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Compression ability improvement by solvation/desolvation process: application to paracetamol for direct compression

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Summary

Pure paracetamol for direct compression was prepared by recrystallization in dioxane followed by an appropriate drying process. The polyhedric crystals obtained exhibit a sintered like structure. This porous texture induces plasticity and greatly improves the compressibility. The residual solvent content is clearly less than 100 ppm when the drying is progressive. We have attempted to explain the formation of the sintered texture with the intention of applying this process to other drugs or excipients in order to improve their compression ability. In contrast to the usual hydration/dehydration process applied to lactose, the advantage of this process is the finding of a stable desolvated form; the desolvation of a solvate with organic solvent results in stable material whereas the anhydrates are often unstable.

Introduction

Previously, the influence of particle size on the various properties of solids has been studied extensively. Furthermore, the crystalline structure was intensively envisaged. Nevertheless, in addition to these very important factors, a new aspect of solid particles needed to be studied: the texture of the crystals. Texture can be defined as an arrangement of areas of matter inside the elementary particle (Figlarz et al., 1967; Lefebvre et al., 1989). This texture can confer on the solid particle some degree of porosity and a certain isotropy which can improve the compression properties and dissolution rate.

Paracetamol is a substance which exhibits very poor compression ability. In a previous paper, we reported the preparation of a new form of paracetamol for direct compression (FGH paracetamol) and described its various properties (Fachaux et al., 1992).

The great advantage of this material is the fact that the paracetamol is a pure substance according to the pharmacopoeia monograph, whereas

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the paracetamol forms for direct compression currently on the market are all compounds of paracetamol with gelatin, PVP, starch or starch derivatives.

The compression ability of FGH paracetamol has been studied. These crystals exhibit good technological properties: flowability, die filling, hardness/pressure profile. No capping was observed on formulated tablets containing 500 mg of paracetamol. On the other hand, the hydrophilicity was sufficiently high to result in a very rapid rate of dissolution from tablets.

Two recrystallization processes are available for the preparation of FGH paracetamol: recrystallization by cooling of a supersaturated dioxane solution; recrystallization during the stirring of a dense dioxane suspension of ground standard paracetamol (20% w/v).

It was observed that the two types of crystals, only differ by their habit and their particle size: the habit of the crystals obtained from the suspension is very irregular, and their particle size is smaller than that of crystals obtained from supersaturated solution.

The aim of this work is to understand the mechanism of formation of the very particular texture of the FGH paracetamol crystals in order to apply this process to other materials.

Materials and Methods

Materials

The following were used: FGH paracetamol (prepared according to Fachaux et al., 1992); standard paracetamol as a reference (Rhône Poulenc) (coarse and fine crystals); dioxane 'Technique' grade (Prolabo).

Several types of dioxane (technique, normapur, for spectroscopy) from different manufacturers have been tested (Prolabo, Merck, Baker), acetone normapur (Prolabo), ethanol normapur (Prolabo), tetrahydropyrane, tetrahydrofuran, cyclohexanone.

Methods

Crystals were observed by optical microscopy using a Wild Leitz M 20 microscope, in transmitted light, before and after drying of the crystals.

The morphology of the dried crystals was investigated by means of a Jeol CX 100 scanning electron microscope.

Thermogravimetry A Mettler TA 3000 TG 50 thermogravimetric system was used to record mass loss of 2–5 mg samples of non-dried crystals, under a flow of nitrogen. The high instability of the paracetamol solvate formed obliged us to work on crystals which were still impregnated with the recrystallization solvent. Crystals were blotted dry between two filter paper sheets.

The analysis was carried out similarly on dried crystals. The heating rate was 10°C/min. The starting temperature was 25°C, and the final temperature 120°C.

DSC The DSC thermograms were recorded on a Mettler TA 3000 DSC 20 differential scanning calorimeter. 2–5 mg samples, in the same states as in thermogravimetric analysis, were heated at a rate of 10 and 1°C/min over a temperature range of 25–190°C, under a nitrogen flow. The lids of the pans were not used in order to make it easier for the solvent to escape, and to overcome side effects in the released solvent.

Infrared spectrophotometry Solid paracetamol samples were studied as KBr pellets and fluorolube mulls. Spectra of paracetamol solutions in methyl and ethyl alcohol, dioxane and acetone were measured with a liquid cell equiped with AgCl windows. In each case, the contribution of dissolved paracetamol was calculated by subtraction of the spectrum of the pure solvent.

During this study, the spectrometer was a Nicolet 170 SX Fourier transform infrared spectrometer 64. Interferograms were co-added and the spectra were calculated at 4 cm^{-1} resolution.

For the study of the desolvation process, spectra were recorded on a sample of the precipitate obtained after cooling at room temperature of a saturated solution of paracetamol in dioxane at 50°C. Crystals were still impregnated with the recrystallization solvent. Every 2 min, a spectrum was recorded with a Bruker IFS 48 FTIR spectrometer. The resolution was 2 cm^{-1}.

X-ray powder diffraction X-ray powder diffractometry was carried out either at room temperature by using an X-ray diffraction device

(Siemens) fitted with a Guinier de Wolff camera (CuK_α radiation, $\lambda = 1.54178$ Å) or versus temperature by using an X-ray diffraction device (Siemens) fitted with a Guinier Lenne Camera. The temperature ranged from 11 to 88°C, and the heating rate was 6.4°C/h.

On account of the high instability of the eventual solvates, the starting temperature was low (11°C), a small cup containing the recrystallization solvent was laid in the device chamber and the crystals disposed on the grid were still impregnated with their recrystallization solvent.

On the other hand, for a more precise indentification of the reflections of the paracetamol samples, an X-ray powder diffraction pattern was obtained by using a powder diffractometer (Siemens D 5000). Silicon was used as internal standard.

Compression ability The compression ability was investigated on an instrumented alternative tablet machine Frogerais OA, by using the 1CP method of Guyot (Lefebvre et al., 1989; Guillaume et al., 1992).

Results and Discussion

Morphological study of the crystals

According to the recrystallization solvent, crystals exhibit acicular, parallelepipedic or polyhedric habits under the microscope. In transmitted light, they look like transparent crystals, except for the crystals which were recrystallized in dioxane: the latter appear as black polyhedric particles: light does not pass through them (Fig. 1b).

Scanning electron photomicrographs at 20 000 × magnification exhibit generally smooth crystal surfaces. However, surprisingly, the surface of the crystals recrystallized in dioxane is very 'chaotic', presenting a multitude of anfractuosities (Fig. 2). This aspect gave the impression of a porous sintered like texture of the particles. This observation was confirmed by mercury porosity measurements which showed a very high porosity consisting of very narrow pores (Fachaux et al., 1992).

This sintered aspect is in agreement with the non-passage of the light through the whole crys-

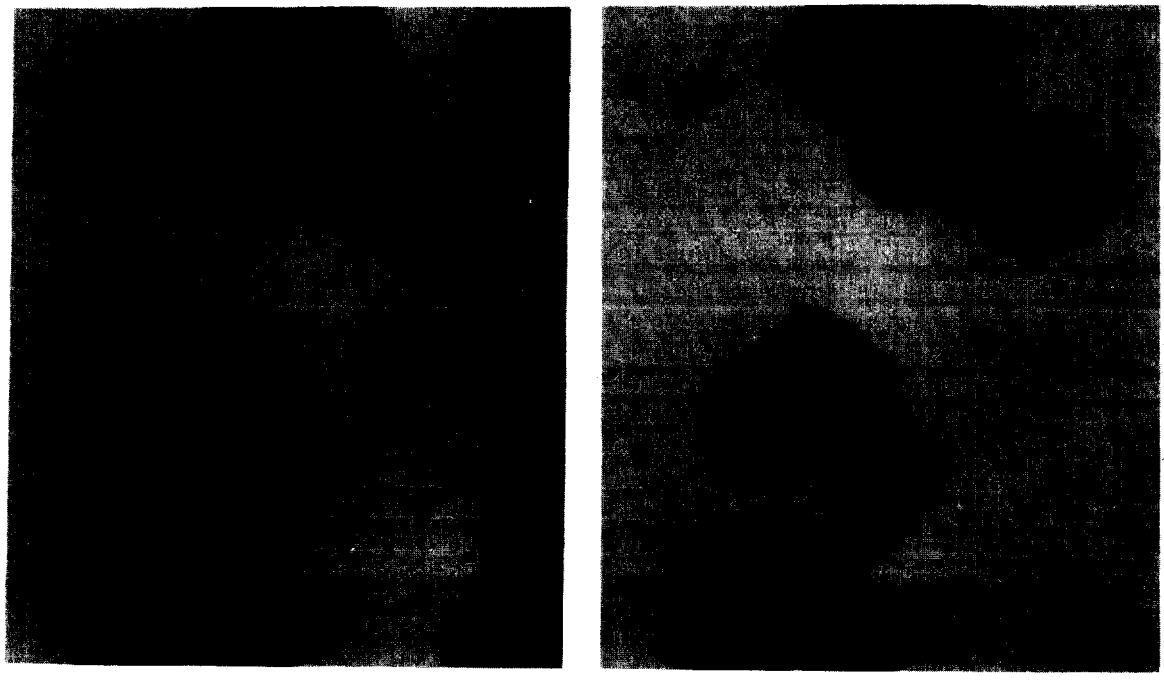

Fig. 1. Aspect of FGH paracetamol under the microscope. (Left) Crystals still impregnated with dioxane; (right) dried crystals.

Fig. 2. SEM micrograph of FGH paracetamol (magnification, 20000).

tal. It should be pointed out that this black appearance is characteristic of the dried crystals.

When the crystals were still impregnated with dioxane, they appeared like transparant polyhedric particles (Fig. 1a). It was observed that the crystals recrystallized in a mixture of dioxane with water, had an intermediate aspect, as can be seen from Table 1.

It seems that the black aspect of crystals, in relation with their sintered like texture, is directly connected to the proportion of dioxane in the dioxane/water mixture.

Compression ability

It was not possible to obtain tablets with either the standard paracetamol usually commercialized, or the paracetamol crystals recrystallized in water or ethanol, irrespective of the compressional force.

In contrast, the crystals recrystallized in dioxane allowed us to obtain tablets having the correct cohesion index. The cohesion index is 'the ratio of the force necessary for the crushing of the tablet between two jaws, to the maximum upper punch force measured during compression'. For convenience, the dimensionless number obtained is multiplied by 10^5: the higher the cohe-

TABLE 1

Main characteristics of the paracetamol crystals

Recrystallization medium	Mean diameter (μM)	Crystal habit	Transparency of the crystals	Aspect on the SEM photomicrographs	Compression ability ('cohesion index')
Ethanol	75	parallelepipedic	+	smooth surfaces	no tablet obtained
Water	75	parallelepipedic	+	smooth surfaces	no tablet obtained
Dioxane/water (2:3)	160	without characteristic habit vry irregular	±		all tablets exhibit capping and have no hardness
Dioxane/water (7:3)	250	irregular parallelepipeds	no some transparent crystals	finely sintered aspect	134 (y_1 = 14–15 kN)
Dioxane	(a) 70	polyhedric and irregular crystals	no	sintered like	310 (y_1 = 10–15 kN)
	(b) 130	polyhedric crystals	no	sintered like	300 (y_1 = 13–15 kN)
Standard commercialized Paracetamol	(a) 320	parallelepipedic	+	smooth surfaces	no tablet obtained
	(b) length: 20–100 width: 5–20	acicular and irregular	+	smooth surfaces	no tablet obtained

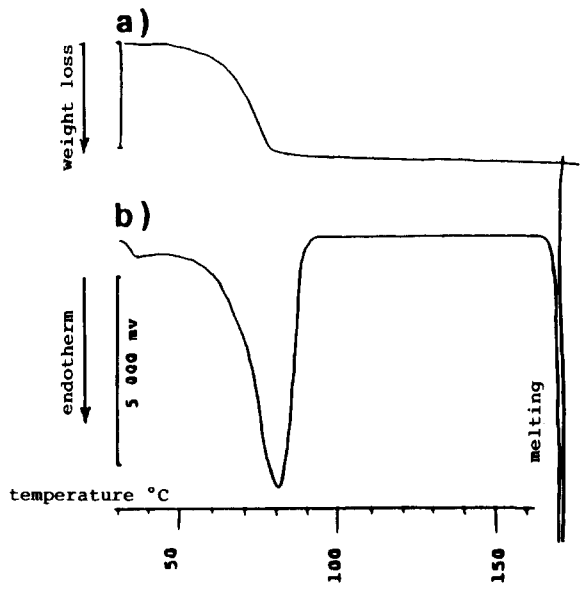

Fig. 3. DSC and TG curves of paracetamol/dioxane hemisolvate.

sion index, the better the compression ability (Guyot et al., 1989).

The same experiment was applied to the crystals recrystallized in a mixture of dioxane with water in the proportions 7:3 and 2:3.

The same observation of intermediate behaviour was made. The crystals recrystallized in the 7:3 mixture of dioxane/water gave tablets with a very weak hardness and a very low cohesion index: it was not possible to envisage tablet production by direct compression with this material. Crystals recrystallized in the 2:3 mixture of dioxane/water did not give entire tablets. Mean data are listed in Table 1.

The cohesion indexes which appear in Table 1 are the means of those obtained with the most appropriate forces: as a matter of fact, we have previously demonstrated that an excessively high level of compression force should be avoided, probably on account of the porous sintered texture of the crystals (Fachaux et al., 1992).

As can be seen from Table 1, there is an obvious relation between the opacity, the sintered texture and the compression ability of the crystals. This is the reason why we have not tested the compression ability of the paracetamol crystals recrystallized in acetone, tetrahydrofuran, tetrahydropyrane and cyclohexanone. These crystals are perfectly transparent.

Attempts to explain the sintered texture of the FGH paracetamol

It appears probable that paracetamol molecules bound with dioxane molecules and formed a solvate. The desolvation of the solvate would produce pure paracetamol due to the escape of solvent. This hypothesis has been entirely confirmed.

Solvation / desolvation study by using thermogravimetry The TG thermograms of the crystals which were still impregnated with dioxane are depicted in Fig. 3. After the weak and progressive loss of mass, corresponding to the interparticular solvent, we could observe a rapid loss of mass of 22% between 50 and 80°C, corresponding stoichiometrically to the desolvation of a hemisolvate: (Table 2). One dioxane molecule is bound with two paracetamol molecules. This phenomenon corresponds to a large endotherm in DSC.

This measurement was made systematically as the main control for each production of FGH paracetamol. After drying, in addition to the residual solvent determination by using gas phase chromatography, a thermogravimetric assay confirmed that desolvation was complete. It should be noted that this hemisolvate is very unstable: the bonds of dioxane with paracetamol could be relatively weak. Yet, it has been found that drying at an excessively high temperature does not allow

TABLE 2

Some data of thermogravimetric assays

Loss of mass (%)	Median temperature of desolvation (°C)	Hemisolvate content on the sample (%)
22.3	69.0	98.9
22.0	64.5	97.6
22.2	69.0	98.3
22.1	70.0	98.2
21.8	70.0	96.8
22.1	70.0	97.9
22.7	69.5	100.0

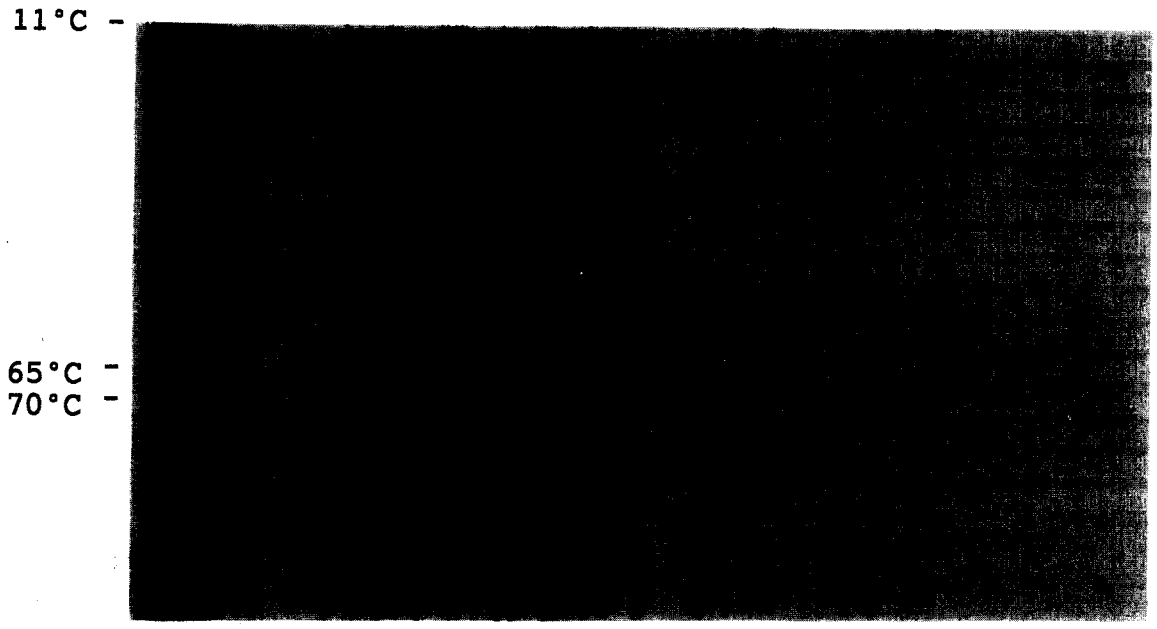

Fig. 4. X-ray powder diffraction patterns of paracetamol/dioxane hemisolvate vs temperature. Crystalline structure changes nearly 65–70°C.

complete desolvation: the drying must be progressive, for example, at 60–100°C within 3 h.

Characterization of the paracetamol/dioxane hemisolvate by use of X-ray powder diffraction

The X-ray powder diffraction pattern of FGH paracetamol was the same as those of the standard commercialized paracetamol and those of all the crystals obtained from the solvents tested in this work. It corresponds to the monoclinic form. (Haisa et al., 1976).

In order to prove the chemical entity of the hemisolvate as a crystalline substance, we carried out an X-ray diffraction study vs the temperature under the conditions previously described: starting temperature 11°C.

The film obtained (Fig. 4) exhibits a certain number of reflections, typical of a crystalline substance, up to 65°C. When the temperature continues to increase, up to 70°C, we can observe the juxtaposition of new reflections beside the previous ones. From 70°C, the only remaining reflections are those which appeared at 65°C. They are those of the monoclinic paracetamol.

The densitogram of paracetamol/dioxane hemisolvate and this of the paracetamol obtained by desolvation are shown in Fig. 5. It is obvious that the hemisolvate identified by using thermogravimetry is a well characterized crystalline substance.

The total modification of the X-ray diffraction during the escape of dioxane is indicative of a complete recrystallization inside the particle itself

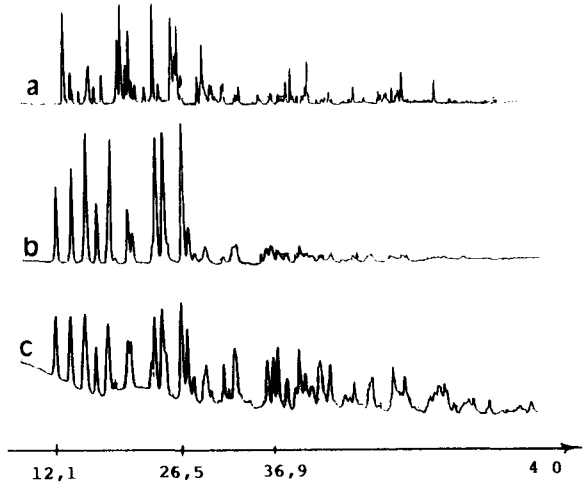

Fig. 5. X-ray powder diffraction patterns of paracetamol/dioxane hemisolvate (a), paracetamol after desolvation (FGH paracetamol) (b) and standard paracetamol (c).

which conserves its external form: this an explanation of the particularly great disturbance of the texture.

Considering the very favourable effect of the solvation/desolvation process on the compression ability of crystals, we investigated the possibility of solvation with other solvents. This is the reason why, supposing hydrogen bond formation with the two oxygen atoms of the dioxane, we tried to use acetone, tetrahydropyrane, tetrahydrofuran and cyclohexanone. However, none of these solvents gave opaque sintered crystals capable of compression. This is the reason why we tried to explain the nature of the dioxane/paracetamol bond.

Attempts at characterizing the paracetamol/dioxane interaction by using infrared spectrometry. The spectra of the two kinds of solid paracetamol (FGH and reference product) are exactly the same above 500 cm^{-1}. This result establishes that there is no chemical modification of the molecular structure.

Comparison of the spectroscopic data of paracetamol in the solid state and in solution (Table 3) shows that intermolecular interactions are strong in the crystal. Molecules are more free in methanol and ethanol but the wave numbers of the characteristic vibrations of the amide function are higher for dioxane and acetone.

The evolution of the infrared spectra during the process of evaporation reveals the formation of an original structure in the solid phase. The first spectrum (Fig. 6a) is essentially due to ligand dioxane, but small bands exist in the 1600–1700 cm^{-1} region. If one of the bands is assigned to dissolved paracetamol (1690 cm^{-1}), the other ones which become stronger in the following spectra are not due to crystalline paracetamol.

TABLE 3

Vibration wavenumbers (cm^{-1}) of paracetamol in different states

Hypothesis of assignment	Solid in KBr pellet	Methanol	Ethanol	Acetone	Dioxane
	503				505
	519				522
	604				
	687				
	715				
	796			797	796
	808				834
	837	839	835	836	
	969				
	1016				
	1108			1105	
	1173	1173	1170	1169	1168
	1227				1220
	1244	1243	1244	1250	
Amide III	1260	1263	1262		
	1328			1313	1311
	1371				
	1442				
	1506			1515	1515
Amide II	1565	1564	1563	1546	1543
Aromatic ring	1610	1611	1612	1608	1608
Amide I	1655	1668	1669		1690
	2794				
CH stretch	2881				
	2929				
NH stretch	3161			3355	3337
OH stretch	3326			3428	

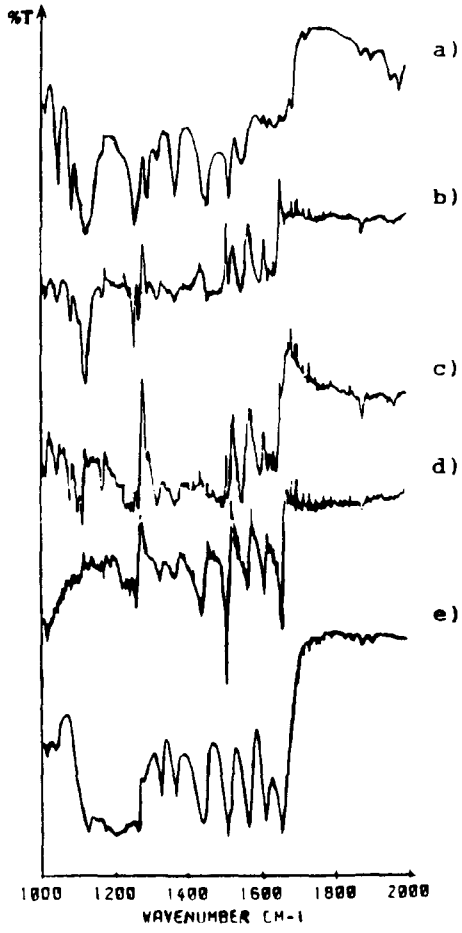

Fig. 6. Evolution of IR spectra of paracetamol/dioxane hemisolvate during the evaporation process (e) Reference paracetamol in KBr pellets.

After a short period, the solvent disappears but the spectrum at this time is completely different from that of the paracetamol (Fig. 6b).

At the end of the process (Fig. 6c), it is possible to show the appearance of the bands of paracetamol before the complete transformation of the spectrum which is very fast. At the end, the spectrum is that of the reference paracetamol (Fig. 6d). This result is in agreement with the existence of a hemisolvate which is very unstable.

Conclusion

With this example of solvation/desolvation of paracetamol, we have demonstrated a method for the improvement of compression ability. This idea is not new: the compressibility improvement brought about by the desolvation process has been previously described by several authors and ascribed to texture disturbance and thermodynamic activation (Huttenrauch and Fricke, 1983). However, up to now, it was a hydration/dehydration process. The most usual application is the dehydration of lactose monohydrate (Lerk et al., 1983).

Nevertheless, the escape of water seems to cause a weaker disturbance than that of a more voluminous molecule such as dioxane. On the other hand, anhydrate forms are often unstable: rehydration occurs more or less quickly. The solution is, on the basis of thermogravimetry, infrared spectrometry, or X-ray powder diffraction, to find an organic solvate of the substance, the compression ability of which can be improved. The desolvation of the unstable organic solvate gave the stable material.

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