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SOLVENT EXCHANGES AMONG MOLECULAR COMPOUNDS
Two extreme cases of pharmaceutical interest

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Abstract

Solid–solid transformations between solvates of pharmaceutical compounds are investigated under various conditions. In the case of Roxithromycin, it is shown that starting from single crystals of the acetonitrile solvate, a transformation towards the monohydrate occurs according to a cooperative mechanism. This smooth exchange of solvent probably involves a transport of matter within channels, and the comparison of crystal structures is consistent with the persistence of the main features of the 3D lattice. By contrast, starting from the DMSO solvate of Dexamethasone acetate, the transformation towards the sesquihydrated form, induced by the immersion of the DMSO solvate in water, is fully destructive and reconstructive. This occurs far-from-equilibrium and is therefore controlled by kinetic factors. The existence of an intermediate liquid phase within the particle is postulated to account for the appearance of whisker-like crystals growing first on high-energy sites of the former particle. An extended analysis of these transformations between solvates shows that they could be classified according to rules previously proposed in the case of desolvation mechanisms.

Keywords: crystal structure, solid–solid transformation, solvates, solvent exchange, whiskers

Introduction

The development of potential new drug substances in the pharmaceutical industry includes most often systematic procedures devoted to the research of polymorphic forms and solvates [1, 2]. In the last years, these investigations drastically increased the number of crystalline forms identified as solvates, in particular in the case of drug compounds of medium and large molecular size [3, 4]. Recent studies [5] have also highlighted that phases identified as non-solvates could actually consist of solvated forms undergoing a spontaneous desolvation during drying, leading to so-called 'isomorphic desolvates' since the original crystal lattice is not affected by the loss of solvent of crystallization.

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This increase of the proportion of crystalline forms identified as solvates or desolvates induces the necessity to characterize them accurately [6, 7] and to understand the relationships between these forms in terms of transformation pathways and relative stabilities as a function of their environment, storage conditions, etc. Such studies include the analysis of desolvation mechanisms and possible recrystallization behaviours, but also investigations devoted to solid–solid transformations which can occur between solvated forms in the presence of a solvent or in a humid atmosphere [8]. Beyond the above-mentioned phenomenon of isomorphic desolvates, it is now well-established that experimental conditions of manufacturing processes such as drying, grinding, compaction, freeze-drying, tabletting, wet granulation, etc. [9, 10] can have a dramatic influence on the behaviour of crystalline forms, for instance by inducing physical transformations of solid state samples [11, 12]. Therefore, investigations devoted to the study of thermally or non-thermally induced desolvations can provide reliable information only if the influence of all experimental parameters are accurately defined and controlled.

In the particular case of hydrates, which constitute the most widespread family of solvates, general models or classifications have been proposed [13], sometimes with the aim of correlating experimental data with structural features [14]. In our unified model for the dehydration of molecular hydrates [15], we have postulated that dehydration behaviours can range from highly cooperative (quasi-topotactic mechanisms leading to 'isomorphous desolvates') to destructive and possibly reconstructive (nucleation and growth mechanisms). In between, there is a discontinuity, from which all the structural information contained in the mother phase is lost. Assuming that experimental conditions can affect the dehydration mechanism, we have suggested that the use of different dehydration procedures could constitute a complementary tool for the research of new polymorphic forms [16].

The present paper consists of an illustration but also an extension of these ideas since we are interested here in understanding solid–solid transformations between solvated forms of pharmaceutical compounds, induced by non-thermally driven processes. The objective of this work is to identify decisive parameters responsible for these transformations under various conditions, and to propose an interpretation of the associated mechanisms on the basis of structural data. The first compound selected for this study is Roxithromycin (Fig. 1a), contained in the antibiotic Rulid and belonging to the family of erythromycin derivatives, and the second one is a steroid, Dexamethasone acetate (Fig. 1b). Since these two drugs are known to exist as hydrates, our methodology

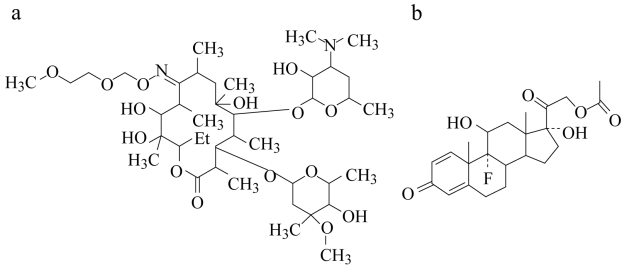

Fig. 1 Structural formulae of a – Roxithromycin and b – Dexamethasone acetate

consisted in submitting single crystals of new solvates formed by these compounds to a humid atmosphere at room temperature, or to immerse single crystals in water in order to promote the formation of so-called 'whisker-like' crystals [17]. Interpretations were elaborated on the basis of physical characterizations of the different phases, microscopy observations and structural analyses.

Experimental

Materials

Dexamethasone acetate (DMA) and Roxithromycin (RTM) monohydrates were supplied by Aventis pharma (Romainville, France). The acetonitrile (ACN) solvate of RTM and the dimethylsulfoxide (DMSO) solvate of DMA were obtained by cooling down to room temperature solutions saturated at 40°C in the corresponding solvents. Single crystals of RTM·ACN and DMA·DMSO were prepared at room temperature from slightly supersaturated solutions by slow evaporation or cooling. Large crystals of RTM·H_2O were obtained from a mixture water/ethanol (65/35 vol%). This adjustment of the solvent composition was performed because of the very low solubility of RTM in pure water.

Characterization techniques

Crystalline phases were identified by means of X-ray powder diffraction (XRPD), with a Siemens D5005 diffractometer equipped with a copper source. All XRPD measurements were carried out in ambient atmosphere. For temperature-resolved XRPD, the heating rate was about 1 K min^{-1}, and the recording time was about 30 min in isothermal conditions.

DSC experiments were performed using a Setaram DSC 141 apparatus. Finely ground samples (from 15 to 20 mg) were introduced in non-covered aluminium crucibles and heated in ambient atmosphere from 30°C to complete fusion at a 2 K min^{-1} heating rate. Samples were weighed after each DSC analysis. When appropriate, similar thermal treatments were applied to larger amounts of solids in order to perform more accurate determinations of mass losses upon heating and to identify the phases by XRPD.

Scanning electron microscopy (SEM) observations were carried out under vacuum using a LEO 1530 apparatus at various magnifications. The physical transformations of single crystals could also be investigated in ambient atmosphere by using a hot stage optical microscope equipped with a digital camera, in a magnification range varying from 20 to 100, at a 2 K min^{-1} heating rate.

^{1}H-NMR analyses were performed in DMSO-d6 with a Bruker Avance 300 (300 MHz) spectrometer.

Structural investigations

The crystal structure of RTM·ACN was determined at 100 K by X-ray diffraction measurements using a Smart Apex system (Bruker) equipped with a CCD detector

and a MoK_α source (λ=0.71073 Å). A structure solution was obtained with direct methods and atomic coordinates were refined with the SHELX-5.10 program [18].

Results

Solvates of Roxithromycin

Characterization and desolvation of RTM solvates

The (1:1) stoichiometry of the hydrated form and of the acetonitrile solvate of RTM was determined by gravimetric measurements and NMR analyses. These two solvates were further characterized by XRPD and DSC. It can be seen from Fig. 2 that the two experimental XRPD patterns present significant similarities in terms of peak positions, from which some structural similarities can be assumed. The thermal behaviour (DSC curves) of the two solvates are presented in Fig. 3. Before the melting peaks occurring at ca. 110°C (acetonitrile solvate – RTM·ACN) and ca. 114°C (monohydrate – RTM·H_2O), these curves are characterized by significant deviations from the base line in the temperature range 50–100°C. Although these deviations cannot be depicted as desolvation peaks, similar experiments stopped at 105°C and followed by accurate measurements of mass losses have established that desolvations are completed at this temperature (experimental mass losses: 2% for RTM·H_2O and 4% for RTM·ACN).

In order to investigate the evolution of crystal packings during desolvation, temperature-resolved XRPD patterns were recorded for the monohydrate in the range 30–105°C (Fig. 4). Most of the diffraction peaks are preserved during dehydration,

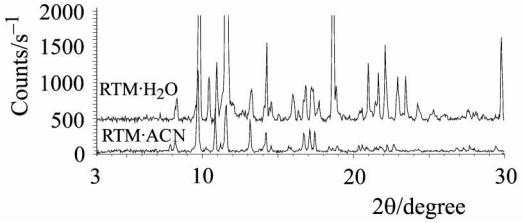

Fig. 2 Experimental XRPD patterns of RTM·H_2O (upper) and RTM·ACN (lower)

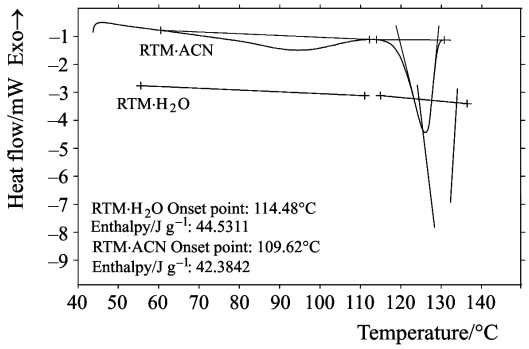

Fig. 3 DSC curves of RTM·H_2O (lower) and RTM·ACN (upper), β=2°C min^{-1}

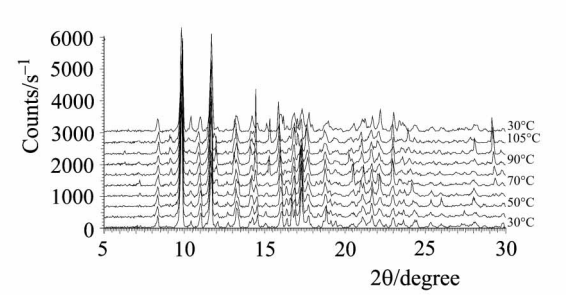

Fig. 4 Temperature-resolved XRPD patterns of RTM·H_2O between 30 and 105°C

indicating a probable cooperative and non-destructive mechanism. Nevertheless, the intensity of a few peaks is affected and new diffraction peaks appear, for instance at 2θ=15.3, 20.5 and 29.3°. These limited changes were also observed for RTM·ACN (data not shown), and could be due to the anisotropic character of dehydration, resulting in a preferred orientation effect. Furthermore, cooling down the powder to ambient temperature and humidity allows to retrieve the monohydrate with a poorer crystallinity. From these data, it can therefore be deduced that dehydration consists of a reversible process, and is associated to very limited structural changes.

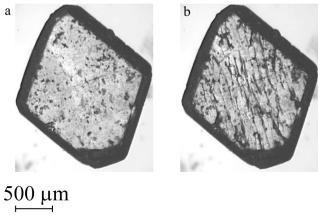

Fig. 5 Optical microscopy photographs performed a – before and b – after heating a single crystal of RTM·H_2O at 50°C

The above interpretation was confirmed by hot stage optical microscopy (scanning mode, 2 K min^{-1}), which allowed to observe the evolution of single crystals of RTM·H_2O upon heating under ambient atmosphere. Photographs presented in Fig. 5 illustrate that heating a well-defined single crystal from room temperature to 50°C induces the appearance of cracks parallel to the main axis of the particle. Further heating leads to an increase of the proportion of these cracks, but the global shape of the initial particle is preserved. These observations are consistent with a cooperative dehydration mechanism along structural channels or planes, and the formation of cracks is likely to be due to macroscopic strains produced by the departure of water molecules [19].

Crystal structure of the acetonitrile solvate and comparison with the monohydrate

Table 1 presents the crystallographic parameters of RTM·ACN as well as the main measurement and refinement conditions. Complete structural data were deposited at the Cambridge Crystallographic Data Center and registered under the deposition number

Table 1 Main measurement and refinement conditions for the crystal structure determination of RTM·ACN. Crystallographic parameters of RTM·H_2O are given for comparative purpose

	$C_{41}H_{76}O_{15}N_2{\cdot}C_2H_3N$			$C_{41}H_{76}O_{15}N_2{\cdot}H_2O$
			this work	from [20]
Molecular mass	878.1 g mol^{-1}	Temperature	100 K	293 K
Scan type	2θ	Space group	$P2_12_12_1$	$P2_12_12_1$
Dx	1.213 g cm^{-3}	*Z*	4	4
Wavelength	0.71073 Å	*a*/Å	11.8341 (6) Å	24.195 (8) Å
F (000)	1912	*b*/Å	16.9560 (9) Å	16.935 (6) Å
θ limits	1.70–26.39°	*c*/Å	23.9549 (12) Å	11.686 (5) Å
Nb of measured reflexions	38678	*V*/Å^3	4806.8 Å^3	4788 Å^3
Nb of independent reflexions	9840	μ/cm^{-1}	0.91 cm^{-1}	6.4 cm^{-1}
Nb of observed reflexions	9480 (F_0>4σ(F_0)	*R*/wR_2	2.71/7.07%	4.7%/–

CCDC-195692. Table 1 also includes data published for the structure of RTM·H_2O [20], for which atomic coordinates were retrieved from the Cambridge Structural Database (ref. code FMPROA). The comparison of crystallographic parameters indicates identical space groups and very similar unit cell dimensions. Projections of the two structures along the shortest axes are shown in Fig. 6 and reveal that, despite different locations of molecules in unit cells (in connection with different orientations of crystallographic axes), the two crystal packings are almost identical. In both structures, the main inter-

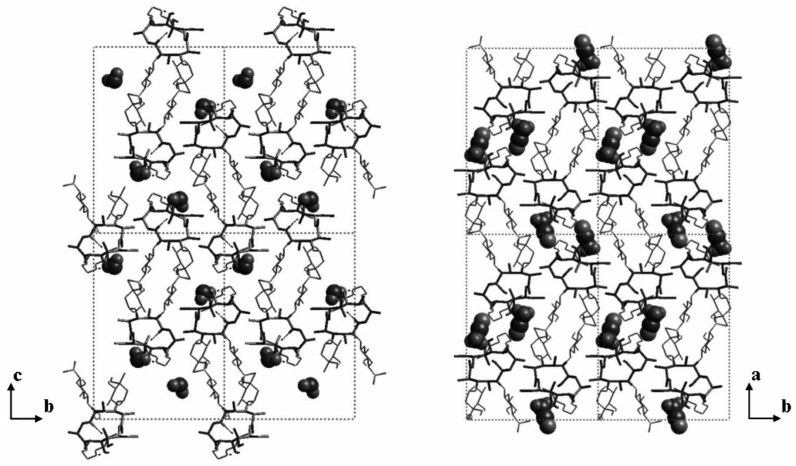

Fig. 6 Projections along the shortest crystallographic axes of the crystal structures of RTM·H_2O (left) and RTM·ACN (right). Solvent molecules are represented as balls

molecular interactions are made of hydrogen bonds formed between hydroxy groups and nitrogen atoms belonging to the two cyclic substituents of each molecule. Because of the 2_1 screw axis parallel to the shortest crystallographic direction, these H-bonds induce the existence of infinite molecular ribbons running around these screw axes. These structures can therefore be described as a stacking of molecular columns, and the structural cohesion between these columns is ensured by van der Waals contacts only. In consistency with these strong analogies, superimpositions of RTM molecules extracted from the two structures revealed very similar conformations.

Solvent molecules are accomodated within structural channel parallel to the above-mentioned molecular columns (corresponding to the *c* axis in RTM·H_2O and to the *a* axis in RTM·ACN). In RTM·H_2O, each water molecule participates to three hydrogen bonds with the closest RTM molecule. By contrast, the acetonitrile molecule, in the RTM·ACN structure, can only be involved in a weak intermolecular H-bond of the (CH···O) type, and plays mainly a spacefilling role in the crystal packing.

Solvent exchange in the RTM structure

Well-defined single crystals or fragments of RTM·ACN were carefully extracted from the mother liquor and maintained under a 100% relative humidity at room temperature. After 48 h, optical microscopy observations (Fig. 7) showed that the initial particles had lost their transparency, but the global shape was preserved. The analysis of the resulting phase by means of XRPD and NMR revealed that all acetonitrile molecules had been replaced by water, leading to the exact (1:1) stoichiometry of RTM·H_2O.

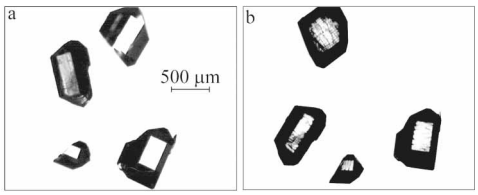

Fig. 7 Optical microscopy photographs showing the evolution of the aspect of single crystals (or fragments) during the solvent exchange
a – RTM·ACN→b – RTM·H_2O

Similar results were obtained when using a two-step procedure. As a first step, RTM·ACN was desolvated by heating single crystals at 50°C during 12 h, and the complete loss of acetonitrile from the lattice was established by gravimetric measurements. The desolvated particles were then maintained in humid atmosphere (RH 100%) for 24 h, which led to the monohydrate, without significant change of the morphology. Owing to the high vapor pressure of acetonitrile at room temperature, it was also observed that single crystals of RTM·ACN transformed spontaneously into the monohydrate after a few weeks under ambient humidity and temperature.

It can be postulated that the main driving force for the exchange of solvent described above consists of the high vapor pressure of water around the crystal. In such an environment, the vapor pressure of the acetonitrile molecules contained in the

crystal lattice becomes high, and can quite easily overcome the energy of a weak H-bond. Simultaneously, water molecules can penetrate within the crystal and stabilize the lattice by filling empty space, and by forming several H-bonds with RTM molecules. Therefore, the solvent exchange proceeds in a cooperative, non destructive way, and it can be assumed that most solvent molecules are either evacuated or inserted in the crystal lattice along structural channel parallel to the short crystallographic axis. Because these channels are actually not so large (Fig. 8), the mechanism is probably not fully topotactic, and it can be envisaged that the loss of transparency of single particles results from the formation of crystal defects during the solvent exchange, but without complete destruction of the long range order.

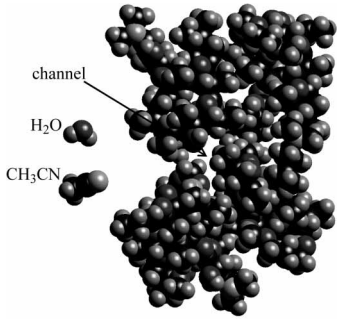

Fig. 8 Spacefill representation of the RTM·H_2O structure showing the relative size of channels, and comparison with the molecular size of solvent molecules

This probable mechanism presents important similarities with that depicted for cooperative dehydration of molecular crystals [15]. The persistence of the main intermolecular contacts and of the crystallographic order induces in both cases the existence of a filiation between mother and daughter phases, as well as a transmission of structural information during the solid–solid transformation.

Solvates of Dexamethasone acetate (DMA)

Characterization and crystal structure of the DMSO solvate

Previous studies have shown that DMA exhibit polymorphism and can exist as solvated forms [21]. The crystal structure of the monohydrated variety was published in 1975 [22], and we have recently described the structure of a DMSO solvate [23]. In this structure (Fig. 9) as in the structure of the monohydrate, DMA molecules are arranged as helicoidal molecular columns around the 2_1 screw axis parallel to the shortest crystallographic direction, and the stability of these columns results from strong (OH···O) hydrogen bonds. Different packing modes of the neighbouring columns exist in the two structures, but a common feature consists of the presence of solvent molecules in channels parallel to these molecular columns. In the DMSO solvate, each solvent molecule is involved in a hydrogen bond with a hydroxy group of the closest DMA molecule.

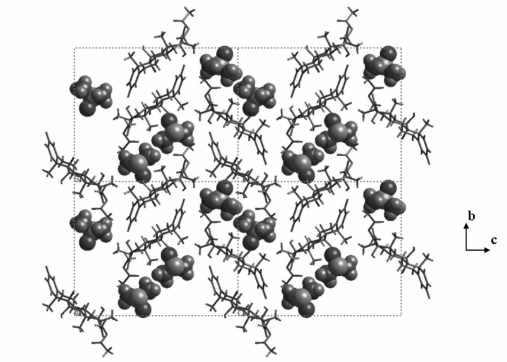

Fig. 9 Projection along the *a* axis of the crystal structure of DMA·DMSO. Solvent molecules are represented as balls

Our preliminary investigations devoted to DMA have also shown that XRPD was suitable for the unambiguous identification of various crystalline forms of interest (monohydrate, non-solvated polymorph II, sesquihydrate and DMSO solvate) [23].

Formation of whisker-like crystals of Dexamethasone acetate

Large, well-defined and transparent single crystals of DMA·DMSO were obtained at room temperature by slow cooling of a supersaturated solution. After careful elimination of the surrounding mother liquor, several of these crystals were immersed in water for a few minutes. It could be observed by optical microscopy that a large number of very small needles (called whisker-like crystals [17] or simply whiskers) appeared at the surface of the former single crystal, initially at the edges and at the extremities, i.e., on {110} faces [23]. Simultaneously, the particle became opaque, and XRPD analyses combined with gravimetric measurements revealed the transformation of DMA·DMSO towards the sesquihydrate of DMA. The characterization of this phase also revealed its very low stability referred to the DMA monohydrate. Owing to the conditions required for the preparation of DMA·3/2 H_2O, this observation is in agreement with the Ostwald law of stage.

In order to get more detailed insights in the formation of whisker-like crystals, SEM observations were carried out. These investigations allowed to visualize initial particles covered with whisker-like crystals, and revealed that the formation of these numerous whiskers had actually occurred from a limited number of nucleation sites, often located on edges of the initial particle (Fig. 10). The reason why most whiskers are lying on sur-

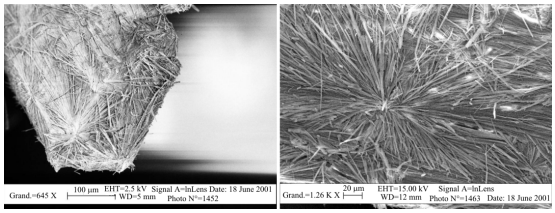

Fig. 10 SEM photographs showing whisker-like crystals grown after the immersion in water of single crystals of DMA·DMSO

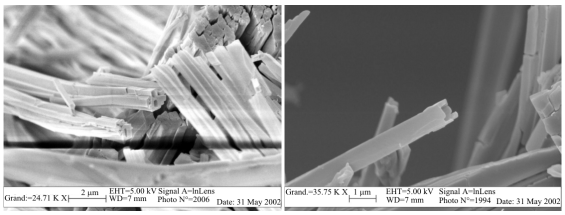

Fig. 11 SEM photographs revealing the hollow structure of protruding whisker-like crystals in the aqueous medium

faces of the initial crystal is probably connected to the metallation step necessary during the sample preparation for SEM observations. It can therefore be assumed, in consistency with optical microscopy observations, that the growth of whisker-like crystals occurs along all possible directions from a nucleation site [24]. SEM was also used with higher magnifications for a more detailed characterization of whisker-like crystals. These observations showed that many of these particles exhibit a hollow structure (Fig. 11). Furthermore, whisker-like crystals present a regular and well-defined habitus, with a diamond or square-shaped section, and a mean diameter close to 1 µm. Although the stoichiometry of the samples observed under SEM conditions could not be established, the consistency between optical microscopy [23] and SEM observations indicates that the samples were not significantly affected by experimental constraints.

Hypothetical mechanism for the formation of whiskers

The above data can be used in order to formulate some hypotheses regarding the nucleation and growth mechanisms of whisker-like crystals, from which conditions for the appearance of such particles can be derived.

The first step concerns the formation of nucleation sites, which is mainly observed in high-energy regions (edges and crystal defects). When a single crystal of the initial phase is immersed in water, it must be supposed that this solvent has to penetrate, at least to a certain extent, within the crystal lattice. This penetration is likely to be easier in high-energy sites, but could also be facilitated on faces along which DMSO molecules can be preferentially evacuated, i.e., {110} faces [23]. Because of the full miscibility between water and DMSO, a solution phase may appear within the former particle, and may be able to dissolve DMA molecules up to its saturation.

The internal pressure resulting from the penetration of water induces that this solution containing DMA dissolved in a DMSO–water mixture (rich in DMSO) probably moves rapidly out of the particle, so that an interface appears between the solution and water. At this interface, the precipitation of whisker-like crystals occurs because of the very low solubility of DMA in water, and DMSO molecules are dispersed in the aqueous medium. The rapid growth of hollow whiskers protruding out of the initial particle is induced by the evacuation of the saturated solution. Indeed, the solidification probably occurs almost instantaneously at the interface with water, this solidification could proceed according to a ‘chimney mechanism’, and the formation of a channel within each whisker could constitute a way to feed their growth.

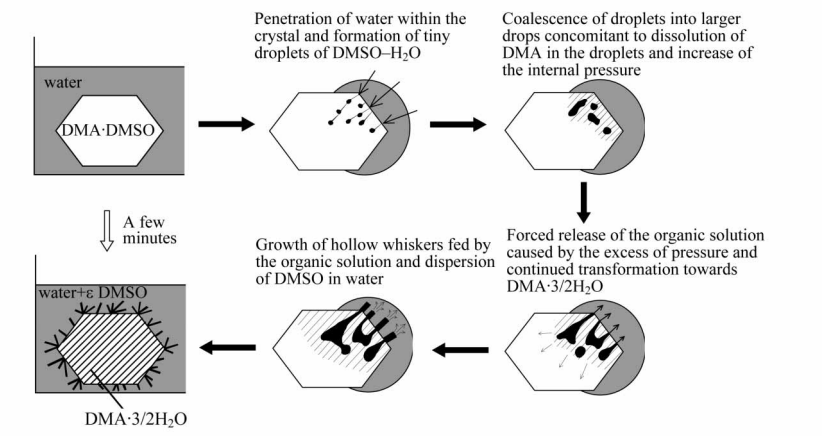

Fig. 12 Hypothetical mechanism for the formation of whisker-like crystals

From this hypothetical mechanism summarized in Fig. 12, several features appear as necessary and general conditions for the formation of whisker-like crystals:

1) The solubility of the solute should be high in the initial solvent, in which it crystallizes as a solvate (here DMSO).

2) The solute must be almost non-soluble in the solvent in which crystals are immersed (here water).

3) The two solvents should be miscible.

4) The solid–solid transformation (which consists here of a transformation between solvates) proceeds through a destructive–reconstructive process.

Discussion

The solid–solid transformations studied in the present paper occur between solvated forms of pharmaceutical compounds, and can be interpreted, discussed or compared from several points of view.

• Considering first the conditions in which these transformations are carried out, it appears that very different types of driving force can induce a transformation between solvates. Indeed, the exchange of solvent in the RTM structure occurs under smooth and close-to-equilibrium conditions, whereas the formation of whiskers composed of the sesquihydrate of DMA from the DMSO solvate is achieved in far-from-equilibrium conditions and is therefore controlled by kinetic factors.

• As a consequence of the above statements, the mechanisms allowing to describe these transformations are different. In case of immersion of the DMSO solvate in water, the crystallization of a new packing probably results (at least partially) from the formation of an intermediate liquid phase. By contrast, the transformation between the acetonitrile solvate and the monohydrated form of RTM is likely to be promoted by the easy departure of ACN molecules from the initial crystals, as shown by

the thermal behaviour of this solvate. Since the monohydrate is probably of higher stability in the presence of a saturated humid atmosphere, it can be easily envisaged that ACN molecules can be progressively evacuated from the crystal lattice along structural channels and replaced by water molecules. Assuming a strictly continuous mechanism, this induces that no desolvation occurs since regions of the lattice occupied by solvent molecules are always filled.

From a structural point of view, the hypothetic mechanisms described above induce that these solid–solid transformations can be classified according to rules similar to that previously used in the case of dehydration mechanisms of molecular crystals [15]. Indeed, a cooperative and continuous exchange of solvent within a preserved crystal lattice obviously implies that important structural similarities exist between the mother and daughter phases, from which it can be deduced that there must exist an important structural filiation. In the case of a transformation including a crystallization step from a supersaturated liquid phase, mainly controlled by kinetic factors, no structural information of the mother phase is transmitted to the daughter phase, and it can be assumed that the formation of a new solvate actually occurs only because its nucleation is facilitated by the presence of large amounts of solvent in the surrounding medium.

As a complementary indicator, another aspect of the comparative analysis based on structural data could also take into account the relative volume occupied by solvent molecules in the initial crystal packing. Assuming that each non-hydrogen atom roughly occupies a similar volume in the asymmetric unit, it can be assumed that structures in which the relative volume occupied by the solvent is small are more likely to undergo solvent exchanges through cooperative mechanisms. In consistency with this statement, the solvent volume fraction is about 4.9% in the case of RTM·ACN whereas it reaches 11.8% in the DMSO solvate of DMA.

Conclusions

The present study shows that the general reaction:

$$\text{solute}\cdot(\text{solvent 1})_n \xrightarrow{(\text{solvent 2})} \text{solute}\cdot(\text{solvent 2})_p$$

where solvent 1 and solvent 2 are fully miscible, does not proceed via a fixed scheme.

Evidence is given that the transformation from the acetonitrile solvate towards the Roxithromycin monohydrate occurs in close-to-equilibrium conditions, in consistency with the important similarities between crystal structures. By contrast, the formation of the sesquihydrate of Dexamethasone acetate from the DMSO solvate is performed far-from-equilibrium by suspending particles of the initial solvate in water. The solvent exchange proceeds through a destructive–reconstructive mechanism. This diversity of mechanisms can be compared to that reported in previous studies devoted to desolvation processes, but also constitutes an extension of the possible pathways for the preparation of new solvates or solid forms with desired physical properties.

The procedures investigated in the present report could also be applied to the particular cases of mixed solvates. Owing to the advantages resulting from the use of

solvent mixtures for crystallization purposes [3], and to the continuously increasing proportion of such heterosolvates and 'hydrate solvates' contained in the Cambridge Structural Database [4], future work will aim at preparing original mixed solvates by using the solvent exchange procedures. We also intend to investigate the behaviour of mixed solvates and their ability to undergo solid–solid transformations involving only one of the two (or more) solvents present in the crystal lattice.

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