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SOLVENT-INDUCED PHASE TRANSFORMATIONS OF HYDRATES

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Abstract

An increase of the specific surface area of solid phases is often desirable e.g. for the bioavailability of pharmaceuticals or in chemical processes. Such an increase can a.o. be achieved by suspending crystalline substances in a solvent that induces phase transformations. Hence, the original substance has to be in a metastable state in the solvent. If the stable phase after transformation has in addition a very low solubility in the solvent, a dendritic growth is forced to occur because of the high local supersaturations during the phase change. This dendritic growth of the stable phase in term leads to needle- or whisker-like crystals, which have the desired larger specific surface area in comparison to the initial crystalline substance.

In order to investigate this phenomenon several hydrates of salts were chosen, which undergo phase transformations to their anhydrates accompanied by a corresponding loss of crystal water when suspended in excess in lower alcohols. Consequently, anhydrous forms were created by dehydrating these hydrates. The transformation rate or in this case the dehydration level can thus be indirectly measured by Karl-Fischer titration. The thermodynamic background of the dehydration phenomena can be clarified by solubility studies of the hydrates and anhydrates in water/alcohol-mixtures.

Keywords: dehydration, increase of the specific surface area, pseudopolymorphism, solubility measurements of metastable phases, solvent mediated phase transformation

Introduction

For quite some time the interest of pharmaceutical and chemical industry in the behavior of polymorphs and pseudopolymorphs, i.e. solvates and hydrates, is increasing. Due to the relevance of the dissolution rate, bioavailability or solid properties of crystals the knowledge of the parameters influencing the desired modification is a question of increasing importance. Up to date there are no predicting possibilities for the number of available modifications.

When evaluating the appearance of polymorphic phases the temperature as well as the solvent has to be varied. Since some substances are capable of crystallizing as pseudopolymorphs, i.e. they bind the solvent in a certain molar ratio in the lattice, attention must be paid to this behavior, too.

Our main interest is the phase transformation of organic and inorganic hydrates of salts occurring in lower alcohols. To our knowledge only one investigation exists dealing with this phenomenon which is Ali [1] and Barber and Ali [2]. However, the authors do not yet use the term pseudopolymorphism. From our point of view they

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do not sufficiently explain the underlying mechanisms. Pseudopolymorphic phase transformations of pharmaceuticals obviously have more relevance, as it is reflected in the work e.g. of Byrn [3], Giron [4], Grant (Ghosh *et al.* [5], Zhu *et al.* [6, 7]), Haleblian [8], Kuhnert-Brandstätter [9], Marti [10, 11], McCrone (Woodard *et al.* [12]), and Shefter [13].

When polymorphic or pseudopolymorphic phases appear it is the usual procedure to detect and to use the most stable one which consequently has the lowest solubility and the lowest free energy. Unfortunately, this is inconsistent with the demand for high dissolution rates, because the phase with the lowest solubility in a certain solvent usually has the lowest dissolution rate. To achieve the desired dissolution rates, though, concessions are made to the stability and other physical properties of the phase as long as these do not prevent processing of the corresponding substance. One of these physical properties is the shape of the crystals. Needle- or whisker-like crystals considerably complicate processes like formulation and tabletting, however, they lead to a significant increase in the specific surface area thus improving the dissolution behavior and chemical reactions.

Experimental

Kinetics

To exclude the influence of temperature and pressure, all experiments were performed isothermally at 25°C and under ambient pressure (isobar). From a screening of several organic and inorganic hydrates it is known that most of the salts crystallized from an aqueous solution, tend to transform into lower hydrates or the anhydrate, when suspended in lower alcohols (Nordhoff [14, 15]). Therefore, seven salts were randomly chosen for our investigations. The inorganic substances were copper sulphate pentahydrate ($CuSO_4{\cdot}5H_2O$), magnesium-sulphate heptahydrate ($MgSO_4{\cdot}7H_2O$), sodium sulphate decahydrate ($Na_2SO_4{\cdot}10H_2O$), sodium hydrogenphosphate dodecahydrate ($Na_2HPO_4{\cdot}12H_2O$), sodium carbonate decahydrate ($Na_2CO_3{\cdot}10H_2O$) and barium chloride dihydrate ($BaCl_2{\cdot}2H_2O$). The organic substance was tricalcium dicitrate tetrahydrate ($C_{12}H_{10}O_{14}Ca_3{\cdot}4H_2O$; ‘calcium citrate’). By means of XRD-measurements it could be guaranteed, that in no case solvation, for example into a methanolate occurred.

First of all, each salt was suspended at a mass ratio of 1:10 in methanol. As mentioned above the solubility of the hydrates in the chosen solvent must be low (approx. <<3wt%) in order to reach the high local supersaturations during the phase change. Therefore, only a small part of the hydrate dissolves while the major part remains undissolved thus forming a suspension. After a few seconds these samples were stored quiescently in a thermostated water bath for later optical observations of the suspensions.

An image analyzing system, consisting of a microscope with a CCD-camera connected to a VCR was used. This way, it was possible to record the phase transformations.

To investigate the kinetic behavior, each sample was kept constantly stirred at exactly 25°C (±0.1°C). Since each phase transformation of hydrates is accompanied by a change in crystal water (dehydration), it is possible to determine the transformation through the change in water content in the liquid phase by Karl-Fischer titration. For this reason small liquid samples were taken (approx. 10 μl) over a certain period of time depending on the dehydration behavior. The water content of these samples was measured using a Mettler-KF coulometer 684. The measurements were terminated, when the water content did not change significantly anymore.

To quantify the degree of conversion (dehydration) the water balance was calculated from the measured water contents to define a dehydration level D as a function of time (Eq. (1)).

$$D=\frac{m_{\mathrm{cw}}}{m_{\mathrm{cw,max}}} \quad \text{with} \quad m_{\mathrm{cw}}=\frac{x(m_{\mathrm{l}}+m_{\mathrm{cwh,sol}}+m_{\mathrm{h,sol}}(\text{waterfree}))-m_{\mathrm{cwh,sol}}-m_{\mathrm{wl}}}{1-x} \qquad (1)$$

where: m_{cw} mass (mg) of crystal water, already dehydrated from the hydrate,

$m_{\mathrm{cw,max}}$ mass (mg) of crystal water, that can be maximally dehydrated, (which is the mass of stoichiometric crystal water),

x measured water content (wt%) in the liquid phase at time t (min),

m_{l} mass (mg) of solvent (alcohol, including the initial water content, see m_{wl}),

$m_{\mathrm{cwh,sol}}$ mass (mg) of crystal water from dissolved hydrate,

$m_{\mathrm{h,sol}}$ mass (mg) of dissolved (waterfree) hydrate,

m_{wl} mass (mg) of the initial water content in the solvent.

Hence, D=0 corresponds to no dehydration while D=1 to a complete dehydration. In the latter case the entire crystal water of the undissolved hydrate can be found in the liquid phase and the hydrate is completely transformed into the anhydrate. In order to be able and calculate an accurate water balance for the undissolved hydrates, two water contents have especially to be taken into consideration: the crystal water from the dissolved hydrate $m_{\mathrm{cwh,sol}}$ and the initial water content in the solvent m_{wl}. Moreover, attention has to be paid to the preparation of the liquid samples for Karl-Fischer titration. It has to be assured, that none of the crystals in the liquid phase are in the sample for the titration, because this destroys the measurement. To prevent this problem the samples were given the opportunity to settle (stirrer off). If this is not sufficient, microfiltration was applied. The overall stochastic error of the Karl-Fischer titration measurements can be assumed to be less than 10%.

With regard to identical thermodynamic conditions and Eq. (1) the stirred samples were not prepared at a constant mass ratio, but in a way that the water content after complete dehydration is always the same. This water content was chosen to be 1 wt%. Consequently, the mass ratios of the different hydrates to the solvent are different, depending on the stoichiometric crystal water content.

Thermodynamics

The main objective when considering dehydration phenomena is to detect the phase with the lowest solubility in a certain solvent. Here, such phases can be several hydrate forms, normally stable at room conditions, but also the corresponding anhydrous forms. Dealing with these pseudopolymorphs it has to be taken into account, that every change in the crystal modification, i.e. the composition of the hydrate, is accompanied by a change of the properties of the solvent, because the crystal water is mixed with the initial solvent (if they are miscible, which holds for water/alcohol systems). Therefore, solubility measurements were carried out, but isothermally at 25°C with different water/alcohol mixtures as the thermodynamic parameter under variation.

The same hydrates employed for the kinetic investigation, which are stable at room temperature, as well as the corresponding anhydrates were used for solubility measurements in water/methanol mixtures. Due to the changing properties of the solvent during the dissolution process the hydrates were not added in excess, but in small increments. This technique is inconsistent with the definition on how to prepare a saturated solution. According to the definition a solution is only at equilibrium when its specific solid phase is present.

In the case discussed here all the solid phases present in the suspensions transform, when they are not the thermodynamically stable ones. Therefore, a hydrate transforms in methanol into a hydrate with a lower stoichiometric water content or the anhydrate, respectively, thereby increasing the water content of the solvent. Hence, suspending hydrates in excess leads to a not neglectable increase of the solvent's water content. This error is depending on the mass ratio of the hydrate present in the system to the mass of the solvent, as well as on the specific alcohol/water mixture. Additionally the stoichiometric hydrate change is important for this influence. The increasing water content must be taken into account, when detecting the real solubility of a certain hydrate at a specific alcohol/water mixture. The technique of adding increments of hydrates to the solvent is therefore applied.

The samples were visually observed over a period of at least 48 h. That means that if the crystals are not fully dissolved, the sample is continuously stirred for at least 48 h. Visual detection of the saturation conditions usually leads to errors because small crystals (nuclei) cannot be seen without a magnification technique. To evaluate this error the detected solubilities of the hydrates in water were compared to the literature data (e.g. [16]). The differences did in no case exceed 5%. Therefore, this maximum error was assumed for all measurements in water/alcohol mixtures.

After each solubility measurement another small amount of the salt was suspended in a certain water/methanol mixture for further characterization of the solid phase. The samples were filtered and the solid phase – still humid – was prepared for DSC measurements. These measurements were performed using a Mettler TA Instrument DSCl2E with unsealed Al-crucibles, sample masses between 5 and l0 mg and a heating rate of 5 K min^{-1} under nitrogen gas purge. The humidity of the samples is most important for the stability of the sample during preparation and measurement. In case of using too dry a sample, phase transformations could not be excluded. In order to distinguish between endothermic peaks due to the evaporation of solvent from the surface of the samples and those resulting from the actual dehydration of the salt, they were compared to DSC results from the initial hydrate and anhydrate phases.

Results and discussion

Micrographs of the dehydration phenomena

Two examples of the dehydration of inorganic hydrates in methanol (quiescent samples) are given in Fig. 1.

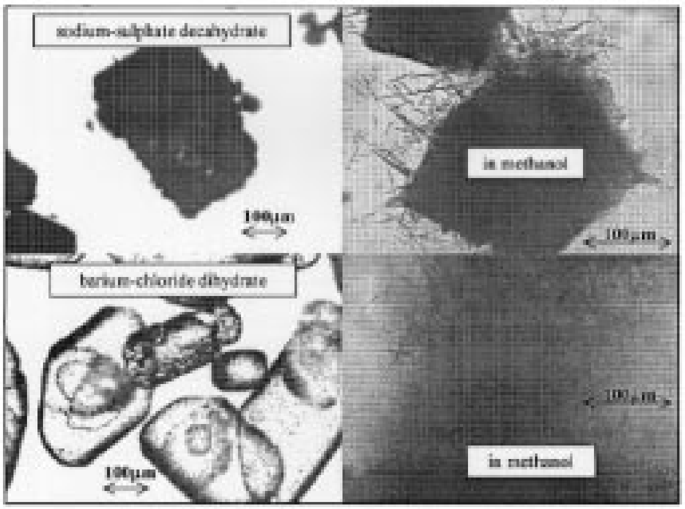

Fig. 1 Habiti of the original and dehydrated crystal hydrates

As can be clearly seen, suspending the hydrates in methanol leads to an unequivocal change in their habiti. The sodium sulphate decahydrate, usually transparent, already appears opaque since it is fairly unstable at the given conditions on the slide which causes a thermally induced dehydration resulting in the observed opacity (upper left). From the micrograph in the upper right the needles or whiskers growing on a hydrate's surface in methanol can be seen. Barium chloride dihydrate shows a similar behavior. However, the basic crystals cannot be recognized in the methanol anymore since the dehydration of the hydrate already is completed (cf. lower micrographs). The whiskers found for both salts can be attributed to the high local supersaturations during the phase change which in turn are caused by the low solubilities of the hydrates in methanol. The dehydration is a solvent mediated phase transformation in the sense of the definition of Cardew and Davey [17].

The original suspension of barium chloride and methanol, from which the sample for the micrographs are taken from, is a gel. It looks like a solid phase without any solvent. However, as is typical for gels the solvent is bound in the cavities between the solids (here needles). Stirring these samples would break the needles resulting in a flowable suspension.

From the photographs a qualitative idea of the increase of the specific surface area can be deduced. Assuming that the initial hydrate crystals are spherical having a diameter of 400 µm the specific surface area increases by a factor of more than 300 if these spheres are transferred into a number of whiskers (anhydrates) of 3 µm in length and 1 μm in diameter. The assumption regarding the length of the whiskers becomes correct, if breakage of the thin whiskers e.g. by stirring the suspension is taken into consideration. The increase in specific surface area is dramatically stronger, if the diameter of the whiskers is distinctly smaller than 1 μm.

Dehydration behavior

Results of the kinetic investigations of the seven hydrates are depicted in Fig. 2.

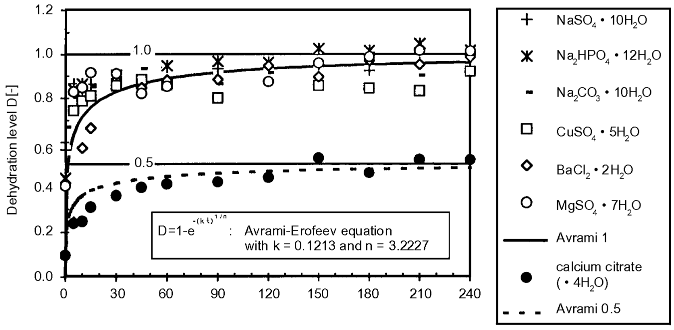

Fig. 2 Dehydration level of the hydrates stirred in methanol at 25°C over the time

All samples show a logarithmic increase of the dehydration over the time, which is quantified by the dehydration level, calculated from Eq. (1). As mentioned in the experimental part, a complete dehydration causes a final water content of 1 wt% in the liquid phase in each case due to the specifically different mass ratios hydrate/solvent. A complete dehydration, i.e. a solvent mediated phase transformation into the anhydrate, corresponds to a dehydration level equals 1. Hence, the obtained anhydrous forms remain anhydrous since they are thermodynamically stable (see 'solubility measurements'). Taking the deviations resulting from errors of the Karl-Fischer titrator into account the dehydration behavior of the hydrates can be regarded as equal. They dehydrate within 5 min up to approx. 60%, within 1 h up to 90% and after 3 h they reached 95% of dehydration.

The calcium citrate tetrahydrate ('calcium citrate'), however, reveals a special behavior. Obviously the dihydrate is the thermodynamically stable phase in methanol but not the anhydrate. Therefore, the dehydration level converges at 0.5 and not at 1 as it would be the case for complete dehydration of 'calcium citrate'. As evidence it was not possible to characterize that dihydrate via XRD-measurements, because a dihydrate is not yet mentioned in literature. However, the powder pattern is completely different from that of the tetrahydrate.

To quantify the measured dehydration level, several empirical equations known from the field of decomposition reactions (e.g. Byrn [3]) were applied to the data. It was found that only an equation of the type of an Avrami-Erofeev equation is able to fit our experimental results. That is the strong increase at the beginning followed by the decline of the curve's slope after approximately one hour is the difficulty. A non-linear regression of the data for Eq. (2) yields the following kinetic parameters: k=0.12 and n=3.22.

$$D = 1 - e^{-(kt)^{1/n}} \tag{2}$$

The upper limit of D is always marked by 1 with exception for calcium citrate, where the limit of D is 0.5. The dehydration behavior might be governed by two phenomena: l.) The boundary layer of water surrounding the phase transforming hydrate increases in thickness with time during the unstationary stirring phase. Consequently, the water can leave the boundary layer only by diffusion, which is a limiting factor. 2.) The driving force of the dehydration, i.e. the solubility difference of the two phases, decreases with increasing water content in the bulk (cf. also the results of the solubility measurements). However, the other empirical equations from literature [3] taking these phenomena into account did not fit the experimental values. Therefore, the use of the Avrami-Erofeev equation is interesting for technical aspects, however, it seems not easy to reveal a physical meaning for the molecular processes.

Solubility measurements

It is always difficult – and sometimes impossible – to obtain the true solubility, especially for metastable phases. In the case of metastable phases the solubility – or more exactly, the ‘metastable’ solubility – should be always higher than the solubility of the stable phase. However, the measurements usually yield the same solubilities for the hydrate and the anhydrate for a certain mixture of water and methanol. This is because in most cases the hydration of the anhydrate or the dehydration of the hydrate, is much faster than the dissolution, so that it is only possible to measure the stable phase in the solvent as an equilibrium value. However, the two typical phases of magnesium sulfate, the heptahydrate and the water-free anhydrate, behave exceptional. Results obtained are shown in Fig. 3.

Three areas can be distinguished in the diagram (Fig. 3). On the left hand side at high methanol contents of the solvent the anhydrate is the stable phase. That means that the solubility of the anhydrate is lower than the hydrate. The grey shaded area in the middle should be the area of the transition point, where both phases, the anhydrate and the hydrate are stable. The third area on the right hand side is the one where the hydrate is the stable phase, and the anhydrate has the higher solubility. Consequently, the phase transformations from the hydrate to the specific anhydrates (Figs 1 and 2) are reversible, i.e. depending on the water content in the methanol/water mixture. It is suggested to use the term ‘enantiotropic system’, since the behavior is quite similar to polymorphic systems (transition point, reversibility, stability). The units, solubility in [$\text{mol}_{\text{anhydrous substance}}/\text{l}_{\text{solution}}$] and water/methanol mixture in (vol%) were chosen in order to make the results comparable with measurements of Grant and co-workers [5–7], as explained in the following.

As mentioned above it is not possible to measure the solubility of the hydrate at the desired water/methanol mixture, because dissolution as well as dehydration of undissolved hydrate phase (e.g. in excess) significantly influence the mixture’s composition. The solubility in pure alcohol on the other hand cannot be measured too, even if the initial water content in the methanol is neglected. For that same reason it can be seen in Fig. 3, that the first hydrate measurement on the left hand side (grey triangle) amounts to approx. 0.5 $\text{mol}_{\text{anhydrous substance}}/\text{l}_{\text{solution}}$ in a mixture containing approx. 7 vol% water. At this point precipitation of the anhydrate occurs, the solubility of which strongly decreases (most left black triangle). The solubility of the anhydrate is reached, namely at the same water content.

In the grey area of the transition point both solubilities are fairly low and no precipitation is observed. To the right of this range the solubilities of both phases increase with increasing water content in the mixture. In some cases the solubilities of the anhydrates are slightly higher, however, hydration and precipitation phenomena take place as well. In pure water (most right grey circle) the anhydrate has a solubility higher than that of the hydrate. However, a new phase precipitates, namely the hydrate. Thus reducing the absolute amount of water in the liquid phase due to the incorporation of water in the precipitated hydrate at the corresponding molar ratio. Therefore, the true solubility of the black circle is that of the white triangle, namely that of the hydrate (see most right arrow). The solubilities of the precipitated anhydrates behave in the same way. They seem to be smaller than the solubilities of the hydrate if the transfer of water from the mixture into the lattice of the precipitated hydrate is not taken into consideration. Its true solubilities are represented by the diagonal arrows in the diagram.

The real solubilities of the metastable phases, i.e. the anhydrate in mixtures with a higher water content and the hydrate in mixtures with a higher methanol content can only be measured if the solubilities are within the metastable zone of the stable phase. This behavior is represented in Fig. 4 following the considerations of Nyvlt [18].

The diagram shows the solubility of two phases in dependence on the thermodynamic parameter such as temperature, pressure or the composition of the mixture of solvents. In order to be able to compare Fig. 3 with Fig. 4 an ‘enantiotropic’ system with a transition point at a certain value of the considered thermodynamic parameter was chosen. The dashed lines denote the specific limits of the metastable zones of the two phases I and II. In case 1 the solution is supersaturated at point A with respect to phase II as the metastable phase (Ostwald’s rule of stages). Phase II precipitates until a saturated solution is reached (point B). However, this saturation is out-

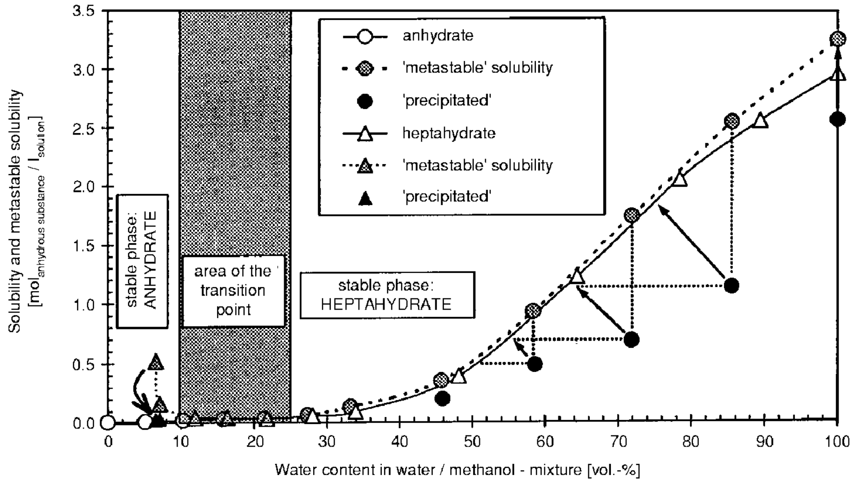

Fig. 3 Solubilities and metastable solubilities of the heptahydrate and the anhydrate of magnesium sulphate as a function of the water content in a water/methanol mixture at 25^{o}C

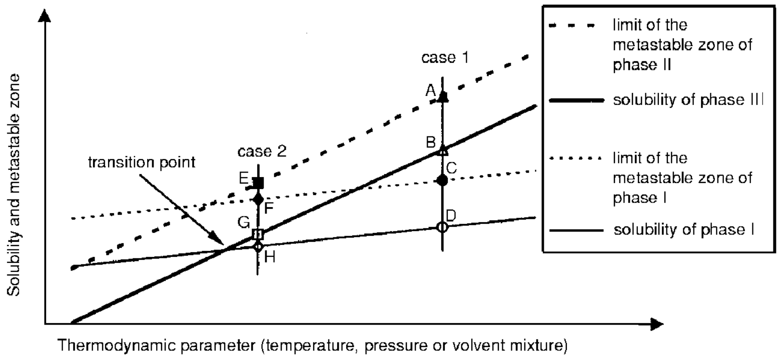

Fig. 4 Solubilities and limits of the metastable zones of an enantiotropic system

side the metastable zone of the stable phase I. Therefore, a spontaneous, i.e. without any induction time, phase transformation from the metastable phase II to phase I takes place. The solid phase of II transforms into I and besides that additional precipitation of phase I takes place until the saturated state is reached (point D).

Case 1 can be related to the dehydration behavior of hydrates in water/methanol mixtures as shown in Figs 2 and 3. The dehydration of the hydrate in methanol does not require any induction time. The solubilities of the metastable phases on the other hand cannot be reached, since they are outside the metastable zone of the stable phase. The real stable phase always precipitates.

Case 2 is the only, but here not obtained possibility to measure the solubilities of the metastable phases. A saturated solution of the metastable phase II is within the metastable zone of phase I (point G). Such a solution can be stable for hours, months or even years. To our opinion these circumstances may be an important aspect of the phenomenon of appearing and disappearing pseudopolymorphs and polymorphs described in literature, e.g. Woodard *et al.* [12] or Dunitz *et al.* [19].

Comparing Figs 3 and 4 it can be summarized, that the dashed lines in Fig. 3 (namely both ‘metastable’ solubilities) represent the limits of the metastable zones (case 1) for the heptahydrate and anhydrate of magnesium sulfate in water/methanol mixtures due to the precipitation phenomena. However, it should not be forgotten, that the limit of a metastable zone always depends on the experimental conditions, such as speed of generating supersaturation or surface characteristics of the vessel, too.

Detection of the transition point

In order to obtain the transition point Grant and co-workers [5–7] introduced an extrapolation procedure for the solubilities of solvates in solvent-mixtures. The solubility curves of the different appearing phases are measured in their specific stable zones and extrapolated into their corresponding metastable zones. This procedure, however, cannot be used in Fig. 3, since the extrapolated solubilities would be in no way reflected by reality: The solubility of the hydrate in ‘water rich mixtures’, extrapolated in ‘methanol rich mixtures’ would be ‘negative’ while the solubility of the anhydrate in ‘water rich mixtures’ would be smaller than that of the hydrate, i.e. the stable phase would be the anhydrate.

Here another simple procedure is introduced for our hydrated salts in methanol. Small amounts of the hydrate were added to pure methanol while the water content is permanently measured by Karl-Fischer titration. Dehydration occurs, thus increasing the water content of the methanol until the transition point is reached. At this point, both phases, namely anhydrate and hydrate are stable and the water content does not change any more. Further addition of hydrate does not change the water content, since these amounts of the hydrate are stable.

Exemplary results of these measurements for a suspension of 9.2757 g magnesium sulphate heptahydrate in 30.0627 g methanol can be seen in Fig. 5. The mass-based water-contents which are provided by the Karl-Fischer titration first must be converted into volume-based water contents considering the specific solubility of magnesium sulphate. The theoretical water content of the solution, if the hydrate completely dehydrates amounts to 11.4 vol%. However, the water-content from Fig. 5 converges to approx. 8.3 vol%, which is the water content at the transition point.

This behavior can not be clearly seen from Fig. 3, since the intersection or transition point deduced from the solubilities of the anhydrate and hydrate phases would be expected between 10 and 25 vol%. One possible explanation to these findings could be experimental errors due to the very small solubilities in this region. Further work has to be done using the described technique with a variety of different substances (hydrates or solvates) in order to elucidate the origin of the deviations found in our measurements.

Characterization of the solid phases

As an example of the characterization of the solid phases from the solubility measurements Fig. 6 shows four curves of DSC measurements with magnesium sulphate taken from the samples of Fig. 5.

As expected, the DSC measurement of the dry anhydrate shows no peaks at all between 20 and 400°C. If this sample would contain adhering solvent, a wide peak would appear between approx. 64.5 and 100°C corresponding to pure methanol and pure water, respectively, and the mixtures of both lying in between. In comparison to Fig. 5, measurement No. 3, the solid phase from a water/methanol mixture of approx. 7.67 vol% exhibits this behavior. The transition point is not reached, i.e. the anhydrate is still the stable phase. The only peak existing is the one of the adhering solvent with a composition of approx. 7.67 vol%.

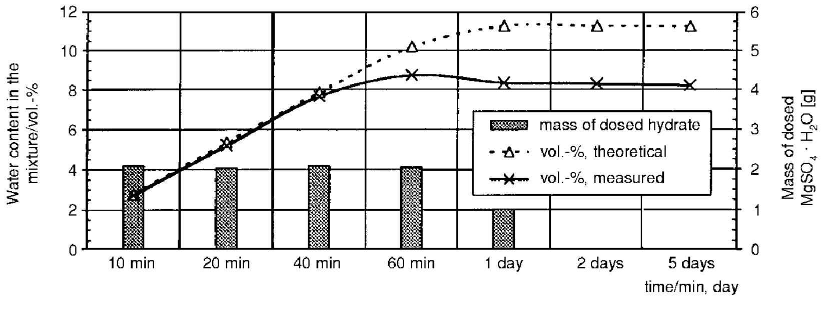

Fig. 5 Determination of the transition point for a magnesium sulphate heptahydrate/methanol system

The dry heptahydrate on the other hand shows seven peaks corresponding to the loss of 7 mol of crystal water, consequently. The solid phase from measurement No. 4 is a mixture of both phases, therefore due to the excess hydrate phase at the transition point. As already explained for Fig. 5 the added hydrate transforms into the anhydrate accompanied by an increase in water content of the liquid phase until the transition point is reached (approx. 8.3 vol%). Since a little bit more of the hydrate than in equilibrium at the transition point is added, predominantly anhydrate with a small amount of hydrate should be the solid phase (by definition of the transition point).

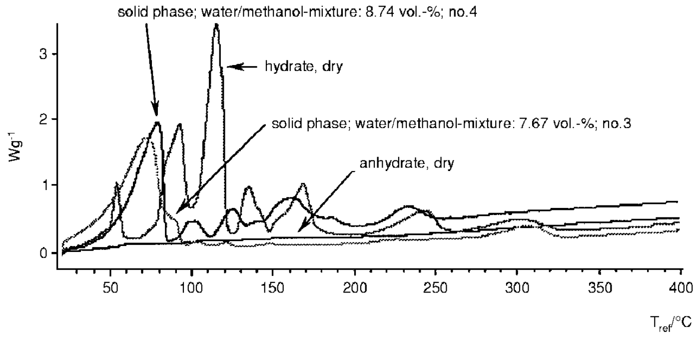

Fig. 6 Characterization of the solid phases of the magnesiumsulphate heptahydrate - water/methanol system via DSC measurements with respect to Fig. 5

This situation can be recognized from Fig. 6: The first peak of the curve corresponding to measurement No. 4 in Fig. 5 results from the evaporation of the adhering solvent with a composition of approx. 8.3 vol% water in methanol which is the composition at the transition point. The temperature is slightly higher than for No. 3, because the water content of No. 3 is correspondingly lower. The peaks following the first one are much smaller than the transformation peaks of the pure hydrate due to the small content of hydrate in the solid phase. Besides, the loss of crystal water seems to occur at higher temperatures. The loss of the last molecule of water at approx. 300°C cannot be seen.

The DSC measurements of the solid phases of hydrate/solvate in solvent-mixture systems can be used for the characterization of the stable phase. However, both phases, the stable and the unstable, are required at the desired value of the thermodynamic parameter under consideration in order to be able and differentiate between the evaporation peaks of the adhering solvent and the peaks corresponding to the loss of the crystal solvent.

Conclusions

Several hydrates tend to dehydrate when suspended in excess in methanol. Due to the high local supersaturations during the phase change dendritic or whisker-like growth of the stable phase, i.e. the anhydrate is forced to appear. This change in habitus increases the specific surface area which can influence dissolution rates and chemical reactions. The dehydration occurs logarithmically, which can be modeled by a type of the Avrami-Erofeev equation.

The hydrate/anhydrate in water/methanol system is a reversible, i.e. enantiotropic pseudopolymorphic system, as shown by the solubility studies. As the thermodynamic parameter the solvent composition was changed while temperature and pressure were kept constant. The phase transition takes place immediately since the solubility of the metastable phase lies outside the metastable zone of the stable phase. A transition point appears, where the hydrate and the anhydrate are stable at the same time, namely at a certain point of the water content in the solvent. In addition, the transition point can be determined by adding small amounts of hydrate to methanol and by measuring the water content stepwise. The results were controlled by DSC measurements. Additional characterizations would be necessary to describe the produced substances in detail and also for a complete understanding of the underlying chemical and physical processes.

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