Influence of microwave technology on cocarboxylase hydrochloride particle diversity and drying efficiency

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ABSTRACT

Two possible ways of crystallite downsizing of cocarboxylase hydrochloride namely mechanical milling and precipitation under high supersaturation conditions were studied as well as their influence on the drying parameters of the produced powders. It was found that both methods allowed shortening drying times of powders. However, precipitation from highly supersaturated solutions was found to have a more significant effect on cocarboxylase hydrochloride drying in comparison with the milling as the crystallites produced by the former method have smaller sizes ($< 10\ \mu m$) without additional disintegration and contain much less inclusions of mother liquor. Obtaining solutions with high supersaturation degrees was achieved due to application of microwave irradiation at the evaporation stage that provided uniform gradientless heating of cocarboxylase aqueous solutions. The results of this work can be applied for producing other fine-crystalline substances and materials when particle sizes play a key role in the manufacture of products with the desired qualitative characteristics.

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1. Introduction

Due to continuously growing requirements to the quality of chemical and pharmaceutical products and standardization of production procedures, development of certain finishing technologies – crystallization, filtration and drying – has become urgent over the last ten years [1–3]. These important industrial processes significantly influence many properties of the substances, e.g. polymorphism [4], crystal shape, particle size distribution [5]. Namely, the particle sizes of active pharmaceutical ingredients are an extremely important parameter influencing their following processing and efficiency of drug manufacture [6,7], which should meet the requirements of up-to-date standards [8,9]. Moreover, the economical aspects of the final technologies should be considered during the development of batch production.

Cocarboxylase hydrochloride (hereafter CX·HCl) represents one of interesting and important examples of pharmaceuticals from technological viewpoint. CX·HCl is a thermo sensitive substance; therefore drying is one of the most problematic production stages, which should be conducted very carefully in order to avoid product degradation. However, in most of the works dedicated to CX·HCl preparation [10–14] this factor is not paid much attention to whereas

according to our data on drying CX·HCl obtained by the known methods overall drying times may reach 80 h or even more resulting in inconsistency of drying processes, high energy consumption costs and the risk of product deterioration.

One of the powerful methods to speed up the drying process is application of microwave irradiation. It was demonstrated that microwave drying of different substances and materials resulted in considerable shortening of process duration [15–19]. It has been reported [20–22] that replacement of conventional thermal heating by microwave irradiation allowed reducing the overall drying time of CX·HCl by up to 7 times. The possible explanation for drying acceleration could be the enhanced diffusion of solvents under the influence of microwave irradiation [23]. It is well known that in microwave heated materials concentration and temperature gradients have the same direction. Consequently, concentration diffusion and thermo diffusion [24] run in one direction which results in the total diffusion enhancement in contrast to thermal heating when they have opposite directions. This is the reason of drying time shortening under the influence of microwaves.

Time of diffusion also depends on the crystallite size influencing the total time of drying process. Therefore regulation of particle sizes of a material is very important from a drying efficiency viewpoint.

In the present paper we demonstrate the influence of dispersity of CX·HCl powders on the microwave drying efficiency. The profound effect of microwave irradiation used at the evaporation stage of cocarboxylase solution foregoing precipitation and drying processes has also been shown in terms of powders drying acceleration.

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2. Experimental procedure

2.1. Materials

Aqueous solutions of CX·HCl were procured from Kharkov State Plant for Chemical Reagents (Ukraine).

2.2. Equipment

2.2.1. Laboratory scale equipment

Experimental laboratory microwave installation used in the laboratory experiments consisted of multimode microwave cavity (1), standard microwave oscillator of rated capacity of 850 W at 2.45 GHz (2), pressure and temperature sensors (3 and 4 respectively), vacuum trap (5) and vacuum pump (6). A photo of this experimental installation is shown in Fig. 1. In order to set the pressure at the level beyond the region where the risk of disruptive discharge exists (generally 3–4 kPa is enough), and to increase the effectiveness of solvent removal during drying an air purge was blown through the microwave cavity, with air velocity being regulated by the throttle embedded into the cavity door.

2.2.2. Industrial scale equipment

Drying and evaporation on the pilot and industrial scale were carried out with the use of the industrial rotary vacuum microwave equipment "Pharma-Micro" [25,26], consisting of the revolved multimode microwave resonator (drying chamber), generator of microwave irradiation having a maximal output power of 1.5 kW, and the control unit for operating in the manual or automatic mode. The temperature and pressure were controlled by means of the thermocouple and pressure indicator respectively.

2.3. Solution evaporation

2.3.1. Microwave evaporation

According to various methods described in the literature [10–14] CX·HCl is obtained by precipitation from aqueous solutions concentrated under vacuum with ethanol or acetone. Various methods give different details of the procedure, such as the optimal final post evaporation concentration, the nature of the precipitator or the solution to precipitator optimal volume ratio; however the main idea remains the same consisting of the precipitation, isolation of the crystalline product followed by drying under vacuum conditions. It is important, that in none of the methods have the details of the drying procedure

been given. In our laboratory experiments the vessel containing 3 L of the aqueous CX·HCl solution having a concentration of ~0.5 wt.% (hereafter wt. will be omitted in the designation of the concentration), obtained by the known methods [10–14], was placed into microwave cavity and heated by microwave irradiation under a lowered pressure (3–4 kPa, measurement accuracy ±0.3 kPa) to boiling point and evaporated at a temperature not higher than 30 °C (accuracy ±0.1 °C).

In the case of the evaporation of larger portions of solution the industrial rotary vacuum microwave equipment "Pharma-Micro" was used.

2.3.2. Thermal evaporation

The aqueous CX·HCl solution (3 L) having a concentration of ~0.5% after separation on ion-exchange resins was evaporated on the rotary vaporizer at a temperature not higher than 30 °C (accuracy ±0.1 °C) and pressure 3–4 kPa. For the evaporation of larger portions the initial solution was periodically added to the one being evaporated.

2.4. Determination of saturated solution concentration (solubility measurements)

Saturated solutions were prepared using 200 mL jacketed glass crystallizer, magnetic stirrer ensuring proper mixing in the crystallizer. The samples were weighed using analytical balances. The concentration of the saturated aqueous solution of CX·HCl was estimated according to the following method: the weighed substance sample added by portions (30 min interval between the portions) was dissolved in 100 mL of distilled water at 30 °C under agitation. After each portion the clarity of the solution was checked visually followed by next addition. The first portions were about 1 g and near the saturation point determined in preliminary crude experiments the amounts were lessened to 0.1 g. When after the last added portion any undissolved particles were observed in the solution the further addition of the substance was stopped. The solution was agitated for two additional hours, which were found in the preliminary experiments to be enough for the equilibrium to be reached, the solution was then allowed to stand for an additional 2–3 h to settle, and then the supernatant was filtered by suction.

The concentration of the filtered supernatant was determined spectrophotometrically by measuring the absorbance of tested and standard solutions at 245 nm.

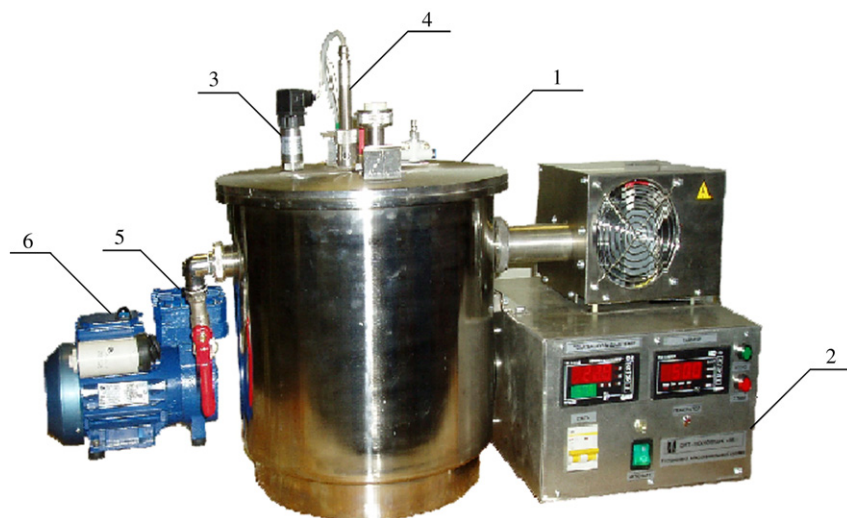The measurements were made in duplicate.

Fig. 1. Photo of experimental laboratory microwave installation. 1 — multimode microwave cavity; 2 — microwave generator (oscillation frequency 2450 MHz); 3 — pressure sensor; 4 — temperature sensor (IR-pyrometer); 5 — vapour trap; and 6 — vacuum pump.

2.5. Preparation of supersaturated aqueous solutions

Supersaturated solutions were prepared by evaporation of solutions with known concentration in a microwave field under a lowered pressure (3–4 kPa) at a temperature of 30 °C.

The supersaturation degree was evaluated by Eq. (1):

$$\sigma = \frac{C_{super} - C_0}{C_0}. \tag{1}$$

2.6. Precipitation of cocarboxylase hydrochloride

CX·HCl was obtained by the precipitation method by reverse addition of the pre-cooled supersaturated aqueous feed solution (T = 1–3 °C) to ethanol, in which CX·HCl is practically insoluble, having the same temperature, in 1:2 volume ratio with 0.1 mL/mL min dosing rate under agitation (stirrer speed ca. 600 rpm). This technique allowed very fast crystallization due to very high supersaturation generated upon addition promoting rapid nucleation. The mentioned ratio of the feed solution to precipitator was found to be optimal allowing maximal yield of the crystalline product. Prior to drying the samples were washed with an appropriate amount of cooled ethanol (1–3 °C) to remove residual mother liquor from the surface of crystals and filtered.

2.7. Microwave drying

2.7.1. Laboratory scale experiments

Preliminary laboratory drying experiments were performed on the experimental laboratory microwave installation (Fig. 1). The test sample of CX·HCl after filtering or centrifuging was placed into the microwave cavity (1) which then was evacuated to the residual pressure 3–4 kPa, and was heated by microwaves to a temperature of 55 °C during 20–25 min with 5 °C/min step and dried at this temperature until the required humidity had been achieved. The value of microwave power input was varied within the 50–100 W range. The moisture content in the samples was determined by the loss on drying method. The measurements were made in duplicate.

2.7.2. Industrial scale experiments

About 3 kg wet CX·HCl having an initial humidity of 10–15% was loaded in the drying chamber, evacuated, a pressure of 3–4 kPa was adjusted in the chamber by purging dry air or inert gas. The product was heated by microwave irradiation to 55 °C, the temperature being raised gradually as the moisture content decreased, and dried at this temperature until the 0.5% humidity had been achieved. Periodically throughout the process drying was stopped and samples were taken for humidity measurements (loss on drying) made in duplicate. Drying rates at different intervals were calculated from the measurements results. The microwave power was varied in the range of 70–250 W. The correlations between lab-scale and pilot-scale experiments shouldn't be made in terms of microwave power applied, as this value depends in a great deal on the resonator (drying chamber) efficiency (the ratio of the load volume to the resonator volume). In our case lab-scale experiments were conducted with the use of multifunctional equipment, which is applied for a wide range of microwave-assisted process, and were rather aimed at the study of the influence of MW irradiation on drying behavior of CX·HCl in general and were not optimized with respect to the resonator efficiency (the load occupied less than 1% of drying chamber capacity, whereas the optimal load is, according to our findings [26], 50–60%). In larger scale experiments this factor was considered and the load reached up to 15 vol.% of the resonator volume corresponding to one production batch.

The constant rotation of the drying chamber was used to enhance mass transfer and provide temperature uniformity. To break agglomerates of crystallites and ensure product homogeneity the powders were subjected to rough milling after the removal of free moisture (when the critical moisture had been achieved) for which purpose a non-standard coarse grinder was used. The procedure was the following: the powder after "predrying" was loaded in the grinder by 150–200 g portions and subjected to grinding to achieve the powder free from agglomerates but not to break the particles themselves.

2.8. Crystal sizing

CX·HCl crystals were sized by means of an optical microscope Axioskop 40 (Zeiss) equipped with a digital camera. The amounts of particles in the samples taken for measurements were up to 500.

3. Results and discussion

3.1. Uncontrolled crystallization

According to the known methods [10–14] CX·HCl was obtained by precipitation from its aqueous solutions (the concentration of aqueous solutions after evaporation generally does not exceed 25%) by the addition of ethanol as a precipitator. The obtained samples isolated from the mother liquor by filtering by suction or centrifuging were then dried in microwave field under vacuum. However, the drying times were long enough and irreproducible in different samples. The drying periods of an average sample are shown in Fig. 2, featuring a short heating period due to volumetric inertialess microwave heating, the constant drying rate period (free moisture is removed) which ends abruptly followed by the falling rate period characterized by a sharp reduction of a drying rate and taking the most of the drying process. Interestingly, the removal of the adsorbed moisture corresponding to the constant drying rate period took only 30–40 min, whereas to obtain the dry powder with the moisture content at a level of ≤0.5% up to 15 h or more was required. Thus, the fluctuations of the starting moisture content in the range of 10–15% did not influence the overall drying times significantly. However, for our experiments the samples with equal starting moisture contents were taken to rule out any subjectivity. The most part of the drying process was required for the reduction of the moisture content from 1.5–2% to ≤0.5% that corresponded to the falling drying rate period being crucial for the whole drying process. Thus, in the case of uncontrolled crystallization a moisture content of 1.5–2% is the critical moisture. It will be shown in this work (see later discussion) that the
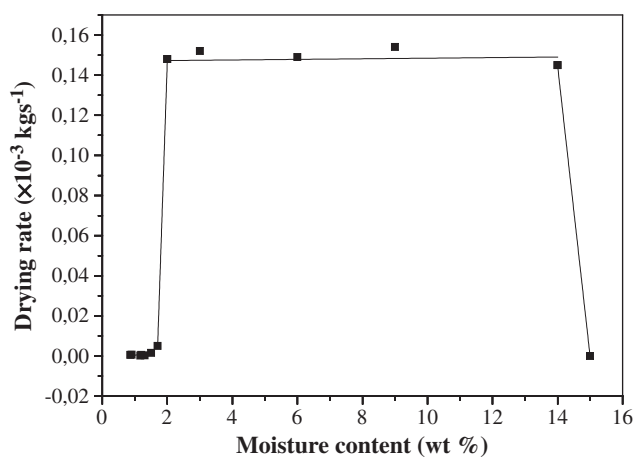

Fig. 2. Drying rate of CX·HCl for microwave drying of 3 kg wet substance obtained by uncontrolled precipitation. The end of the constant rate period and the beginning of the falling rate period designated by the sharp curve bend correspond to 1.5–2% moisture content.

critical moisture value changes with the variation of crystallization technique.

To find out the reason of prolonged drying time, and consequently, the possible ways of drying acceleration, the microscopic examinations of different samples of CX·HCl were carried out. It was found that the powders of CX·HCl obtained by uncontrolled crystallization have a wide crystal size distribution (from 20 to 120 μm), being very variable in different batches. Accordingly, the inconsistency of drying times was assumed to be directly connected with the variability of crystallite sizes. Though it was quite difficult to accurately correlate crystallite sizes with drying times of powders due to wide crystal size distribution it was observed that drying times were less for the powders consisting of smaller particles. If this observation was not delusive the evidence of drying time shortening with particle downsizing should become more distinct with more uniform powders. At this, the task arose to obtain fine uniform powders to achieve shortened drying times. There are two possible facile ways of producing fine-crystalline powders that can be applied on an industrial scale. The first way is particle breakage by mechanical milling, which does not require the interference in the crystallization process. The other way is to revise and improve the upstream crystallization procedure.

To find the most effective way of drying acceleration the comparative studying of the dependence of drying times on the mean particles sizes was performed for both methods.

3.2. Milling

One of the simplest ways of obtaining fine particles is milling. Our experiments on drying milled samples (milling was conducted after removal of the adsorbed moisture, i.e. after a moisture content of 1.5–2% had been attained, with the use of Bosch coffee-mill) showed that diminishing of CX·HCl mean particle sizes by 5–7 times allowed reduction of total drying time (till 0.5% moisture was achieved) from 15 h for unmilled samples to 6.5 h for the samples with the mean crystallite size 17 μm. It is quite reasonable, as the particles after breakage become smaller in size and the path length from the inclusion location to the particle surface becomes shorter, thus, less time is required to remove inclusions from the particles. The milling experiments were vivid demonstrations of shortening of drying times with the reduction of CX·HCl crystallite sizes confirming our supposition. Before proceeding with the experiments on crystallization we find it necessary to give some considerations on the nature of the moisture that is the reason of prolonged drying.

It is well known that during crystal growth the mother liquor may be captured by the growing crystal resulting in multiple inclusions. The amount of inclusions depends on the nature of solvent and crystallized substance and their interactions, crystal growth rate, etc. It is often quite a challenging task to obtain crystals free of inclusions. Thus, it was assumed that in the process of CX·HCl crystallization multiple inclusions of the mother liquor in crystallites were formed and it was the "captured" moisture that was the reason of the prolonged drying times. Unfortunately, because of very small sizes of CX·HCl crystallites and still smaller sizes of supposed inclusions it was hardly possible to view the latter directly under a microscope. However, the existence of the inclusions can be proved by the following reasoning.

Supposing, solid particles contain some inclusions, in that case the change in the moisture content during drying should follow the law of diffusion in solids, known as Fick's law (Eq. (2)) [27,28]:

$$J = -D \times grad(X). \tag{2}$$

As it follows from Eq. (2) the dependency of particle concentration on the diffusion time is exponential (Eq. (3)):

$$X = X_0 \times exp(-t / \tau). \tag{3}$$

According to Eq. (3) in order to accelerate the drying process the τ value designating characteristic drying time required for the concentration of included particles (solvent molecules in the case) to be reduced by e times should be decreased. Supposing that the diffusion coefficient D is independent of the crystallite sizes one may assume that τ decreases with the diminishing thereof, as the distance between the particle and crystallite surface becomes shorter. Thus, the effectiveness of the drying process in a great deal depends on the sizes of crystallites constituting the powders being dried.

The relative moisture change vs. time logarithmic dependences for the falling drying rate period are linear indicating the exponential decay of the moisture content during drying (Fig. 3) signifying the diffusion behavior of the moisture removal from inside the crystallites. This is a good confirmation that the drying times of CX·HCl are limited to the captured moisture removal rate. It is also obvious that drying times decrease with the reduction of particle sizes.

3.3. Precipitation under high supersaturation

The reassuring results obtained in the milling experiments stimulated us to the investigations of the crystallization procedure which improvement seemed a more efficient way of obtaining fine powders and drying acceleration. Generally, when applying the precipitation method saturated feed solutions are added to the precipitator or vice versa, and due to rapid supersaturation growth small nuclei are rapidly formed. However, wide particle size distribution and its inconsistency for different samples of CX·HCl obtained by uncontrolled precipitation are the evident signs of non-uniform crystallization proceeding. As the nucleation rate is a function of supersaturation, it is quite possible that in our case supersaturation was not sufficiently high for rapid nucleation giving very fine powders. Possible reasons explaining this fact may be significant concentration gradients emerging upon the addition of the aqueous CX·HCl solution to ethanol or a big latent period of crystallization or altogether. To achieve more uniform nucleation and as a result more uniform and fine powders we tried to minimize the conjectural influence of these factors by providing higher supersaturation levels. The latter, in turn, was achieved by obtaining the supersaturated aqueous solution of supersaturation degrees higher than 1 at the evaporation stage and introducing them to the precipitator.
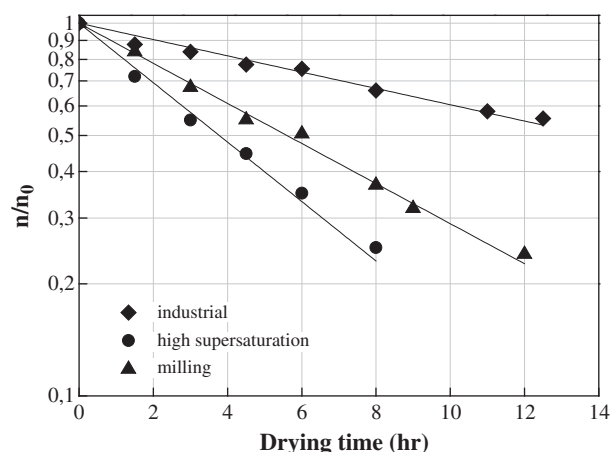

Fig. 3. Change in the relative moisture content with time (only for the falling rate period) for the samples of CX·HCl obtained by conventional methods (with the mean particle sizes up to 120 μm) (♦), milled samples (17 μm) (▲) and fine-crystalline powders (8 μm) produced from highly supersaturated solutions with $\sigma = 2.7$ (●). The increase of the slope angles indicates the decrease in drying times for the milled and "high supersaturation" samples compared to those obtained by uncontrolled precipitation.

To study the dependence of particle sizes on the supersaturation degree of aqueous solutions the experiments on obtaining solutions in a wide range of supersaturation degrees – from 0.3 (~14%) to 3 (~45%) – were carried out. For procedure standardization the following parameters were applied: temperature of aqueous solution and ethanol — 1–3 °C; keeping up the temperature not higher than 3 °C during the whole process; intensive agitation preventing sputtering the mixture from the vessel, the stirring rate being constant in all the runs. These parameters were chosen from the viewpoint that cooling and vigorous agitation are the factors favoring nucleation.

It was additionally found in our experiments that the conventional heating applied for evaporation can hardly allow obtaining the solution with supersaturation degrees higher than 1.0. It can be explained by the hypothesis that when evaporation is carried out under thermal conditions with "through-the-wall" heating the temperature gradients grow as the concentration increases which results in premature crystallization before high supersaturation is achieved. This is the reason why concentrations of aqueous solutions mentioned in the known sources generally do not exceed 25% barrier (the supersaturation degree at a level of 1.0). Microwave heating providing volumetric inertialess heating of the solution allows uniform bulk heating, minimal temperature gradients and sufficient increase of supersaturation. However, in the case of applying microwave heating for the evaporation of solutions the significant factor is a depth of microwave irradiation penetration (or skin-layer depth), estimated by Eq. (5) [29]:

$$\varsigma = \frac{\lambda}{\pi \times tg\delta \times \sqrt{\varepsilon}} \qquad (5)$$

where ζ is the skin-layer depth, cm; λ is the microwave radiation wavelength, cm; ε is the dielectric constant of the solution; and $tg\,\delta$ is the dielectric loss tangent.

It was shown previously [30] that aqueous cocarboxylase solutions have the values of skin-layer depth in 30 to 50 cm region depending on the concentration that allows an application of microwave heating for evaporation of such solutions even on the industrial scale. Using the MW technique it was shown that the increase of the supersaturation degrees of aqueous solutions resulted in considerable particle downsizing (Fig. 4).

Additionally, it was found that the optimal supersaturation degree was 2.5–2.7, corresponding to the mean crystal size 8–10 μm. The higher supersaturation values are not considered in this work as such solutions are hardly operable because of high viscosity.
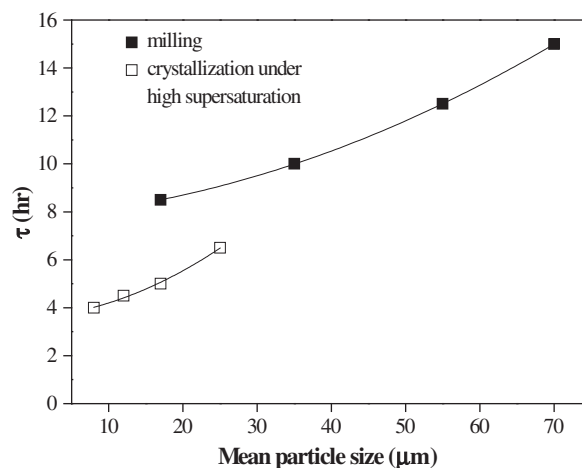
Fig. 5. The variations of diffusion times (τ) with the mean particle sizes for the powders obtained by mechanical milling upon uncontrollable precipitation and for the ones prepared by precipitation from highly supersaturated solutions.

The drying behavior of the samples obtained by the known methods [10–14] without milling, after milling and fine-crystalline samples from highly supersaturated solutions was studied.

On the basis of the experimental data obtained τ values were determined for all samples (Fig. 5). It is evident, that both mechanical milling and microwave-assisted technique resulted in drying acceleration. However, milling was not so effective as precipitation from highly supersaturated solutions (high supersaturation precipitation) since τ values were quite different for the equal particle sizes in both cases. Fig. 6 demonstrates the decrease in critical moisture with diminishing particle sizes and, correspondingly, with supersaturation growing. We suppose that in this case the decrease in critical moisture correlated with the decrease in the inclusion level. The supposition is based on the following considerations. It is well known that the number of inclusions in crystals, specifically, inclusions of the mother liquor depends on the crystal growth rate — at higher growth rates more inclusions are formed [31,32]. However, it was assumed that, in spite of high growth rates, due to the rapid nucleation, also favored by high supersaturation conditions, and shortening of the overall crystallization process duration the crystallites would stop growing before a considerable amount of the mother liquor had been captured. Thus, obtaining fine particles approaching the nuclei sizes from highly supersaturated solutions should lead to a decrease in the inclusion level.
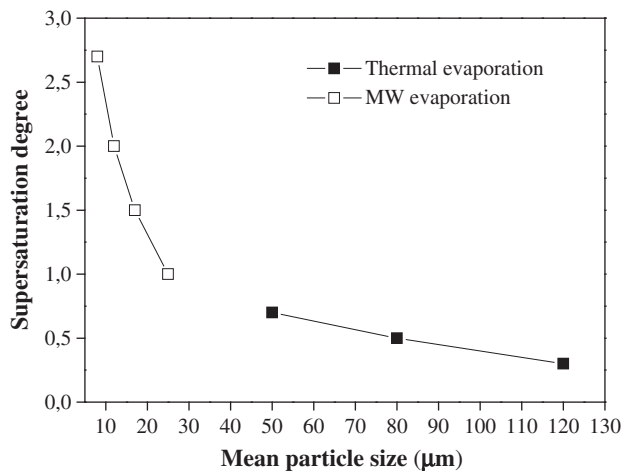

Fig. 4. Effect of supersaturation degrees of cocarboxylase aqueous solutions on the mean particle size upon precipitation. Obtaining highly supersaturated solutions became possible only by the mean of microwave-assisted evaporation.
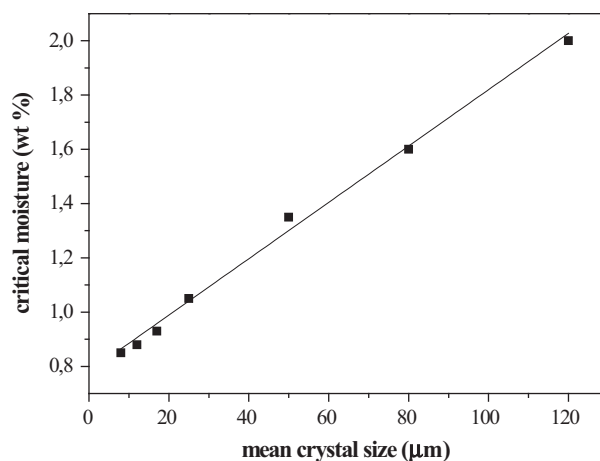

Fig. 6. Dependence of the critical moisture content on the mean crystal size. The crystals with a mean size of 25 μm and less were possible to obtain only with the use of a microwave-assisted evaporation.

From the results obtained the privilege of the crystallization procedure resulting in fine powders over the milling approach is evident, as milling only allows the change of crystal sizes being the only parameter influencing the drying rate, while the improvement of the crystallization procedure and accurate control of the process parameters additionally resulted in the decrease in the captured moisture content, altogether leading to considerable drying time shortening.

The total effect produced by the decreasing diffusion time τ in combination with halving critical moisture content in the microwave-assisted method was the shortening of the overall drying times up to 2–2.5 h that is 3 times less than when mechanical milling had been applied.

4. Conclusions

Thus, the extensive investigations of crystallization (precipitation) and drying processes of CX·HCl were carried out resulting in the optimization of the crystallization parameters and accelerating of the product drying. Highly supersaturated CX·HCl aqueous solutions were obtained for the first time by means of evaporation under microwave irradiation. The supersaturation degrees at a level of 3 were reached, that were much higher compared to the conventional thermal evaporation. The improved crystallization procedure of CX·HCl by salting-out from the microwave evaporated highly supersaturated aqueous solutions was developed. This improved technique allowed us to achieve uniform powder dispersity and consistent low critical moisture content of the CX·HCl powders which was the result of the decrease in the amount of mother liquor inclusions in crystallites. In total all these parameters provided the reduction of the product overall drying times from up to 15 h to 2–2.5 h, which resulted in considerable energy cuts, stabilization of crystallization and drying procedures, and lessening of the equipment wear out, being a strong base for development and standardization of crystallization and drying procedures.

Nomenclature

σ	relative supersaturation degree of the aqueous cocarboxylase solution
C_{super}	concentration of the supersaturated solution (wt.%)
C_0	concentration of the saturated solution (wt.%)
J	flow of diffusing particles = number of particles/m^{2}s
D	diffusion coefficient
X	diffusing particle concentration (in this work X is designated as the moisture content at time t, wt.%)
X_0	critical moisture content (wt.%)
t	drying time required for the diffusing particle concentration to be reduced from X_0 to X (h)
τ	diffusion time, designating the time required for X to be reduced by e times (h)

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