2,

1:5, and 1:10. AMB HCl solution was added dropwise to the antisolvent then the crystallization ran for 24 hours at 25 °C. The system was gently shaken.

Slow cooling with an alternating temperature profile (ATP)

A nearly-saturated solution of AMB HCl (in W/MeOH = 1:3 solvent) at 60 °C was used. The appropriate cooling–heating program starts from 70 °C in order to make sure that every single particle was dissolved. Then the gradual cooling (-0.3 °C/min) of the solution was started until around 50 °C when seeding crystals must be fed into the system. Next, the solution is gradually cooled to 30 °C and warmed back to 50 °C (0.3 °C/min). This step is repeated four or five times until the sample is cooled to 10 °C.

Determination of the metastable zone

Five different concentrations of AMB HCl solutions (in W/MeOH = 1:3 solvent) were used for the experiments. The cooling rate was 0.3 °C/min.

Risk assessment and factorial design

As a first step, the definition of the QTPP and determination of CQAs, CMAs and CPPs was necessary. These factors were designated on the basis of literature data, pilot experiments, and personal experiences. The following quality tools were applied during the risk assessment: Ishikawa diagram and Pareto analysis. LeanQbD Software is used for the evaluation of risk severity scores. After the evaluation of the risk assessment, the dependent and the independent variables of the following factorial design can be defined. As a result, dependent variables could be measured and Statistica 13 for Windows program was then used for the statistical evaluation and polynomial correlations were defined and the significance of the factors was determined.

SA method for parameter optimization

The SA method was further perfectionated via applying a factorial design to it, which was based on the results of the risk assessment. DMSO was chosen as a solvent and ethyl acetate was the antisolvent in their 1:5 ratio. The saturation of the solution was 440 mg/ml.

Non-typical crystallization methods for on-line measurements

The applied process parameters are summarized in Table 1, based on the results of the parameter optimization.

Table 1. The applied parameters during the experiment set, SA. Column dT means the temperature difference between the solvent and the antisolvent

Sample name	Mixing time (min)	dT (°C)	Mixing type	Reactor type and solvent volume
SA 1 A	30	0	horizontal shaker	jacketed reactor (78 ml)
SA 1 B	90	0		
SA 1 C	30	10		
SA 1 D	90	10		
SA 2 A	30	0	marine propeller	jacketed reactor (500 ml)
SA 2 B	90	0		
SA 2 C	30	10		
SA 2 D	90	10		

ATP method for the on-line investigations

W/MeOH mixture (ratio 1:3) was chosen as a solvent, which was saturated with the API at 60 ºC. Process parameters are summarized in Table 2.

Table 2. Process parameters of ATP method for on-line observations are summarized.

Sample name	Mixing type	Reactor type and solvent volume
ATP 1	horizontal shaker	jacketed reactor (120 ml)
ATP 2	marine propeller	jacketed reactor (750 ml)

Product assays

Images were taken with a JVC digital camera connected to the microscope and the computer. Image J program was used for the installation of scale bars.

For the determination of mean particle size and particle size distribution, aspect ratio and roundness a LEICA Q500 MC Image Processing and Analysis System was used (minimally 1000 particles). The morphology of the particles was examined by SEM. A sputter coating apparatus was applied to induce electric conductivity on the surface of the samples. Air pressure was 1.3-13.0 mPa.

Powder diffractograms were collected with a BRUKER D8 Advance diffractometer system equipped with a Våntec 1 line detector with Cu $K_{1\alpha}$ radiation (= 1.5406 Å) over the interval 3-40 ° 2θ, using 40 kV and 40 mA with rotation switched on. The measurement conditions were as follows: filter, Ni; time constant, 0.1 s; angular step 0.007°, sample holder: Si low background sample holder. The DSC curves were collected with a Mettler Toledo DSC 821^e apparatus within the temperature interval of 25-300 °C with an Ar gas intake of 10 L/h.

Heating was linear with a heating rate of 10 °C/min. The mass of the samples was between 2 and 5 mg in a 40 µl Al pinned crucible with lid. The TG curves were collected with a Mettler Toledo TGA/DSC 1 STAR^e System within the temperature interval of 25-300 °C with an N_2 gas intake of 10 L/h. Heating was linear with a heating rate of 10 °C/min. The mass of the samples was between 9 and 12 mg in a 100 µl Al sample holder.

Flow time, the angle of repose and bulk density were measured with Pharma Test PTG-1 Powder Characterisation Instrument with Teflon funnel and with the manual method written in the VIII. Pharmacopoeia (Medicines 2005) with a glass funnel. Bulk and tapped density were determined by the STAV 2003 Stampfvolumeter and based on the results, Carr index and Hausner factor were calculated.

The mechanical strength of the crystal agglomerates was numerically characterized by an individually-developed mechanical strength tester apparatus and the associated computer software that is able to visually display the fracture curve.

The residual solvent content was determined by the headspace gas chromatographic method using an Agilent 7890B PAL RSI85 apparatus equipped with a Shimadzu 2010 Plus AOC-5000 headspace injection system.

4. RESULTS

Solubility and MSZW

Based on the results of the AMB HCl solubility tests, the solvents for each crystallization method were determined, which is shown in Table 3.

Table 3. The solvent systems for each crystallization types

Crystallization method	Solvents	Antisolvents	Emulsifiers
QESD	W/EtOH (1:1) and W/MeOH (1:3)	*n*-heptane, *n*-hexane, *n*-pentane	Span80/Span20
SA	DMSO	ethyl-acetate	-
ATP	W/EtOH (1:1) and W/MeOH (1:3)	-	-

In our case the metastable zone (Fig. 1.) is relatively wide, thus spontaneous nucleation may occur only at lower temperatures. Once it happens, crystallization is always a fast process which is disadvantageous in terms of particle size enlargement. Therefore, in our subsequent experiments of ATP method, we applied a tightly restricted seeding procedure to promote a slow crystallization process yielding large crystals.

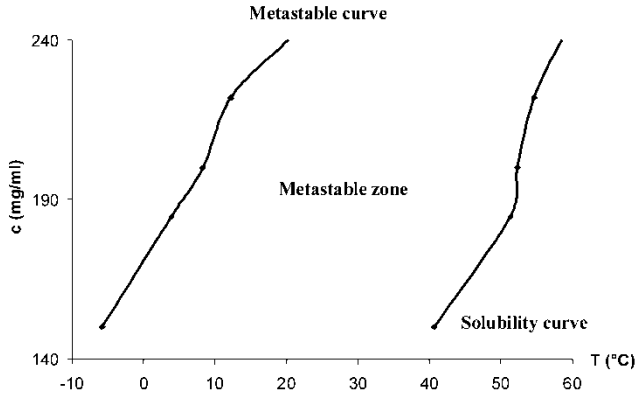


Fig. 1. Metastable zone of AMB HCl in W/MeOH = 1:3 solvent

Characterization of QESD, SA and ATP products

Products of the QESD method

It was revealed that the modification of the solvent system can induce significant differences in crystal morphology and size. The compositions of the emulsion systems are summarized in Table 4.

Table 4. Compositions of the applied QESD systems.

	Solvent	Antisolvent	Bridging liquid	Emulsifier (20 µl)	Total solvent volume (ml)
QESD 1	W/MeOH = 1:3	heptane	MeOH	Span80/Tween20	15
QESD 2	MeOH	pentane	MeOH	Span80/Tween20	15

Fig. 2. shows the effect of the solvent system on crystal size and morphology.

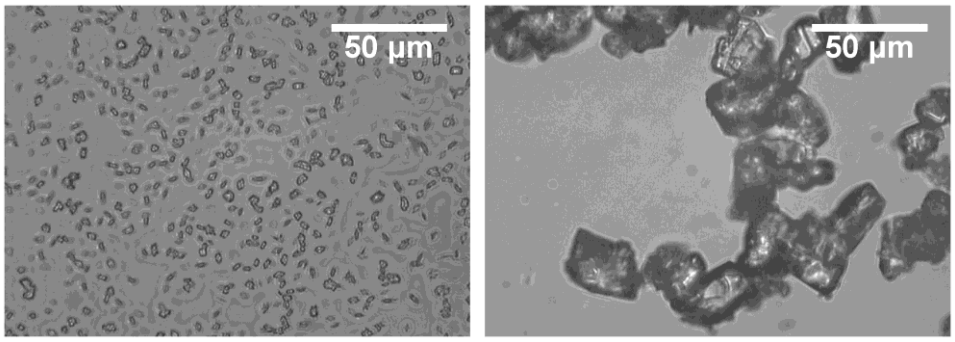


Fig. 2. Changes in particle size in different solvent systems
(left, A: QESD 1; right, B: QESD 2)

Products of the SA method

Changing the good solvent/antisolvent ratio induced differences in crystal size. The properties of the SA products are summarized in Table 5. The solvent/antisolvent ratio of 1:5 was found to produce the largest mean particle size (SA 15: 865 µm), although all of the products were

found to have an increased particle size (SA 12: 618 μm, SA 110: 140 μm) compared to the raw material (13 μm).

Table 5. Properties of the SA products

	Solvent	Antisolvent	Solvent/antisolvent ratio	Total solvent volume (ml)
SA 12	DMSO	ethyl acetate	1:2	20
SA 15			1:5	
SA 110			1:10	

Light microscopic images of the products are shown in Fig. 3.

The light microscopic images also revealed that these large and nearly-spherical crystals produced by the SA method are not individual crystals but crystal agglomerates.

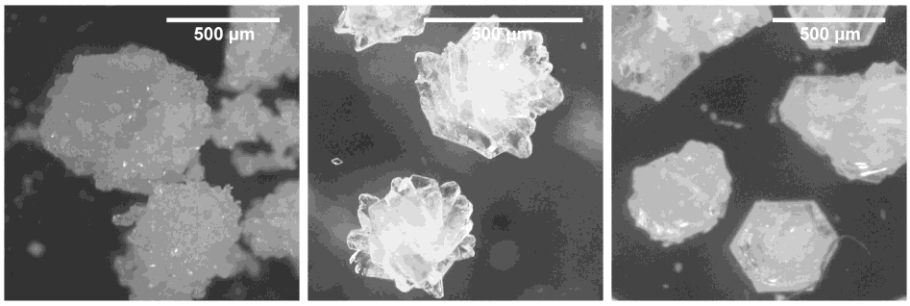


Fig. 3. Crystals produced by the spherical agglomeration method using various ratios of a DMSO/ethyl acetate system (left to right: SA 12, SA 15, SA 110)

Products of the ATP method

For this method two types of mixers were used, a marine propeller and a horizontal shaker. For the different mixers, different crystal morphologies were obtained as shown in Fig. 4.

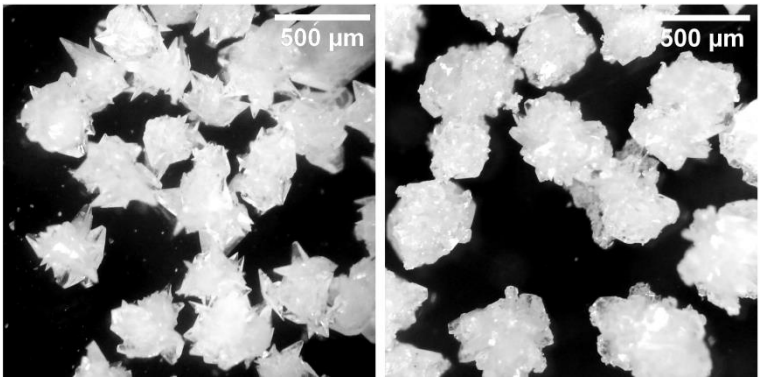


Fig. 4. Effect of different mixer types on crystal habit (left: marine propeller; right: horizontal shaker)

Using the marine propeller resulted in crystals with a spiny surface while using the horizontal shaker resulted in larger crystals with a smoother surface. In both cases, size enlargement (from 13 μm to 260 and 295 μm) was observed.

It can also be concluded that, based on the XRPD, DSC and TG studies, no polymorphic transitions happened during the crystallizations.

Results of the parameter optimization

Spherical agglomerates of SA method were optimized. Based on preliminary experiments and literature data, a Pareto chart was generated showing the severity scores of CMAs and CPPs. Mixing time and type, dT (temperature difference between solvent and antisolvent) and composition (solvent/antisolvent ratio) were the factors with the highest severity scores. During the following experiments, these factors were the independent variables of the factorial design. The Pareto analysis of CQAs led us to the following conclusions: roundness, aspect ratio, and particle size were the factors with the highest severity scores, and, according to this, these were the dependent variables of the factorial design in the next step (Table 6).

Table 6. Factors and levels of the factorial design based on the results of the risk assessment and Pareto-analysis

Factor	**Levels**			**Number of levels**
	Low	Center	High	
Mixing type (qualitative)	horizontal shaker/marine propeller			2
Composition (solvent/antisolvent ratio)	1:5	-	1:10	2
dT (°C)	0	10	20	3
Mixing time (min)	30	90	150	3

From the statistical analysis, significant effects could be determined, which are summarized in Table 7.

Table 7. Significant effects of the factorial design, based on the of the statistical analysis

Dependent variable	Significance of the factors									R^2	Adjusted R^2
	X_1	X_2	X_3	X_1X_2	X_1X_3	$X_1X_4^2$	X_2X_3	$X_2X_4^2$	X_3^2		
Average size (µm)	+	+	+	+	+	-	+	+	-	0.74	0.58
Aspect ratio	+	+	-	-	+	+	-	-	-	0.61	0.41
Roundness	+	-	-	-	+	-	-	-	-	0.38	0.25
Yield (%)	+	-	+	-	+	-	-	-	+	0.65	0.49

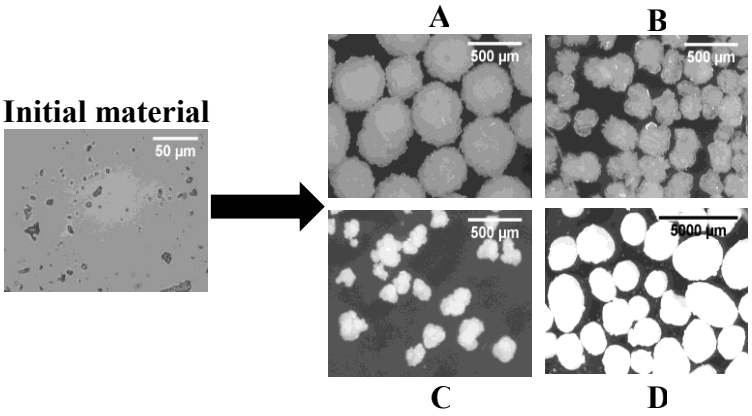
X_1 : Mixing type X_2 : Composition X_3: Mixing time X_4 : dT

In the table, there are only the factors, that had asignificant (positive or negative) effect on the system. We can see that mixing type and its linear combination with mixing time affected each parameter significantly.

Light microscopic investigations

During the statistical evaluation of the factorial design of the products, it became clear that four of them (A, B, C, D) have proper average size, aspect ratio, and roundness values compared to the target product. These were determined by light microscopic analysis. Exposures of the initial material and products A, B, C, and D are shown in Figure 5.

Figure 5. Light microscopic exposures of the SA agglomerates



In Table 8. the average size, aspect ratio and roundness values of the products and the initial material and the optimal factors for the SA crystallization are collected (parameters of A, B, C, D products).

Table 8. Results of the particle size and morphology analysis. Optimal parameters for the SA crystallization method

	Initial material	**A**	**B**	**C**	**D**
Average size (µm)	13.12	248.17	176.82	142.50	441.53
Aspect ratio	1.67	1.34	1.43	1.45	1.40
Roundness	2.37	1.41	1.37	1.88	1.49
Yield (%)	-	37.46	32.17	14.14	18.98
Applied parameters					
Mixing type	-	Horizontal shaker			
Composition	-	1:5			
Mixing time (min)	-	90 (M)	30 (L)	90 (M)	30 (L)
dT (°C)	-	0 (L)	0 (L)	10 (M)	10 (M)

Powder rheology tests

Product B was chosen for this experiment because the highest amount could be produced of this one. Powder rheological properties were investigated and it was revealed that product B had far better powder rheological properties than the initial material (Table 9.). The Carr

index and the Hausner ratio also showed improvements. This can facilitate the tableting process.

Table 9. Improvements in powder rheological properties comparing the initial material and the SA (B) product.

	Bulk density (g/ml)	Tapped density (g/ml)	Flow time (s)	Angle of repose (°)	Carr index	Hausner factor	Classification *(Carr 1965)*
Initial AMB HCl	0.54	0.81	unmeasurable	unmeasurable	32.67	1.49	**Very poor**
SA product	0.43	0.53	13.6	31.3	18.8	1.23	**Fair**

Mechanical strength test

Mechanical strength tests were carried out in order to examine the mechanical stability of the crystalline material. The fracture curves of the products showed enough mechanical strength to maintain their spherical morphology with ~2.5-3.2 N of fracture forces (Table 10.), which is a specifically high value regarding the average size of the particles.

Table 10. Mean values of the fracture forces of SA products based on 20 measurements

Sample	Fracture force (N)
A	2.95 ± 0.06
B	3.02 ± 0.04
C	2.53 ± 0.07
D	3.13 ± 0.04

Results of the FBRM observation of the non-typical methods, SA and ATP

With the help of FBRM, spherical agglomeration mechanism of SA/A, B, C, D products was observed. Conclusions, differences, similarities were summarized. The same was performed for the ATP crystallization. SA and ATP methods were compared in the case of using a double-walled glass reactor of 250 ml with a total solvent volume of 80 ml and, as a scale-up, a jacketed reactor of 750 ml with a total solvent volume of 500 ml, while applying different types of agitation (horizontal shaker and marine propeller, respectively). Particle size differences are shown in Tables 11-12.

Table 11. Comparison of the particle sizes of the crystals produced under different circumstances of the SA method

Initial material						
Aspect ratio		Roundness		Average size (μm)		
1.67		2.37		13.12		
SA 1-2						
Sample name	**Small reactor, horizontal shaker (SA 1)**			**Large reactor, marine propeller (SA 2)**		
	Aspect ratio	Roundness	Average size (μm)	Aspect ratio	Roundness	Average size (μm)
A	1.36	1.48	123	1.30	1.71	178
B	1.36	1.51	125	1.31	1.78	175
C	1.37	1.54	100	1.35	1.74	158
D	1.33	1.50	157	1.30	1.65	136

It can be concluded that a scale-up of one order of magnitude could be achieved. Roundness showed somewhat better values in the case of the SA 1 experiments due to the rolling effect of the horizontal shaker. The average size values seemed to increase when the marine propeller is used, which could be caused by the turbulent flowing. In this case, individual particles were able to agglomerate with each other from both sides, while the horizontal shaker shaped spherical crystals by rolling them at the bottom or the walls of the reactor, which means that one side is always hampered from cohesion to another particle. Although this effect caused lower particle size values, the horizontal shaker helped to improve the roundness values of the crystals by the constant rolling. Our result achieved with the ATP method, are summarized in Table 12.

Table 12. Comparison of the particle sizes of the crystals produced under different circumstances of the ATP method

Initial material						
Aspect ratio		Roundness		Average size (μm)		
1.67		2.37		13.12		
ATP 1-2						
Cycle number	**Small reactor, horizontal shaker (ATP 1)**			**Large reactor, marine propeller (ATP 2)**		
	Aspect ratio	Roundness	Average size (μm)	Aspect ratio	Roundness	Average size (μm)
1st	1.37	1.55	141	1.50	1.64	125
2nd	1.29	1.67	219	1.29	1.46	152
3rd	1.30	1.41	345	1.23	1.52	183
4th	1.30	1.35	395	1.24	1.38	197
13th	1.30	1.32	404	1.27	1.31	298

In the case of ATP methods, samples were taken out after the 1st, 2nd, 3rd, 4th and 13th cooling cycles to describe the level of the improvements in the particle size, aspect ratio, and roundness. We can see that in the case of ATP 1 the size enlargement is more significant than in the case of the ATP 2 method. It can also be concluded that, while the average particle size constantly increased with the number of cycles, roundness seemed to show only a slight improvement and the aspect ratio values stagnated after the 3rd cycle.

The residual solvent contents of the optimized products were investigated and it can be concluded that they were are under the Class 2 and Class 3 limits which are described in the ICH Q3C Guideline.

5. SUMMARY

The main aim of my Ph.D. work was to find the most suitable spherical crystallization process for the active agent, AMB HCl and to reveal the parameters, which had the largest effect on the crystal-formation mechanism. The optimization of the parameters was also carried out.

A) Application and comparison of the typical and non-typical spherical crystallization methods

The first study on the different spherical crystallization methods of AMB HCl was carried out with the application of typical and non-typical spherical crystallization methods, such as QESD, SA, and ATP. With regards to the particle size analysis of the products, we can say that the non-typical methods were more suitable for producing large-size, spherical crystals. Powder rheological attributes of the non-typical products have improved compared to the initial material and a large improvement was experienced.

B) Optimization of the SA method

QbD principles were utilized for the product development. After an Ishikawa diagram has been outlined based on pilot experiments and literature data, QTPPs, CQAs, CMAs, and CPPs were assigned. Pareto charts were drawn by the Lean QbD program. Based on the data, dependent and independent variables of the factorial design were determined and crystallizations were carried out. Dependent variables (average particle size, aspect ratio and roundness) products were measured and compared. Powder rheological parameters of the products were compared to those of the initial material and it was revealed that a considerable improvement happened, which allows the product to be used for direct compression tablet making.

C) On-line observation of the crystallization mechanisms in the case of the non-typical methods

The critical crystal formation section of each process was determined. In case of the SA method, it is in the first 10 minutes of the mixing, after the addition of the solvent to the antisolvent. In the case of the ATP method, the largest improvement in mean particle size, aspect ratio, and roundness showed up after the second cooling cycle. Differences between the effects of agitation methods were unfolded. It also became clear, that with the ATP method, the formation of individual crystals is more likely, while, with the SA methods, agglomerates form.

6. PRACTICAL RELEVANCE OF THE RESULTS

This is the first study in the topic of the spherical crystallization and its optimization of the active agent, AMB HCl. The novelty of the research was, that even though a well-applicable protocol is generally known for the selection of the spherical crystallization methods for different APIs, none of them is suitable for such compounds as AMB HCl, which has individual solubility properties, since it is low in water but also low in ethanol. Based on our results, the most suitable crystallization methods can be selected and the optimized parameters can be used. Since a “scale-up” was also carried out in case of the ATP and the SA methods, it can be concluded, that someday these may be transferred into industrial use. Spherical crystals generated by the above-mentioned methods have far better powder rheological properties than the initial material and this way they are applicable to direct compression tablet making. This tableting method is cheaper, quicker and more economical than the original tableting methods that are preceded by a wet or dry granulation step.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Gyulai, O.; Szabó-Révész, P.; Aigner, Z.:

Comparison study of different spherical crystallization methods of ambroxol hydrochloride

Cryst. Growth Des., 2017, 17 (10), 5233-5241

DOI: 10.1021/acs.cgd.7b00764 IF: 4.055

II. Gyulai, O.; Kovács, A.; Sovány, T.; Csóka, I.; Aigner, Z.:

Optimization of the critical parameters of the spherical agglomeration crystallization method by the application of the Quality by Design approach

Materials 2018, 11(4), 635

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III. Gyulai, O.; Aigner, Z.:

A szférikus kristályosítás típusai, jelentősége a gyógyszeriparban

Acta. Pharm. Hung. APHGAO 88, (043) 17-26. (2018) IF: 0.00

IV. Gyulai, O.; Aigner, Z.:

On-line observation of the crystal growth in the case of the non-typical spherical crystallization methods of ambroxol hydrochloride

Powder Technology 336, 144-149 (2018) IF: 2.942

PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

Oral presentations

1. Az ambroxol-hidroklorid szférikus kristályosításához szükséges paraméterek beállítása; **Gyulai Orsolya**, Aigner Zoltán; 9th MKE Round Table Conference, Balatonszemes, 6-7 May, 2016
2. Az ambroxol-hidroklorid szférikus kristályosításának módszerei; **Orsolya Gyulai**, Clauder Ottó Emlékverseny, Budapest, 20-21 October, 2017
3. A szférikus agglomeráció paramétereinek optimalizálása faktoriális kísérleti terv alapján; **Gyulai Orsolya**, Aigner Zoltán; 10th MKE Round Table Conference 19-20 May, 2017
4. Optimization of the parameters of the spherical agglomeration method; **Orsolya Gyulai**, Zoltán Aigner, ICG 2017 – Italian Crystal Growth, Milan, 20-21 November, 2017
5. Közvetlen préselésre alkalmas szférikus kristályok előállítása, **Gyulai Orsolya**, Aigner Zoltán; 11th MKE Round Table Conference, Balatonszemes, 4-5 May, 2018
6. Following crystal growth with the help of FBRM technique in case of ambroxol hydrochloride spherical agglomerates; **Orsolya Gyulai**, Zoltán Aigner, 9th Global Chemistry Congress, Lisbon, 23-24 July, 2018

Poster presentations

1. Spherical crystallization of ambroxol-hydrochloride; **Orsolya Gyulai**, Piroska Szabó-Révész, Zoltán Aigner; 5th International School of Crystallization (ISC2016) Granada, 29 May – 3 June, 2016
2. Refining the parameters of spherical crystallization methods; **Orsolya Gyulai**, Piroska Szabó-Révész, Zoltán Aigner, 23rd International Workshop on Industrial Crystallization - BIWIC 2016, Magdeburg, 6-8 September, 2016
3. Optimization of the parameters of spherical agglomeration; **Orsolya Gyulai**, Zoltán Aigner, FIP PSWC 2017 – Pharmaceutical World Congress , Stockholm, 21-24 May, 2017
4. Optimization of the parameters of spherical agglomeration; **Orsolya Gyulai**, Zoltán Aigner, ECS 4 – 4th European School of Crystallography, Warsaw, 2-7 July, 2017
5. Parameter optimization of the spherical agglomeration method; **Orsolya Gyulai**, Anita Kovács, Tamás Sovány, Ildikó Csóka, Zoltán Aigner, BBBB Conference, Balatonfüred, 5-7 October, 2017