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A Facile Microwave-Mediated Drying Process of Thermally Unstable / Labile Products

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Abstract:

The drying behavior of (*S*)-*N*-acetylindoline-2-carboxylic acid, precipitated (1a, 17 wt %) and nonprecipitated (1b, 5 wt %), and *N*-acetyl-(*S*)-phenylalanine ((*S*)-2-acetamido-3-phenylpropanoic acid, 2), both pharmaceutical intermediates, and of cocarboxylase hydrochloride (thiamine pyrophosphate, 3), a coenzyme, a bioactive form of vitamin B_1, being a thermolabile substance, has been determined in straightforward drying setups. The method of supplying energy to the system had a profound influence on the drying rate and on the internal temperature of the samples during drying. The drying time of (*S*)-*N*-acetylindoline-2-carboxylic acid (1b) with the low moisture content (5 wt %) could be reduced by a factor 4 using microwave irradiation instead of conventional heating, while keeping the sample temperature under 35 °C. *N*-Acetyl-(*S*)-phenylalanine (2) with a higher moisture content (22 wt %) demonstrated a decrease in drying time by a factor 2.5 to 4 depending on the applied microwave powers. A reduction in drying time of the precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid (1a, 17 wt % moisture) by a factor 2 was demonstrated for drying at 150 W of microwave irradiation instead of using a water bath at 70 °C. A dramatically shorter drying time by a factor 10 was found for cocarboxylase hydrochloride (3, 15 wt % water) on lab-scale which could be reproduced on pilot-plant scale. To achieve with conventional heating similar drying times as under microwave irradiation for the four examples, extremely high energy inputs should be applied, necessitating extremely high temperature differences between the heating source and the sample. The results reveal that microwave irradiation is less energy-consuming and is particularly useful for effective drying of thermally unstable materials in short periods of time.

Introduction

Drying is one of the oldest and most common unit operations in chemical engineering and is an essential procedure for purifying and isolating products.[1] Drying is one of the highest energy-consuming and most expensive processes in the pharmaceutical industry. Microwave irradiation has attracted much attention in different fields dedicated to studying benefits and drawbacks of microwaves as an unconventional source of heat[2−9] and has become a popular heating technique for various processes including synthesis, solution concentration and drying of food,[10−14] fruits,[15] chemicals,[16,17] agricultural products,[18] polymers,[19] ceramics,[20] pulp and paper,[21] textiles,[22] in mineral processing[23] as well as in wood processing industries.[24] Although drying of pharmaceutical powders with microwave heating has been shown to increase drying rates and product stabilities during the drying process,[25,26] application in the pharmaceutical industry is still limited. The main property of microwaves is to directly deliver energy from the source to the microwave-absorbing sample. Field inhomogeneity of domestic microwave ovens, culminating in uneven heating rates, dictate the use of dedicated equipment for microwave processing.[27]

Conventionally heated drying processes are limited by the thermal conductivity of the substances. When the thermal conductivity is low, the drying process becomes slow, and

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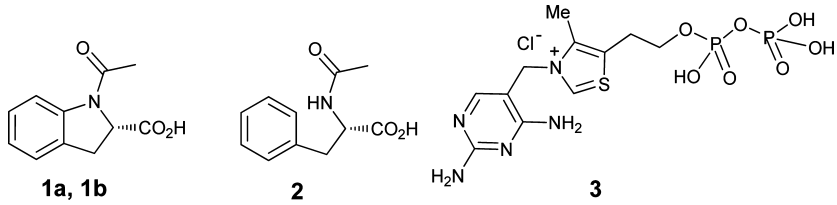

Figure 1. **(*S*)-*N*-acetylindoline-2-carboxylic acid (1a, 1b), *N*-acetyl-(*S*)-phenylalanine (2), and cocarboxylase hydrochloride (3).**

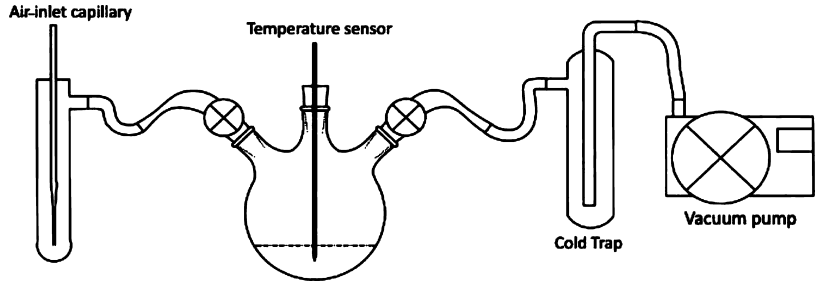

Figure 2. **Setup for the drying experiments under conventional and microwave heating conditions. With a capillary tube, a constant air purge provided a constant level of humidity in the apparatus.**

moreover, considerable temperature gradients may induce overheating of the sample surface which can be extremely risky for thermosensitive materials from a quality and a safety point of view. Vacuum drying is often used to reduce the boiling temperatures of volatiles and to reduce the risk of overheating as well. However, drying under reduced pressure becomes even more challenging due to ineffective convection in many cases. The problem of heat transfer may be solved by introducing microwave dielectric heating.[28−34]

The present paper deals with microwave-assisted vacuum drying of two pharmaceutical intermediates, based on earlier work,[35] and of a coenzyme of vitamin B_1 with different thermosensitivities, see Figure 1. The first one, *N*-acetylindoline-2-carboxylic acid, precipitated (**1a**) and nonprecipitated (**1b**), an intermediate in the synthesis of perindopril (an ACE inhibitor drug working to lower blood pressure),[36,37] is a relatively thermostable substance. The second intermediate, *N*-acetyl-(*S*)-phenylalanine ((*S*)-2-acetamido-3-phenylpropanoic acid, **2**), a versatile building block for the synthesis of various active pharmaceutical ingredients (APIs) and intermediates, is also a relatively thermostable substance. The third, cocarboxylase hydrochloride, thiamine pyrophosphate **3**), a coenzyme and bioactive form of vitamin B_1, is a thermolabile substance. The study was aimed at establishing the advantages of microwave over conventional heating in terms of drying efficiency, product quality, and energy savings.

Table 1. **Temperatures, corresponding theoretical power inputs, and actual power inputs in the microwave-assisted experiments[a]**

	T (°C) (water bath temperatures)		
	45	60	75
$Q_{CH,\ estimated,\ t=0}$ (W)	13	42	71
$Q_{MW,\ used}$ (W)	50	100	150
$Q_{MW,\ used\ effectively}$ (W)	∼5	∼10	∼15

[a] MW: microwave heating; CH: conventional heating (oil-bath). See Experimental Section for the calculation method.

Drying Behavior of (*S*)-*N*-Acetylindoline-2-carboxylic Acid

To determine the influence of microwave irradiation on the drying of pharmaceutical intermediates and to clarify whether its application beneficially influences the drying process, a comparison of conventional with microwave heating was made for this substance. The following straightforward drying procedure was selected for small-scale experimentation, see Figure 2. A three-necked flask, containing the static sample, was held at a pressure of 5 kPa and heated by either a water bath or by a multimode microwave apparatus. An air-inlet capillary tube ensured a constant air flow over the sample. This setup guaranteed a constant removal of evaporating moisture from the upper layer of the sample and excluded mass transport limitations in the gas phase. In this way, the diffusion rate of the moisture in the sample and the evaporation rate of the moisture governed the rate of the drying process.

To compare the different heating methods, the power supplied by the water bath to the flask at $t = 0$ was estimated for the applied temperatures, see Experimental Section. The actual power input of the water bath is lower than these values. The water bath temperatures used and the microwave power inputs are collected in Table 1.

The energy efficiency of the microwave irradiation in the used setup is variable during the drying process. Also the

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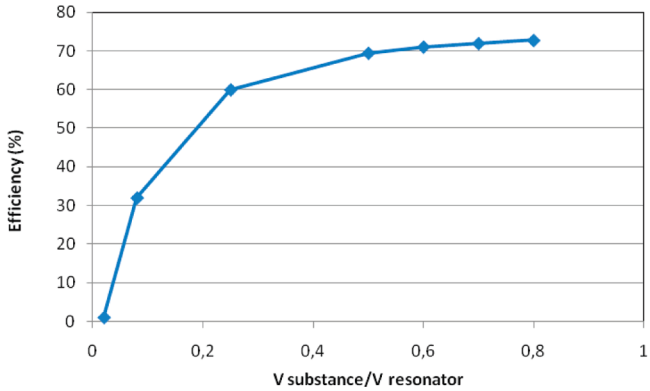

Figure 3. **Microwave energy efficiency as a function of the occupancy of the microwave resonator; $V_{substance}$ = the volume of the substance loaded in the resonator; $V_{resonator}$ = the volume of the resonator.**

efficiency of a microwave is usually proportional to the degree of charging the cavity which makes a direct comparison of the heating techniques cumbersome.[38]

The larger the sample is with respect to the cavity, the higher the microwave energy efficiency becomes; see Figure 3.

The results of preliminary experiments showed that, although the energy efficiency was assumed to be 10%, a power input of 420 W[39] (corresponding to the energy input at $t = 0$ of a water bath with a temperature of 60 °C) strongly outperformed the conventionally heated experiments. Therefore, the used microwave power inputs were determined empirically. The microwave equipment used in the experiments was inaccurate with power settings below 40 W. The selected power inputs of 50, 100, and 150 W were adequate to get comparable drying rates for microwave and conventional heating.

To study the effect of higher moisture contents, and in particular the influence of microwave irradiation on the constant drying interval, i.e. the removal of surface moisture, and on the most crucial falling rate period usually determining the overall drying time, i.e. the removal of moisture in the inner pores, a sample of (*S*)-*N*-acetylindoline-2-carboxylic acid[40] with a moisture content of 5 wt % was subjected to a base/acid precipitation procedure. This resulted in an initial moisture content of 17 wt %.

The particle sizes of the precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid and *N*-acetyl-(*S*)-phenylalanine (*vide infra*) are approximately 3 and 5 times smaller than that of the original grade of (*S*)-*N*-acetylindoline-2-carboxylic acid, respectively, see Figure 4.

The results of the drying experiments using conventional and microwave heating are shown in Figure 5.

The application of microwaves reduced the drying time significantly. The experiments with conventional heating showed a drying time of 35 min at 45 °C which was also obtained with a microwave power of 50 W (corresponding to an actual power input of 5 W). The seemingly very short, constant drying-rate period could indicate that (*S*)-*N*-acetylindoline-2-carboxylic acid mostly contained moisture in the interstitial space. Also in this case, removal of pore moisture was dominant in time and in energy consumption during the drying process. The drying time could be drastically reduced by increasing the microwave power input to 100 W (15 min drying time) and 150 W (10 min drying time). Increasing the temperature of the water, and thus increasing the power input supplied by the water bath to the flask, also decreased the drying time.

Temperatures of 60 and 75 °C corresponded to a 25- and 20-min drying time for conventional heating, see Figure 5 (left). A striking difference between both heating methods is the temperature of the sample. Higher water bath temperatures also increased the sample temperature, shown most pronounced for the final equilibrium temperature at the end of the drying process. To gain a similar drying rate as for the 150 W microwave drying experiments, a temperature exceeding 200 °C should be applied for conventional drying. This would lead to a sample temperature of more than 150 °C, which is impractical and could be detrimental for the stability of the sample.

The temperature measurements were performed at the center of the sample for both heating methods. When applying a conventional heat source, the sample is heated from the outside which creates a temperature profile and a drying front. The temperature has the lowest value at the center of the sample. Therefore, the recorded temperatures of the sample with conventional heating are lower than the average temperature. This is in sharp contrast with drying under microwave irradiation. The volumetric heating distributes the energy relatively evenly over the sample, especially with low loss tangent materials which have a large penetration depth. The insulation of the central point of the sample by the surrounding material causes a minimal heat loss in the center, and therefore, the temperature in the center of the sample in the microwave experiments is the highest. The dielectric properties of the sample also determine the energy distribution in the sample, see Figure 6.[41]

The dielectric loss factor (ε'') of a substance strongly depends on the moisture content of the sample. The dielectric loss factor only increases slightly with a moisture content below the critical moisture content (m_c).

For moisture contents above m_c, ε'' steeply increases with increasing moisture content. As a consequence, a higher moisture content results in a higher loss tangent. So, the higher moisture content regions of the sample are heated more efficiently causing higher evaporation rates than in the regions where the moisture content is relatively low. Finally, as compared to conventional heating the moisture distribution will be more homogeneous when using microwave heating. Consequently, the energy uptake will be relatively even.[42] The even temperature distribution (i.e., no hotspots) and the relatively high drying rate make microwaves of great interest for drying thermally unstable compounds.

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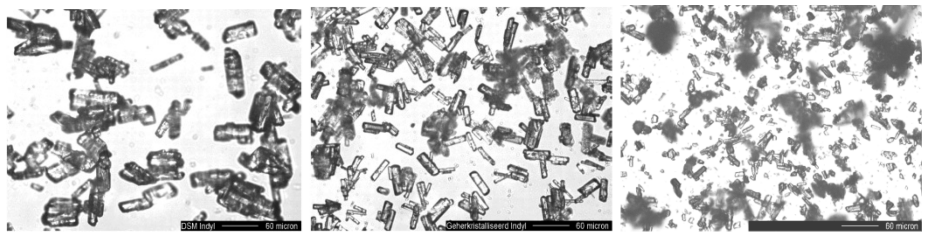

Figure 4. **Microscopic images. Left: original grade of (*S*)-*N*-acetylindoline-2-carboxylic acid. Middle: precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid. Right: *N*-Acetyl-(*S*)-phenylalanine.**

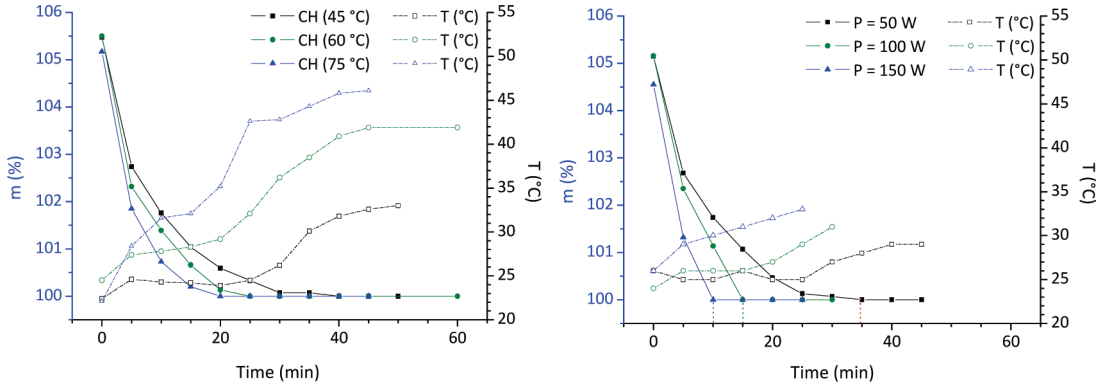

Figure 5. **Drying and temperature profiles for drying of the original grade of (*S*)-*N*-acetylindoline-2-carboxylic acid (5 wt % water) at 5 kPa, at different temperatures and with different microwave powers. Left: conventional heating (CH). Right: microwave heating (MW).**

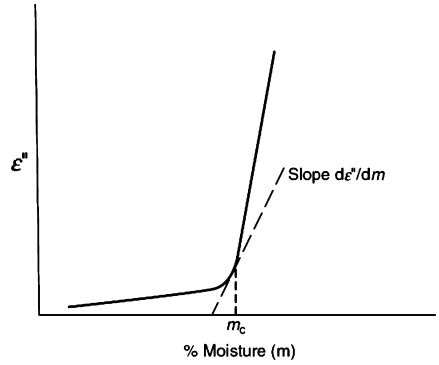

Figure 6. **Dielectric loss factor (ε'') as function of the moisture content, with m_c as the critical moisture content.**

The drying behaviors of the 5 wt % and the 17 wt % samples have been studied for conventional heating (75 °C) and microwave heating (150 W), and the results are collected in Figure 7.

The precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid with 17 wt % water displayed drying times of 70 and 35 min for conventional (75 °C) and microwave heating (150 W), respectively. The original (*S*)-*N*-acetylindoline-2-carboxylic acid grade (5 wt % water) required a drying time of 20 min for conventional heating (75 °C) and 10 min for microwave heating (150 W). The measured bulk temperature during the drying experiments with the precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid was higher (45−60 °C) with microwave heating than with conventional heating (25−50 °C). This contrasts with the observations for the original grade of (*S*)-*N*-acetylindoline-2-carboxylic acid containing 5 wt % water. The higher moisture content of the precipitated grade caused a higher loss tangent of the sample. Consequently, the microwave energy was more readily converted into heat, resulting in an imbalance in the heat supplied by the microwave irradiation and the heat consumed by evaporation of the moisture. The microwave energy, converted into heat in the sample, at 150 W was too high to be compensated by the heat consumption due to evaporation, leading to higher temperatures. When the air flow over the sample is insufficient to remove all of the evaporating moisture, then the air is saturated leading to a higher equilibrium temperature. The higher loss tangent is beneficial for the drying rate of (*S*)-*N*-acetylindoline-2-carboxylic acid, which has relatively good thermal stability. Although the higher energy absorption initially caused faster heating and drying rates, as compared to those of the original grade (*S*)-*N*-acetylindoline-2-carboxylic acid, the higher bulk temperature indicates that microwave irradiation should be applied with due caution for thermally unstable materials.

Drying Behavior of *N*-Acetyl-(*S*)-phenylalanine

To gain more insight into the drying behavior of other solid organic substances using microwave irradiation, the drying behavior of *N*-acetyl-(*S*)-phenylalanine was studied on small scale, see the setup in Figure 2. The sodium salt of (*S*)-phenylalanine was acetylated with acetic anhydride under Schotten−Baumann conditions resulting in a product with a moisture content of 22 wt %, which was immediately suitable for the drying experiments. The particle size of *N*-acetyl-(*S*)-phenylalanine was smaller than that of the original grade of (*S*)-*N*-acetylindoline-2-carboxylic acid, see Figure 4. The drying behavior of *N*-acetyl-(*S*)-phenylalanine with microwave and conventional heating is depicted in Figure 8.

The moisture content of the *N*-acetyl-(*S*)-phenylalanine was even higher than that of the precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid. Such high water content could also lead to superheating of the sample, as described above. This is indeed

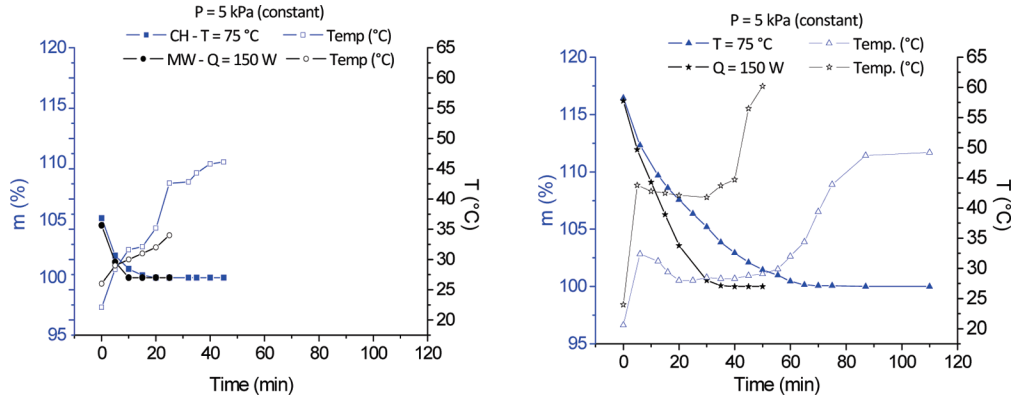

Figure 7. **Weight loss curves and temperature curves for conventional and microwave heating. Left: nonprecipitated (*S*)-*N*-acetylindoline-2-carboxylic acid (5 wt % water). Right: precipitated (*S*)-*N*-acetylindoline-2-carboxylic acid (17 wt % water).**

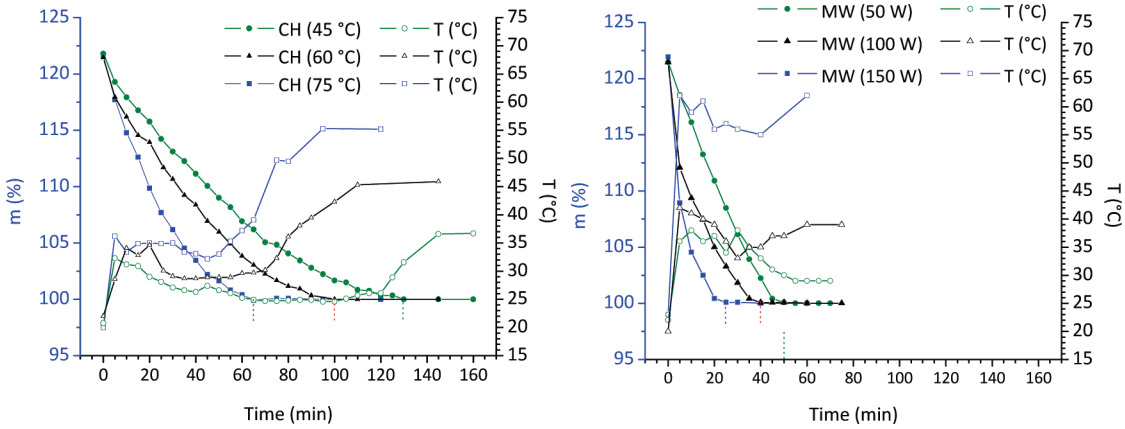

Figure 8. **Drying- and temperature profiles of drying *N*-acetyl-(*S*)-phenylalanine at various temperatures and powers for the conventional at 5 kPa. Left: conventional heating (CH). Right: microwave heating (MW).**

observed for the microwave drying experiment at 150 W, leading to a sample temperature of 60 °C. The drying time for this high-energy input was 25 min, which is extremely short compared to the drying times with conventional heating, for which drying times of 130, 100, and 65 min at 45, 60, and 75 °C, respectively, were registered. At a high bulk temperature of 63 °C *N*-acetyl-(*S*)-phenylalanine remained stable and hence microwave irradiation is a very suitable heating technique for drying this substance. The advantage of lower bulk temperatures combined with a high drying rate under mild microwave irradiation was demonstrated by the drying experiments with a lower microwave power input. The drying times were 40 and 50 min for 100 and 50 W microwave power, respectively. These drying times were shorter than observed for the conventionally heated samples using a water bath of 75 °C, where the sample temperature increased to 55 °C, while the sample temperature under these low microwave power inputs remained below 45 °C. The latter observation indicates that even at high moisture contents microwave irradiation can lead to higher drying rates with lower bulk temperatures, as long as the microwave power is mildly applied.

Drying Behavior of Cocarboxylase Hydrochloride

Having gained a better understanding of the benefits of microwave heating compared to oil bath heating during exploratory drying of some pharmaceutical intermediates in a specially designed small-scale setup in the laboratory, the question was raised how practical the drying efforts could become on larger scales, in particular when more material of thermally unstable substances should be handled. For that purpose, the drying behaviour of a pharmaceutical grade of cocarboxylase hydrochloride was investigated. The thermosensitive enzyme was dried according to different sources from ambient to moderately high temperatures but not higher than 50 −55 °C to avoid degradation.[43−45] The drying times for the enzyme are long enough and can reach even 80 h[46] with conventional heating. Since microwave drying can be most efficient in the case of thermally unstable substances, it was a matter of particular interest to investigate the drying behavior of cocarboxylase hydrochloride with microwave heating.

The drying experiments for this substance were carried out on two scales: in a laboratory environment and on pilot-plant scale.

Laboratory-Scale Experimentation. On laboratory scale a standard 1.5 kW electric vacuum oven for thermal drying of 150−200 g amounts of cocarboxylase hydrochloride was applied. This vacuum convective drying procedure was per-

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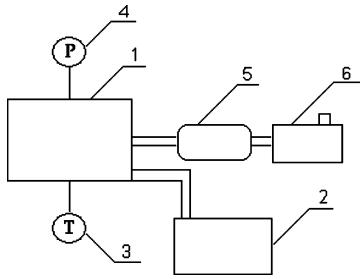

Figure 9. **Schematic image of the experimental laboratory setup used for drying of cocarboxylase hydrochloride with 1: multimode microwave cavity, 2: microwave generator (oscillation frequency 2.45 GHz), 3: temperature sensor (IR - pyrometer), 4: pressure sensor, 5: cold trap, 6: vacuum pump.**

formed with the oven connected to a vacuum system using a water pump, an exhausting vacuum pump and a cold trap. For the microwave-heating experiments an experimental laboratory microwave setup was used, as shown in Figure 9.

Microwave-assisted vacuum drying in both laboratory and larger-scale experiments was conducted under the same conditions including material amounts, initial humidity, temperature, and pressure as in the case of conventional heating. The operating microwave power was within 30−300 W, and the heating rate was approximately 1 °C/min. The moisture content was determined by loss on drying measurements. The drying curves were generated for both conventional and microwave heating, see Figure 10.

The curvature in the range of 1.5−2% critical humidity is characteristic for both curves, showing that the drying rate drastically decreases during the falling rate period. It is evident that the overall drying time with microwave heating is shorter by a factor 10 compared to the conventional process. Apparently, removal of the bound moisture (1.5−2%) is a limiting phase during the whole drying process. Such a dramatic shortening of the drying process can be rationalized by the influence of microwaves on the diffusion times of diffused moisture.

Larger-Scale Runs. The satisfying results in the laboratory encouraged us to move to pilot-plant scale aimed at establishing the scalability and energy consumption efficiency of microwave heating in drying. The larger-scale drying experiments of 3 kg amounts of the enzyme were performed with a rotary vacuum microwave dryer of 35 L chamber capacity (with an optimal filling of about 50% by volume), see Figure 11. The operating microwave power was within 70 and 350 W during the runs, and the rotation rate varied from 6 to 8 rpm, being satisfactory for a thorough agitation of the product. The product temperature was measured with a thermo sensor fixed at the drying chamber wall (bottom part) where the electromagnetic field intensity is close to zero level.

During the constant rate period when the adsorbed moisture at the surface of the particles is removed, see Figure 12, the energy primarily is consumed for evaporation, causing a considerable energy input. For 3 kg of wet product (15.5 wt % moisture) microwave power input ranging from 300 to 350 W was required. The temperature of the product at this stage was determined by the vapour temperature, corresponding to the boiling temperatures of ethanol and water, which did not exceed 30 °C (boiling temperature of water at 30 Torr). After removal of the adsorbed moisture, approximately 30−40 min for 3 kg of material, the temperature rose due to absorption by the product and was determined by the microwave absorbance capacity of the constituents. At this stage much less energy was required. Therefore, after reaching a predetermined range of 50−55 °C for the enzyme, the temperature was maintained by an on/off working regime of the microwave oscillator throughout the drying process. The average value of the microwave power input was about 70 W at this stage and was 5-fold less than at the constant rate period. A rotation of 6−8 rpm was maintained during the whole drying process to prevent any product caking.

To assess the energy efficiency of the microwave drying process with respect to the conventionally heated procedure the actual energy consumption figures were calculated (see Experimental Section for the calculation method). For this purpose the dielectric properties of the enzyme, dielectric constant and dielectric loss, were measured using special equipment,[47] and amounted to 1.95 and 0.03, respectively. The results are presented in Table 2.

The energy efficiencies for both microwave and conventional batch methods were calculated from eq 14 in the Experimental Section. The energy consumption values in Table 2 reveal a tremendous difference between microwave-heated and conventionally heated drying, the efficiency of microwave energy uptake (43%) being in a good correlation with Figure 3 considering that the filling of drying chamber in our runs was only at the level of 15%. Based on this result it may be firmly stated that the level of 70% efficiency may be reached at appropriate filling of drying chamber. Evaluation of the energy uptake $Q_{absorbed}$ during the heating stage was done only for laboratory and batch microwave drying. The closely related thermodynamic and electro-physical $Q_{heating}$ and $Q_{absorbed}$ values (Table 2), the latter being dependent on both the dielectric constants of the substances and electro-technical parameters of the microwave equipment, show that the utilization of microwave energy may be very high under proper conditions. The most reasonable explanation for such an immense difference between microwave and conventional heating is the limited efficiency of conventional heating due to the heat capacity of the material. Therefore, considerably more energy should be supplied for heating than theoretically required. In contrast, microwave heating is not limited by heat resistance due to direct coupling of microwaves with the material and is predominantly determined by the microwave-absorption capacity of the substance, thus minimizing losses to the surroundings. It should be noted that efficient microwave heating was possible in this case despite the relatively low loss tangent of the enzyme.[48]

Discussion

The similarity in chemical structure between (*S*)-*N*-acetylindoline-2-carboxylic acid and *N*-acetyl-(*S*)-phenylalanine can-

(47) Voloshko, A. Yu.; Kramskoy, G. D.; Kramskoy, Ye. D.; Samoilov, V. L.; Seminozhenko, V. P; Chepkiy, A. A.; Shishkin, O. V. *Method for measurement of dielectric constant and dielectric loss*, Ukrainian patent number 34146, 2008.

(48) It is generally accepted that substances with tg $\delta < 0.1$ are considered low microwave absorbing, e.g. the value for water which is considered to have a moderate microwave absorbance capacity is 0.123.

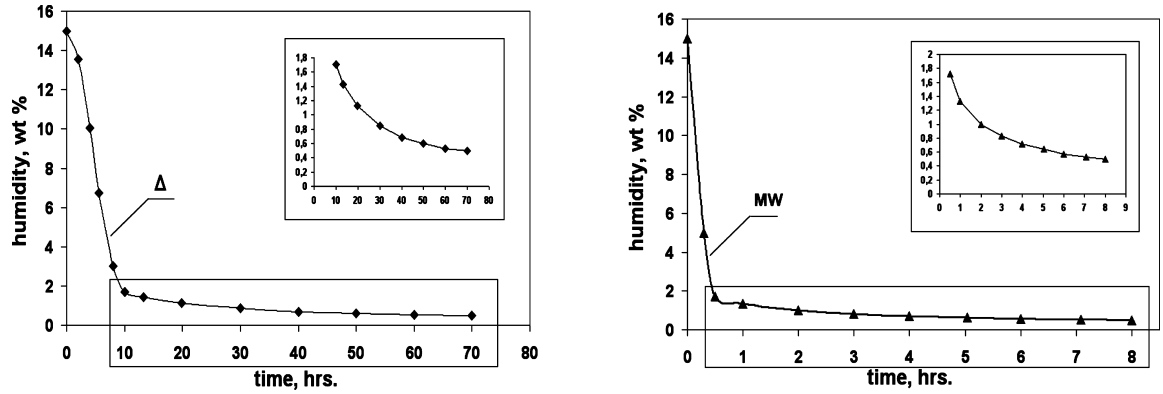

Figure 10. **Kinetics of conventional drying (left) and microwave drying (right) of cocarboxylase hydrochloride (the longer falling rate period is shown with higher resolution in the inset).**

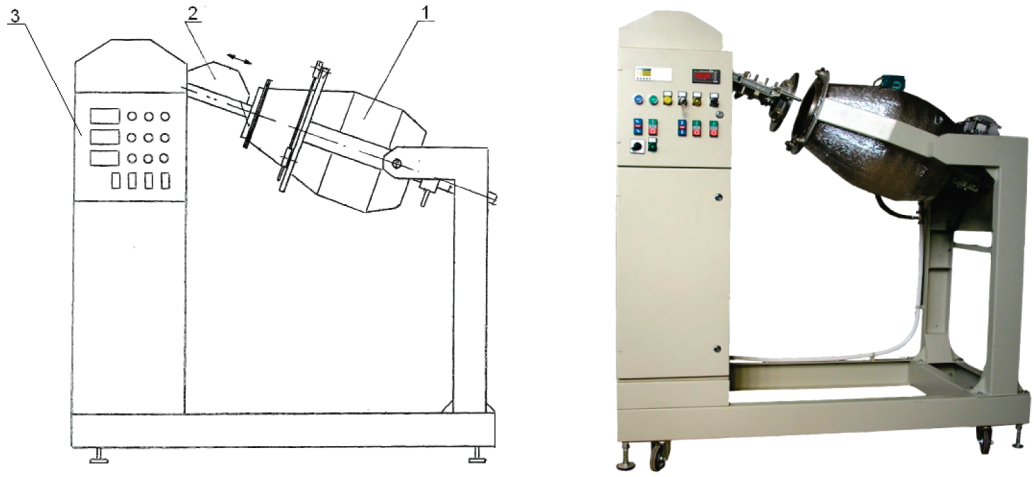

Figure 11. **Industrial rotary vacuum microwave dryer "Pharma-Micro". Right: photograph. Left: principal scheme. (1) Rotary drying chamber with microwave resonator. (2) Microwave oscillator. (3) Control unit.**

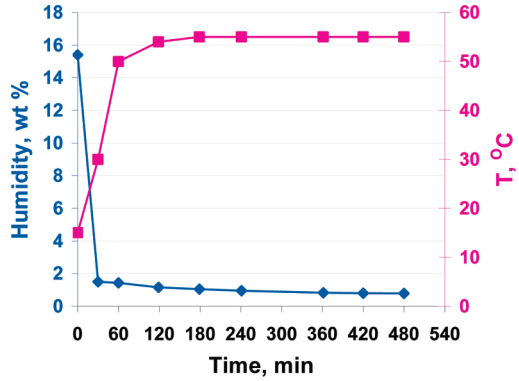

Figure 12. **Microwave drying and temperature curve of cocarboxylase hydrochloride including removal of both free (first stage) and bound (occluded water during second stage) moisture.**

not be directly translated into a similar drying behavior. Also the particle size may influence the drying behavior. A smaller particle size corresponds to a higher specific surface and a smaller channel or pore size. The higher surface area could increase the drying rate, particularly for the unbound water. A smaller pore size may decrease the amount of pore moisture but could inhibit the removal of the moisture from these pores. The packing of the particles of various sizes is also different, leading to a different pore size and a difference in diffusion rate of the moisture through the sample. All of these factors make it hard to predict the effect of a smaller particle size on the drying behavior.

The results of the microwave drying behavior of all three substances show a clear similarity with respect to a faster decrease in moisture contents compared to conventional heating during the constant rate period where free moisture is removed. This observation can easily be explained by the volumetric and inertia-less nature of microwave heating. However, for the enzyme this difference between both heating methods is more expressive than for the pharmaceutical intermediates. Moreover, the effect of instant heating allowed sufficiently precise temperature control, thus avoiding the risk of overheating, the latter being a valid argument in favor of microwave drying of thermolabile substances.

Conclusions

A comprehensive study of drying processes for substances of various natures and properties has been carried out, comparing microwave with conventional heating techniques. From the results described for the drying of (*S*)-*N*-acetylindoline-2-carboxylic acid (both original and precipitated grades), of *N*-acetyl-(*S*)-phenylalanine, and of the enzyme cocarboxylase hydrochloride under conventional and microwave heating, it can be concluded that microwave irradiation leads to considerably higher drying rates. The power input when using microwave irradiation should be chosen carefully. A high power input

Table 2. **Drying characteristics of cocarboxylase hydrochloride during conventional and microwave heating**

	heating method		
	microwave lab	microwave batch	conventional batch
heating time to predetermined temp. (h)	0.25	0.5	5
heater power (W) at first drying step (removal of adsorbed water)	300	350	150[a]
overall drying time (h) (average)	8	8	70
heater power (W) at second drying step (removal of bounded water)	30	70	150[a]
Q input[b] (kJ) (heat source and vacuum pump)	15.5×10^3	45×10^3	420×10^3
Q input[b] (kJ) (heat source only)	10^3	2.5×10^3	40×10^3
Q heating[c] (kJ)	18	380	380
Q vaporization[d] (kJ)	48	700	700
Q absorbed[e] (kJ)	21	400	−
energy efficiency (%)	10	43	∼3

[a] Average value for the whole process. [b] Experimental value comprises heater/vacuum pump power input, calculated from eq 8 in the Experimental Section. [c] Calculated from eq 10 in the Experimental Section. [d] Calculated from eq 11 in the Experimental Section. [e] Calculated from eqs 12 and 13 in the Experimental Section for microwave-assisted drying only.

enables a dramatic decrease of the drying time of the sample but can also lead to overheating and thermal product decomposition. A balance between both overheating and fast drying should be aimed at. However, even for mild conditions the drying rate is much higher than for similar heat-flow rates with conventional heating. It has even been shown that substances with low microwave absorbance may be successfully dried.

To obtain similar drying rates, conventional heating demands much higher heat-flow rates than microwave heating. Higher heat-flow rates lead to rather large temperature differences between the heating element and the sample and to very high temperatures inside the sample, which may be detrimental for thermally unstable materials. Lower temperatures during drying by microwave irradiation make this heating technique extremely appropriate for drying in short periods of time.

Estimations of the energy consumption figures for cocarboxylase hydrochloride revealed a high efficiency for microwave heating which can be up to 70% of energy utilization at 50% filling of the drying chamber. This value can hardly be imagined for conventional technologies.

In brief, the results of this study revealed a number of benefits of microwave heating such as scalability, high drying rates, energy savings (by a factor of 10), accurate temperature control, and better product quality due to a minimized risk of product degradation regardless of the chemical structure and physicochemical properties of the substances.

Experimental Section

All starting materials including wet cocarboxylase hydrochloride (moisture content of ∼15 wt %) were obtained from commercial suppliers and used as received unless indicated otherwise. In case of need the wet cocarboxylase hydrochloride was kept in a refrigerator at $T \leq 10$ °C for no longer than 24 h before drying.

All moisture-sensitive reactions were performed under an atmosphere of dry argon. ^{1}H NMR spectra were recorded on a Varian Gemini (400 MHz). Proton chemical shifts were reported in ppm downfield from tetramethylsilane (TMS).

Drying Procedures of (*S*)-*N*-Acetylindoline-2-carboxylic Acid and *N*-Acetyl-(*S*)-phenylalanine. During the conventionally and microwave-heated experiments, a three-neck 250-mL flask was charged with 15 g of either (*S*)-*N*-acetylindoline-2-carboxylic acid or *N*-acetyl-(*S*)-phenylalanine. A temperature probe was inserted in the central neck and placed at a constant height in the exact center of the sample. An air-inlet tube was connected to another neck of the flask. The air-inlet tube was connected to a capillary tube. The capillary tube ensured a constant air flow. The flask was held at a constant pressure of 50 mbar by an oil pump connected to the third neck. The flask was heated by either a magnetically stirred (750 rpm) water bath of the indicated temperature for the conventionally heated experiments or the power-controlled microwave with the indicated power settings. The weight was measured at constant time intervals. Water losses (in weight) were quantified by:

$$m\% = 100 + \frac{(m_{\text{wet}} - m_{\text{dry}}) \cdot 100}{m_{\text{wet}}}$$

where $m\%$ = decrease in mass (%), m_{wet} = mass of wet substance (g), m_{dry} = mass of dry substance (g). The temperature of the sample was recorded at constant time intervals by either a thermocouple for the experiments with conventional heating or by a fiber-optic sensor in the microwave oven. The dry substances showed no traces of degradation after the drying procedure.

Again, no stirring and a sufficient air purge guaranteed that the evaporation rate and the diffusion rate of the surface and inner-pore bound water governed the rate of the drying process. This time during the runs, not the temperature but the power was chosen as the variable. A commercially available, automated multimode microwave oven MicroSynth from Milestone srl (Italy) was used. This oven operates at 2.45 GHz and is temperature controlled by a fiber-optic sensor. The maximum power input could be adjusted between 0 and 1000 W.

Drying Procedures of Cocarboxylase Hydrochloride. For the laboratory experiments 150−200 g amounts of wet enzyme material (humidity 10−15%) were taken for both conventional and microwave experiments. Drying was performed at 25−30 Torr at temperatures below 55 °C. At the constant drying rate interval when the removal of free moisture took place, the product temperature was ≤30 °C at the given pressure, which was determined by the vapour temperature (ethanol and water).

Then the temperature was increased gradually, to avoid overheating, to 50−55 °C by regulating the power input of an electric heating unit in the case of conventional drying and of a microwave oscillator in the case of microwave-assisted drying. A constant air flow was provided to remove water vapours and to maintain a constant humidity in the drying chamber.

During the microwave pilot-plant scale runs, 3 kg of wet enzyme material after centrifuging was placed in the drying chamber (which was then evacuated to 25−30 Torr) and was dried under the same conditions as those for the laboratory experiments. For a better mass transfer of the moisture, rotation of the drying chamber was provided in the range of 6−8 rpm. The drying curves were generated by measuring the loss on drying at 100 °C in the samples taken during drying at 1.5−2 h intervals (except for the first sampling which was after 0.5 h of drying). The moisture content was determined by measuring loss on drying for each sample in duplicate. After reaching the critical moisture content (1.5−2%) the samples in both conventional and microwave experiments were subjected to mechanical milling for product homogenization and breakage of the agglomerates that might be formed during drying due to particle aggregation.

Base−Acid Precipitation Procedure of (*S*)-*N*-Acetylindoline-2-carboxylic Acid. A 2500-mL three-neck, round-bottomed flask was charged with (*S*)-*N*-acetylindoline-2-carboxylic acid[40] (300 g, 1.47 mol) and was dissolved in NaOH solution (770 mL, 2.0 M). Using a dropping-funnel this mixture was brought to pH 3 with 4 M HCl (approximately 385 mL) under stirring. The precipitated product was then filtered under vacuum and consecutively washed with saturated brine (200 mL) and demineralised water (100 mL). The filtrate was dried in air for two days, yielding 95% (*S*)-*N*-acetylindoline-2-carboxylic acid (99% ee). The moisture content was 17 wt % upon drying in air for two days.

Synthesis of *N*-Acetyl-(*S*)-phenylalanine. A 2500-mL three-neck, round-bottomed flask was charged with (*S*)-phenylalanine (198 g, 1.2 mol). (*S*)-Phenylalanine was dissolved in NaOH solution (300 mL, 4.0 M). Under vigorous stirring and ice bath cooling, acetic anhydride (122.4 g; 1.2 mol) was added dropwise with simultaneous addition of NaOH solution (300 mL, 4.0 M). The pH was maintained at 10. After 2 h, additional acetic anhydride (122.4 g; 1.2 mol) was added dropwise with simultaneous addition of NaOH solution (300 mL, 4 M). Using a dropping-funnel this mixture was brought to pH 3 with 6 M HCl (approximately 25 mL). The precipitated product was then filtered under vacuum and washed with brine (200 mL) and demineralised water (100 mL). The solid was dried in air for two days, yielding 295 g of crude product with a moisture content of 22 wt % and finally pure product (230 g dry product, 93%). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.51 (m, 5H) 4.92 (m, 1H), 3.45 (dd, 2H), 3.20 (dd, 2H), 2.15 (s, 3H) confirmed that all (*S*)-phenylalanine was acetylated. The specific rotation of the dry product was $[\alpha]^{23}_D = +28$ ($c = 1.0$, MeOH), literature: $[\alpha]^{23}_D = +33$ ($c = 1.0$, MeOH).[49]

Calculation of Power Input for (*S*)-*N*-Acetylindoline-2-carboxylic Acid and *N*-Acetyl-(*S*)-phenylalanine.

$$Q = U \cdot A \cdot \Delta T \tag{1}$$

$$A = 2\pi r \partial h \tag{2}$$

Q = power supplied to the flask (W)
U = overall heat transfer coefficient (W/(K.m^2)
A = heat transfer area (m^2)
ΔT = temperature difference (K)
dh = submerged depth of the flask in the water bath (m)

$$\frac{1}{U} = \frac{1}{h_{water}} + \frac{l}{k} \quad h_{water} = \frac{Nu \cdot k_{water}}{D} \tag{3}$$

Nu = Nusselt number
k = thermal conductivity coefficient (W/m K)
D = diameter (m) (0.085 m)

$$Nu = 2.0 + 0.66 Re^{1/2} \cdot Pr^{1/3} \tag{4}$$

$$Re = \left(\frac{\rho \cdot v \cdot D}{\mu}\right)_{H_2O} \Rightarrow \frac{998 \cdot 3.34 \cdot 0.085}{0.000894} \approx 3.2 \times 10^5 \tag{5}$$

$$Pr = \left(\frac{c_p \cdot \mu}{k}\right)_{H_2O} \Rightarrow \frac{4200 \cdot 0.000894}{0.58} \approx 6.47 \tag{6}$$

$$v = 2\pi r \cdot \left(\frac{n}{60}\right) \Rightarrow 2\pi \cdot 0.0425 \cdot \left(\frac{750}{60}\right) \approx 3.34\ m/s \tag{7}$$

Re = Reynolds number
Pr = Prandtl number
ρ = density (kg/m^3) (998 kg/m^3)
v = velocity (m/s)
r = radius flask (m) (0.0425 m)
n = rotational speed stirrer (750 rpm)
D = diameter (m) (0.085 m)
μ = viscosity (Pa/s) (8.94×10^{-4} Pa/s)
c_p = heat capacity (J/kg K) (4200 J/kg K)

Calculation of Energy Consumption Values for Cocarboxylase Hydrochloride.

$$Q_{input} = P \times t \tag{8}$$

Q_{input} = energy input during drying (J)
P = heat source/vacuum pump power (W)
t = drying time (s)

In the case of microwave heating:

$$Q_{input} = P_{MW} \times t \tag{9}$$

Q_{input} = energy input during drying (J)
P_{MW} = microwave power input (W)
t = action (on) period of microwave generator (s)

(49) Smith, H. E.; Neergaard, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 116.

$$Q_{\text{heating}} = m \times c \times \Delta T \quad (10)$$

Q_{heating} = energy required for heating (J)
m = weight of the material (g)
c = heat capacity (J/g·K)
ΔT = difference between the initial and final temperatures (K)

$$Q_{\text{vaporization}} = m \times Q_{\text{boil}} \quad (11)$$

$Q_{\text{vaporization}}$ = energy required for vaporization of volatiles (J)
Q_{boil} = specific boiling heat of volatiles (J/g)
m = weight of the material (g)

$$Q_{\text{absorbed}} = P \times V \times t \quad (12)$$

Q_{absorbed} = energy absorbed by dielectric irradiated by microwaves (J)
P = microwave power absorbed by dielectric in a unit of volume (W/cm^3)[50]
V = bulk volume (cm^3)
t = time (s)

$$P = 0.3 \times E^2 \times f \times \varepsilon'' \times 10^{-6} \quad (13)$$

E = microwave field strength (V/cm)
f = microwave generator frequency (MHz)
ε'' = tan $\delta \times \varepsilon'$ (dielectric loss factor)
tan δ = dielectric loss tangent
ε' = dielectric permittivity

The efficiency of the energy utilization was estimated by:

$$\frac{Q_{\text{heating}} + Q_{\text{vaporization}}}{Q_{\text{input}}} \times 100\% \quad (14)$$

Q_{heating} = energy for heating (J)
$Q_{\text{vaporization}}$ = energy for vaporization (J)
Q_{input} = energy consumed by heat source only (J)

(50) Okress, E. C. *Microwave Power Engineering*; Academic Press: New York and London, 1968.

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