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RESEARCH PAPER

# A New Method of Producing Monoclinic Paracetamol Suitable for Direct Compression

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## ABSTRACT

***Purpose*** To develop a technique of obtaining monoclinic polymorph of paracetamol suitable for direct compression without excipients.

***Methods*** Preparation of spongy monoclinic paracetamol was based on quench-cooling of paracetamol solutions in water-acetone mixtures sprayed into a vessel with liquid nitrogen followed by removal of solvents by freeze-drying. X-ray powder diffraction was used to study annealing of quench-cooled solutions in "paracetamol-acetone-water" and "acetone-water" systems and to find optimum conditions for obtaining fine particles of pure monoclinic paracetamol. Samples were characterized by electron microscopy; compression properties were measured.

***Results*** The preparation technique gave fine monoclinic paracetamol powder containing agglomerates (30–200 $\mu$m) composed of flat particles (linear sizes 1–10 $\mu$m, the thickness 60–150 nm). The spongy sample was suitable for direct compression without excipients, stable on storage, and mechanically robust. Mechanically stable tablets pressed from the spongy sample were better soluble in water than commercially available tablets of paracetamol with excipients.

***Conclusions*** The proposed method gave spongy monoclinic paracetamol samples with improved properties. For inexpensive paracetamol, the method may not yield economic advantage. However, the same method based on freeze-drying solutions in mixed aqueous-organic solvents can be used to prepare new improved forms of other molecular solids for pharmaceutical applications.

**KEY WORDS** direct compression · freeze-drying · microparticles · paracetamol · polymorphs · X-ray diffraction

## INTRODUCTION

Direct compression is the most efficient process used in tablet manufacturing because it is the fastest, simplest and least expensive. Paracetamol (N-(4-hydroxyphenyl)acetamide)—a very common analgetic and anti-inflammatory drug—is an example of an active pharmaceutical ingredient exhibiting poor compactability. It is often considered as model compound when developing new techniques of obtaining new forms suitable for direct compression. The

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thermodynamically stable commercially used form I (1) (monoclinic polymorph, $P2_1/n$ (2)) can be easily obtained by crystallization from various solvents (3) but is not suitable for direct compression (4). The orthorhombic polymorph (form II, *Pcab* (5)) is much better compactable and soluble, but, unfortunately, it is not as easily obtained as form I (6–8). Being metastable in all the temperature range at ambient pressure (1,9), it transforms spontaneously into the stable form I on grinding (10) or on storage (1,8). For the tabletting of form I of paracetamol, the existing technologies use either wet granulation (11), compression of the mixtures of paracetamol-I with various excipients (12–18), or obtaining co-crystals with other compounds (19). An attempt to obtain directly compressible form I by a hemisolvate decomposition to produce sintered-like particles has been described in (20).

The mixtures of paracetamol with excipients having improved compactability and controlled dissolution kinetics have been prepared also by spray drying of solutions containing paracetamol + excipients (15,21–23). However, the concentration of paracetamol in solutions in these works was quite small. The necessity to use and eventually remove large amounts of solvents is an obvious draw-back: the method is energy consuming and is not environmentally friendly.

Freeze-drying is an alternative drying technology, which is widely used in pharmaceutical industry to provide products with improved stability and/or desired physico-chemical properties, such as enhanced dissolution rates or bioavailability. Spray-freeze-drying (SFD, and its variation spray-freezing into liquid (SFL)) is a novel cryogenic atomization technology in which either an aqueous or an aqueous-organic co-solvent solution containing a drug and pharmaceutical excipient(s) is atomized directly into a cryogenic liquid (such as liquid nitrogen, or compressed fluid $CO_2$). Ultra-rapid freezing rates are achieved because of the low temperature of liquid nitrogen and the formation of high-surface area droplets (24,25). The success and the efficiency of each stage in a freeze-drying cycle depend upon process parameters such as pressure, temperature and duration. These parameters should be designed according to the physical properties of the formulations (26).

In relation to paracetamol formulations, it has been shown that freeze-drying of solutions containing 0.1 wt% of paracetamol can be used to obtain sponges based on the associates of paracetamol with sodium alginate, chitosan and their mixtures (18). Freeze-drying, in contrast to physical mixing and kneading in water-ethanol mixture, made it possible to obtain a 1:1 paracetamol/2-hydroxylpropyl-β-cyclodextrine host-guest complex, with solubility almost six times higher than that of pure paracetamol (27). The freeze-dried wafers containing paracetamol mixed with sodium salts of carboxy-methylcellulose and alginine, which formed a porous network and hydrated faster than the denser continuous (non-porous) sheet-like structure of the solvent evaporated films (16,17). A comparison of the mechanical properties and dissolution kinetics of spheres containing 6.7 wt% of paracetamol in the mixtures with such excipients as microcrystalline cellulose and calcium phosphate produced by different techniques has revealed that the samples obtained by freeze-drying were much more porous as compared with those dried by microwaves or by hot air. They were characterized by an improved dissolution kinetics but a smaller crushing strength of pellets (12).

Despite obviously promising properties of the paracetamol-excipient formulations produced by freeze-drying, the number of publications on this topic is rather small. The reason can be sought in the difficulties related to the removal of large quantities of ice by sublimation when aqueous paracetamol solutions are used, leading to very time-consuming experiments required to produce even small amounts of the final solid product. At the same time, it is known that the solubility of paracetamol can be considerably increased if water is mixed with an organic volatile liquid (28–30). For some of these systems, cubic structure II (CS-II) clathrate hydrates (*Fd3m*, $a \sim 17.1$ Å) formation has been observed at low temperatures (31). This could be expected to be favourable for using the system for obtaining spongy samples of pure monoclinic paracetamol by freeze-drying, since the absence of liquid phases is important for preserving the active metastable forms without recrystallization. We have developed a new technique of producing spongy monoclinic paracetamol based on the quench-cooling of paracetamol solutions in water-acetone mixtures sprayed into a vessel with liquid nitrogen followed by the removal of solvents by freeze-drying. In the present contribution we describe the results of X-ray diffraction and electron-microscopy studies of the annealing of quench-cooled solutions in the systems "acetone-water" and "paracetamol-acetone-water." The aim of these studies was to optimize drying conditions for obtaining the final paracetamol product suitable for direct compression.

## MATERIALS AND METHODS

### Preparation Method

Commercial monoclinic paracetamol powder (further on—sample 1) was purchased from Merck. Chromatographically pure acetone and distilled water were used as solvents.

To prepare finely dispersed samples of paracetamol (further on—sample 2), we used acetone-water mixture (water content 15–30 wt%); the concentration of paracetamol solutions in this mixture did not exceed the 95% of the

equilibrium concentration at +25°C as was reported in (30). The solution was quench-cooled by immersing into a vessel with liquid nitrogen.

### An Example of Sample Preparation

10.8 g of commercial monoclinic paracetamol powder was dissolved on stirring at about +30°C in the 26.9 g of an acetone-water mixture (29.9 wt% of water). The solution was sprayed using a pulverizer (diameter of the capillary 0.4 mm, excessive pressure of the spraying gas equal to 1 atm) into a vessel with liquid nitrogen. The mixture of the solid phases formed on cooling was placed onto a massive solid holder preliminary cooled down to liquid nitrogen temperature (with the mass of the holder at least three times exceeding the sample mass), which was then placed at liquid nitrogen temperature into a vacuum chamber; the chamber was closed, and the pressure in the chamber was decreased down to $P<5\cdot10^{-2}$ torr. After that, the chamber was placed into a thermostat at −35°C and held at this temperature for 5 h. Then the thermostat temperature was increased up to −7°C and +30°C and kept for 4 h at each temperature. Further on, the pressure in the chamber was increased up to $P=1$ atm by filling it with dry argon, the chamber was opened, the holder with the sample removed, the sample was transferred into a previously weighted bottle, weighted, and subsequently stored in a dessicator in dry air at room temperature. Yield ~8 g (75%).

## Diffraction Experiments

For X-ray powder diffraction experiments aimed at optimizing drying conditions, we used Bruker D8 Advance equipped with a low-temperature TTK 450 Anton Paar chamber permitting to work under vacuum down to $10^{-3}$ torr. The samples were carefully and gently ground in a mortar at the liquid nitrogen temperature and placed onto a holder, which was preliminarily cooled down to liquid nitrogen temperature. If a diffraction pattern was measured at low pressure, the sample was kept in the chamber for 5 min prior to the start of data collection for an equilibration. Diffraction patterns were measured in the −140 – +20°C temperature range (2Θ scans in the 5–55° range, at a 0.02° step, about 8 min per pattern).

To characterize the final solid products before and after tabletting (samples 2 and 2a), diffraction data were collected at the 4-th station of the VEPP-3 accelerator of the Siberian Centre for Synchrotron Radiation at the Budker Institute of Nuclear Physics SB RAS (Novosibirsk) (32): Debye-Sherrer geometry, $\lambda=0.3685$ Å, Image plate MAR 345, detector diameter 345 mm, pixel size 100 μm. The distance between the sample and the detector (about 370 mm) was calibrated using an NaCl standard. The sample was placed into an aluminium cell with two foam-coated holes for the primary beam and the outlet of diffracted radiation. The short wavelength and the high intensity of the synchrotron beam were necessary to let X-rays penetrate such a thick sample as a tablet (3 mm). Data were integrated using FIT2D (33). A powder pattern from the cleavage surface of the same tablet (sample 2a) was measured also in reflection mode using a longer wavelength (CuKα, 1.54056 Å, Bruker GADDS diffractometer) to achieve a better pattern resolution.

FullProf (34) and XLAT (35) were used to isolate reflections, search for indexing solutions, refine unit cell parameters and develop model diffraction patterns.

## Electron Microscopy and Specific Area Measurements

Scanning electron microscopy (SEM) analysis was carried out with TM-1000 (Hitachi) to obtain a visual image and to evaluate particle size, shape, and surface. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with platinum. For each sample, three series were measured, with over 20 frames taken for each of them.

The specific surface area was determined by the BET method from $N_2$-adsorption/desorption isotherm data using an ASAP-2400 instrument (Micromeritics, USA).

## Compression Properties

The compression properties were tested using a Zwick/Roell Z010 instrument. The upper force limit was equal to 10 kN. All the experiments were carried out using a preliminary densifying load equal to 50 N; the rate of the piston displacement was equal to 0.5–10 mm/min. The diameter of the tabletting-die was equal to 6 mm; the sample mass was equal to 120–150 mg. No lubricating additives were used either in the tests with the commercial paracetamol (Merck) or in the experiments with the paracetamol samples obtained in this work.

Thickness and diameter of the intact ejected tables obtained at a compression pressure about 350 MPa were measured with a manual micrometer with an accuracy of 0.01 mm (Mitutoyo, Japan) immediately after ejection. Tablet porosity was calculated from tablet dimensions, mass, and powder density. Crushing force was measured immediately after compression with a Zwick/Roell Z010. Tensile strength $Q$ was calculated as described in (36):

$$Q = 2H/\pi d\,h,$$

where $H$ is the tablet crushing force, $d$ the diameter, and $h$ the thickness of the tablet.

The upper limit of the compression pressure, 350 MPa, (instead of usual 100–150 MPa applied in tabletting processes) was selected to enable a comparison with the results of previous tests of the orthorhombic paracetamol polymorph (4), which is better compactable than the commercial monoclinic polymorph. Monoclinic polymorph in the same paper (4) was studied up to 120 MPa only.

### A Study of the Dissolution

The dissolution of the robust tablets of sample 2a prepared by direct compression without any additives (diameter 12 mm, compacting force 0.85 MPa, weight 500 mg) was compared with that of commercially available Paracetamol tablets (purchased in a pharmacy) used as a reference (diameter 12 mm, weight of paracetamol in the tablet 500 mg, tablet weight 530 mg, fillers—starch, magnesium stearate). The two tablets were carefully placed at the bottom of vials containing 50 mL of distilled water at ambient temperature (+22°C), and the solutions were not stirred or moved. The changes occurring with the tablets in the water were recorded with a digital photo camera at regular time intervals.

## RESULTS AND DISCUSSION

### Powder Diffraction: A Study of the Processes on Annealing of the Frozen Solutions

The results of the studies of supercooled solutions in the "acetone-water" system have been described in two papers (31,37). Very recent results reported in (37) differ considerably from those which could be expected based on the analysis of the equilibrium phase diagram of the acetone-water system published earlier (31) (Fig. 1). Thus, the authors of (37) have reported the co-existence of three phases simultaneously at −102°C: ice I*h*, supercooled acetone solution with a very low water content, and frozen solution with a high water content. The presence of these phases would mean that the system is in a non-equilibrium state. The presence of the non-equilibrium supercooled solutions in a system is not good for obtaining finely dispersed forms of drugs, since the crystallites can grow in such systems as the excessive solvent evaporates.

In order to identify the phases formed on rapid cooling of the solutions and to register the phase transformations which take place on the annealing of the cooled solutions in the acetone-water and paracetamol-acetone-water systems, we have measured the X-ray powder diffraction patterns in the temperature range from −140 to +20°C at ambient and at low ($P<5\cdot10^{-2}$ torr) pressures *in situ*. Experiments with the samples of the frozen acetone-water solution (30 wt% of water) at

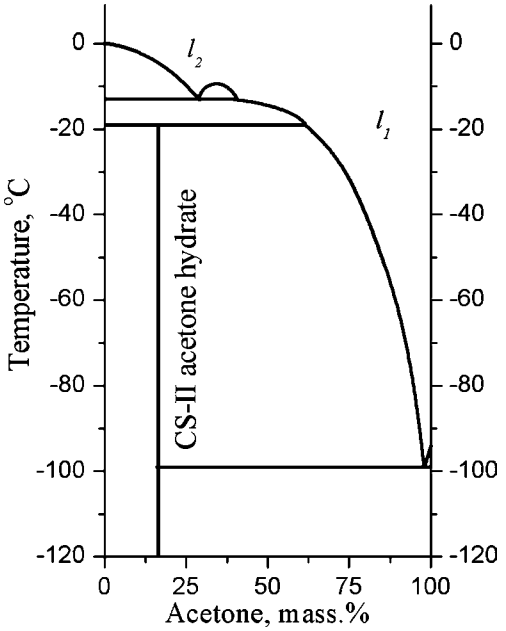


**Fig. 1** Phase diagram of the acetone-water system (based on data from (31)).

ambient pressure (Fig. 2a) have shown that at temperatures below −100°C reflections of the stable low-temperature polymorph of acetone, ice I*h* and CS-II acetone hydrate are present in the powder diffraction pattern. The cell parameters of the stable low-temperature acetone polymorph (rhombic, *Pbca*, refined using 13 independent reflections, $a=8.90\pm0.02$ Å, $b=8.03\pm0.02$Å, $c=22.07\pm0.15$Å at −120°C) were in a good agreement with the previously published single-crystal data ($a=8.873(3)$Å, $b=8.000(4)$Å, $c=22.027(7)$Å at −123°C) (38). At higher temperatures (from −90°C up to −60°C), only the reflections of the CS-II acetone hydrate were present in the diffraction patterns. The presence of a liquid (a solution of water in acetone) in the equilibrium with the hydrate could be observed visually and also manifested itself in the higher background of the powder diffraction patterns collected at these temperatures (Fig. 2a). Decreasing pressure in the chamber at −60°C and keeping the sample at this temperature resulted in the removal of acetone from the liquid phase by evaporation, after which the reflections of ice I*h* appeared (Fig. 2a, held at −60°C). If pressure in the chamber was decreased immediately after the sample was loaded, reflections of the CS-II acetone hydrate, a low-temperature polymorph of acetone and ice I*h*, were present simultaneously in the diffraction patterns collected in the temperature range from −140°C up to −100°C (Fig. 2b). The intensity of the reflections corresponding to the low-temperature polymorph of acetone decreased noticeably as compared with the diffraction patterns measured at the same temperatures at ambient pressure, giving evidence of the removal of acetone from the sample by sublimation. Thus, the diffraction experiments have shown that under these

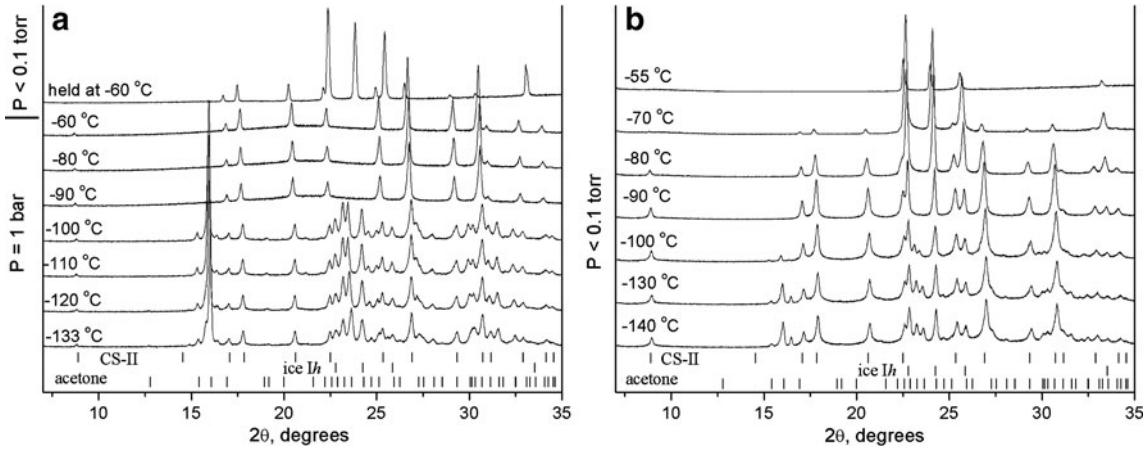


**Fig. 2** Powder diffraction patterns of the frozen acetone-water solution (30 wt% of water) at different temperatures at ambient (**a**) and low ($P < 5{\cdot}10^{-2}$ torr) (**b**) pressures. The positions of the reflections of the CS-II acetone hydrate, ice I*h* and low-temperature polymorph of acetone are shown as ticks at the bottom of the figures.

experimental conditions not all ice I*h* transforms into CS-II acetone hydrate. In the temperature range from −90°C to −70°C only the reflections of CS-II acetone hydrate and ice I*h* were present in the diffraction patterns (acetone was removed by sublimation), and at temperatures above −55°C only reflections of ice I*h* were present. The experiments carried out at low pressures showed that part of the sample transformed into CS-II acetone hydrate, and this phase co-existed with two other solid phases: ice I*h* and solid acetone. In our opinion, the phase termed by the authors of (37) as a "frozen acetone-ice solution" with a high water content could refer to the crystalline sample of CS-II acetone hydrate.

The results of the diffraction experiment with the samples of frozen solutions of paracetamol in the acetone-water mixtures (water content 30 wt%) at low pressures ($P<5{\cdot}10^{-2}$ torr) are shown in Fig. 3. The patterns measured in the paracetamol-acetone-water system differ from those collected for acetone-water system under the same conditions. For example, only reflections belonging to the phases of CS-II acetone hydrate and ice I*h* could be identified reliably at the diffraction pattern measured at −130°C (Fig. 3). It looks as if adding paracetamol to the system resulted in the formation of amorphous acetone on rapid cooling of the solution. Since the experiment was carried out in the vapor region at the acetone phase diagram, acetone was removed by sublimation from the chamber used for diffraction experiments.

The formation of CS-II acetone hydrate and of the low-temperature polymorph of acetone should be expected for the given composition of acetone-water mixture at temperatures below the eutectic melting in the binary system acetone-water under the equilibrium conditions (Fig. 1) (31). Nevertheless, only the reflections of CS-II acetone hydrate and of ice I*h* could be observed in diffraction patterns measured from the sample of frozen paracetamol-acetone-water solutions at ambient pressure. A low quality of diffraction patterns obtained in this experiment is typical for the presence of an amorphous phase (a hump-shaped background) and thus agrees well with our hypothesis about the formation of amorphous acetone. On increasing temperature from −130°C up to −70°C, new reflections appeared, which could not be assigned to any of the known polymorphs of paracetamol or its hydrates. Their intensity increased steadily on heating (Fig. 3). Further increase in temperature resulted in the appearance and growth of reflections corresponding to paracetamol trihydrate (39) and to the monoclinic polymorph of paracetamol. At temperatures above −20°C, the reflections of paracetamol trihydrate disappeared, indicating its decomposition. Only reflections corresponding to the pure monoclinic polymorph

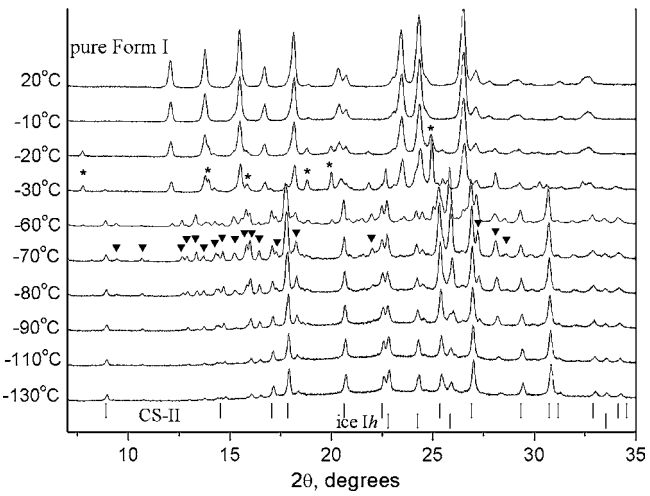


**Fig. 3** Powder diffraction patterns of the frozen acetone-water-paracetamol solution at different temperatures at low ($P<5{\cdot}10^{-2}$ torr) pressure. *the strongest reflections of the paracetamol trihydrate; ▼reflections belonging to the "unknown phase."

I of paracetamol were present at the diffraction patterns measured at −10°C and +20°C (the final drying stage).

The unknown phase observed in the temperature range between −130°C and −70°C can be a paracetamol polyhydrate, an acetone solvate of paracetamol, or a ternary co-crystal of paracetamol with acetone and water. The reflections of the monoclinic polymorph of paracetamol appear in the diffraction patterns collected at rather high temperatures only. This can be interpreted if one assumes that the temperature of the experiment is higher than the glass transition temperature of paracetamol in this system (26), above which the solid-state crystallization of paracetamol takes place. In our experiments, an increase in the intensity of reflections of the monoclinic polymorph of paracetamol was observed even at temperatures when no other solid compounds could be present in the system. This supports the hypothesis that paracetamol I crystallizes from the amorphous state. At the same time, since the reflections of paracetamol trihydrate appear at the moment when the intensities of reflections of the unknown phase start to decrease, one can suppose that paracetamol trihydrate is a solid product of the decomposition of this unknown phase.

## Choice of Optimum Drying Conditions to Obtain Finely Dispersed Paracetamol; Scanning Electron Microscopy

Drying conditions (pressure, temperature, time) for obtaining the product of desirable quality should be optimized for each system individually (26). For our system, pressure was known from the phase diagrams of mono-component systems. Optimum temperature was selected based on X-ray diffraction experiments. Time was optimized empirically by multiple trials. We could conclude that the removal of amorphous acetone by sublimation at temperatures below the temperature of eutectic melting in the binary system acetone-water was the most important stage of drying. An incomplete removal of acetone by sublimation at these temperatures resulted in the formation of a liquid phase (acetone-water solution containing up to 5 wt% of

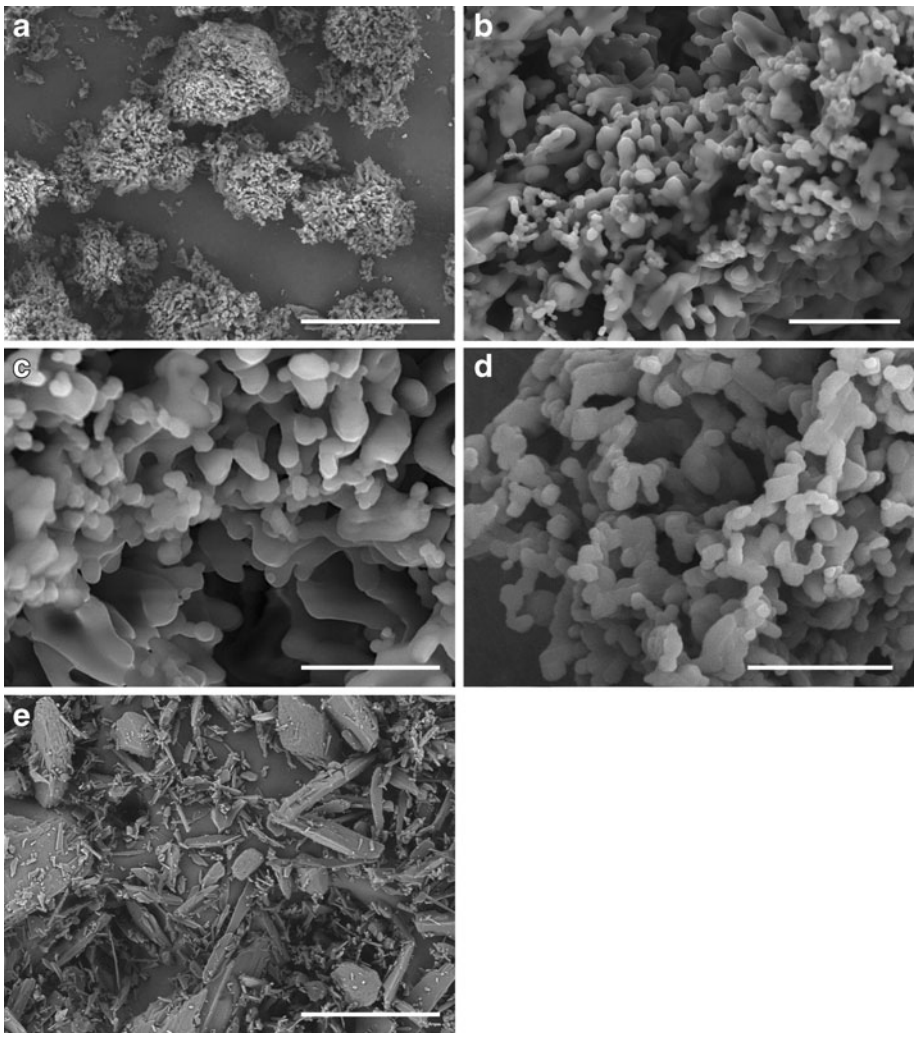


**Fig. 4** SEM images of the samples of finely dispersed paracetamol (sample 2) at different points (**a**-**d**) and raw material (sample 1) (**e**). (**a**, **e**) bar equal to 100 $\mu$m; (**b**, **c**, **d**) bar equal to 10 $\mu$m.

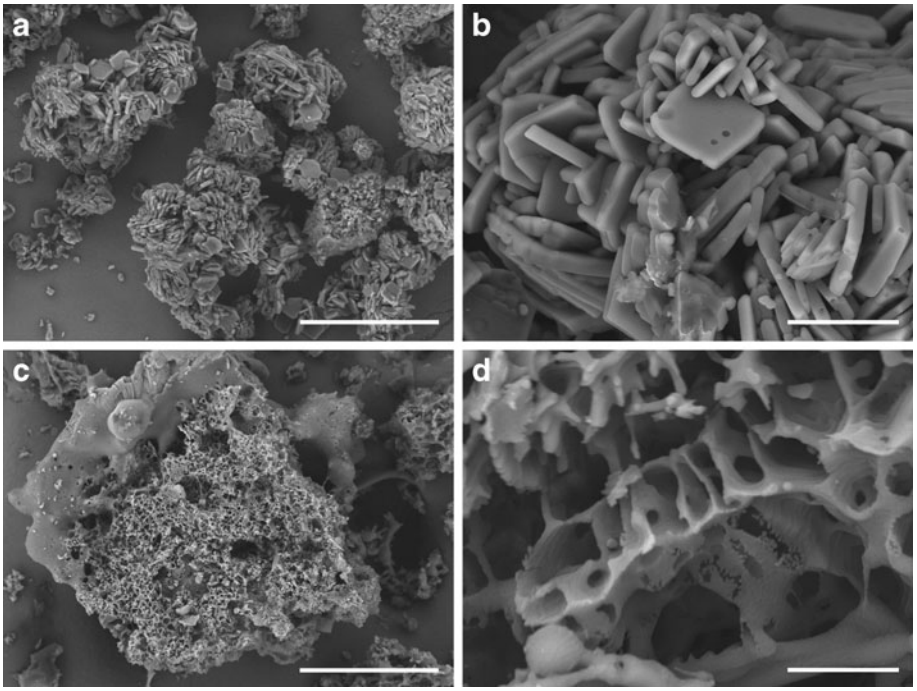


**Fig. 5** SEM images of the samples of paracetamol obtained if the drying conditions are wrong—in the presence of the liquid phase (sample 3) (**a**, **b**); the samples of paracetamol obtained from solutions with low concentrations (sample 4) (**c**, **d**). (**a**, **c**) bar equal to 100 $\mu$m; (**b**, **d**) bar equal to 10 $\mu$m.

water at −80°C). This, in turn, increased the solubility of paracetamol and led to its subsequent crystallization when the solvent mixture evaporated giving well-shaped crystals. The next drying stage at about −35°C aimed at the decomposition of an unknown phase (presumably a polyhydrate of paracetamol, its binary (acetone) or ternary (acetone-water) solvate), a partial removal of ice I*h* by sublimation and a partial decomposition of paracetamol trihydrate. The purpose of drying at −7°C was to remove the remaining ice I*h* and to decompose the paracetamol trihydrate. After that, the temperature was increased up to +30°C, the pressure was increased up to ambient by filling the chamber with dry argon, and the sample (sample 2) removed.

According to the results of the scanning electron microscopy, the sample 2 of paracetamol contained the agglomerates with the sizes 30–200 μm (depending on the cooling technique), composed of flat particles with linear sizes 1–10 μm, and the thickness 60–150 nm (Fig. 4 a–d). For a comparison, SEM photos of paracetamol before processing (sample 1) are shown in Fig. 4e. SEM images of the sample obtained with a wrong drying regime (in the presence of liquid phase; acetone solution with low water content) (sample 3) are shown in (Fig. 5 a, b). One can see that the size of the agglomerates formed on removal of solvents from the frozen droplets is preserved on drying. Still, because of the presence of the liquid phase, the particles grow reaching the size of 2–10 μm and form crystals with well-developed faces.

Relatively recently, paracetamol particles were precipitated from ethanol solution with supercritical $CO_2$ as an antisolvent using the solution enhanced dispersion by supercritical fluids (SEDS) technique (40). The size and shape of planar particles comprising agglomerates prepared in our study (sample 2) definitely resemble those of the particles obtained by the authors of (40). However, the authors of (40) worked with very diluted solutions (0.00835 mol fraction of paracetamol in ethanol solution), while our task was to develop a technique of preparing ultrafine paracetamol powders suitable for industrial application. Therefore, from the very beginning we have chosen the system with the largest possible solubility of paracetamol. Thus, it was of interest to find out if the agglomerates of the particles replicating the shape of the frozen droplets are preserved or degrade as paracetamol

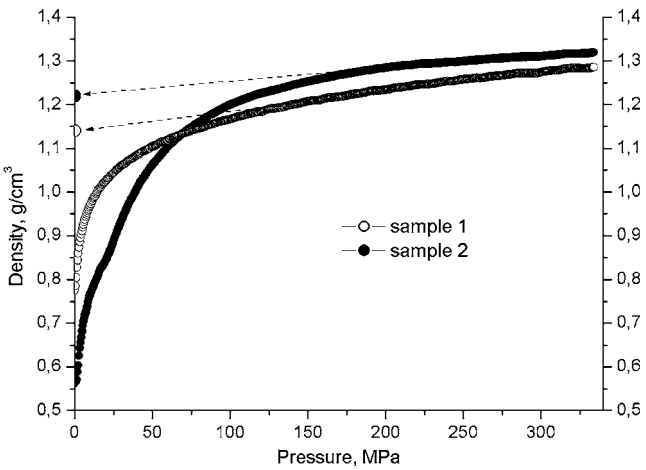


**Fig. 6** The dependence of the density of samples in compression cell *vs* effort at the punch. *Dashed lines* show the extrapolation of the diagram of the samples decompression to the points with final density (measured immediately after the removal of the samples from the tabletting-die).

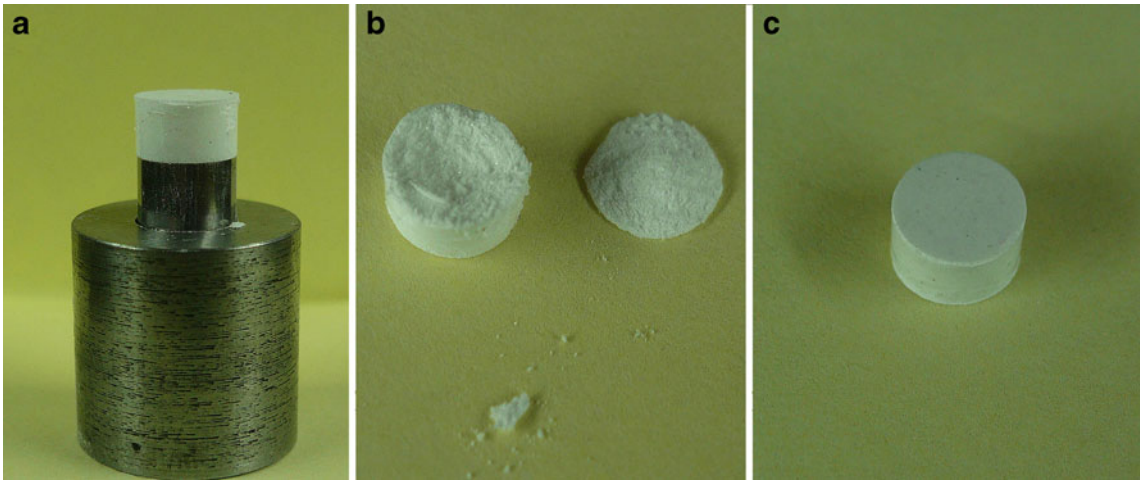


**Fig. 7** Illustration of different compactability of the paracetamol samples obtained in this work and commercial monoclinic polymorph I. The compression pressure was 345 MPa. (**a**, **b**) A tablet prepared by compressing the commercial samples (sample 1), sticks to the punch and is easily damaged during an attempt to remove it from the punch; (**c**) a tablet prepared by compressing sample 2.

concentration in solution decreases. To clarify this point, we used 4.4 wt% solution of paracetamol acetone-water mixture (water content 30 wt%) (sample 4). Scanning electron microscopy (Fig. 5 c, d) studies have shown that with decreasing concentration of initial solution, agglomerates of the same shape of frozen droplets are still present and have a much more porous structure.

## Compression Properties

The samples of finely dispersed paracetamol obtained in this work (sample 2) were shown to be much more compactable as compared with commercial paracetamol-I (sample 1) (Fig. 6). The tablets obtained by compression of the polycrystalline samples of commercial paracetamol stick to the punch and could not be preserved on attempts to eject them from the tabletting die or to measure the crushing force. To prevent this undesirable tablet damage, various lubricating additives (e.g. Mg stearate) are added to paracetamol in industrial formulations. The tablets formed on compression of fine paracetamol powder sample 2 are easily separated from the punch (Fig. 7). The porosity of the tablets measured immediately after the compression (6.0% at 345 MPa) was comparable with that of the tablets prepared from the pure orthorhombic polymorph of paracetamol (5.2% at 335 MPa) (4).

The crushing tests have shown the tablets prepared from the fine paracetamol sample 2 to be much more robust, with the crushing force equal to 1120±150 N (along the rod axis of the cyllindrical tablet) and 46±5 N (along a diameter of the tablet), than those compressed from commercial powder (sample 1) (184±18 N and 8±1 N, respectively) (Fig. 8), so that compressive strength (crushing stress divided by the surface area supporting the load), was equal to 40.00±5.20 MPa and 6.40±0.63 MPa, respectively. The tensile strength of the tablets from the paracetamol sample 2 (1.27±0.27 MPa) was somewhat higher than that for the tablets prepared from orthorhombic paracetamol (~0.95 MPa for the tablets prepared with compression pressure 335 MPa) (4) and considerably larger than the strength required to crush the tablets compressed from the commercial monoclinic paracetamol (0.225±0.03 MPa as measured in this work for sample 1, ~0.2 MPa as reported for a polycrystalline sample in (4), or~0.38 MPa as reported for a sample obtained by spray-drying in (15)). The value is comparable with the tensile strength required to crush the tablets prepared by compacting paracetamol co-crystals (1.15–2.79 MPa) (19) or paracetamol mixtures with carbohydrates obtained by spray-drying (0.45–

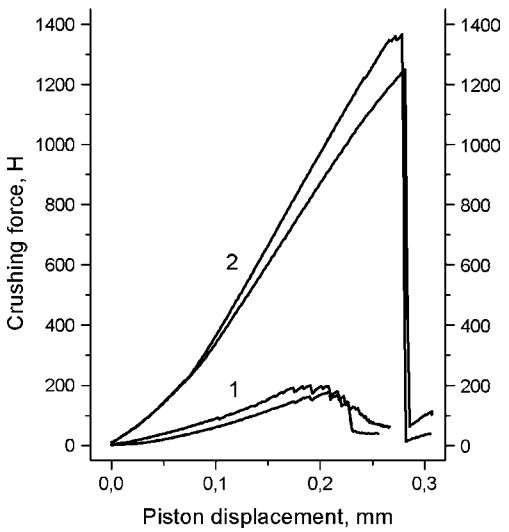


**Fig. 8** The results of testing the crushing force for paracetamol tablets compressed from: 1—commercial sample 1; 2—sample 2. The crushing force is applied along the axis of the tablet.

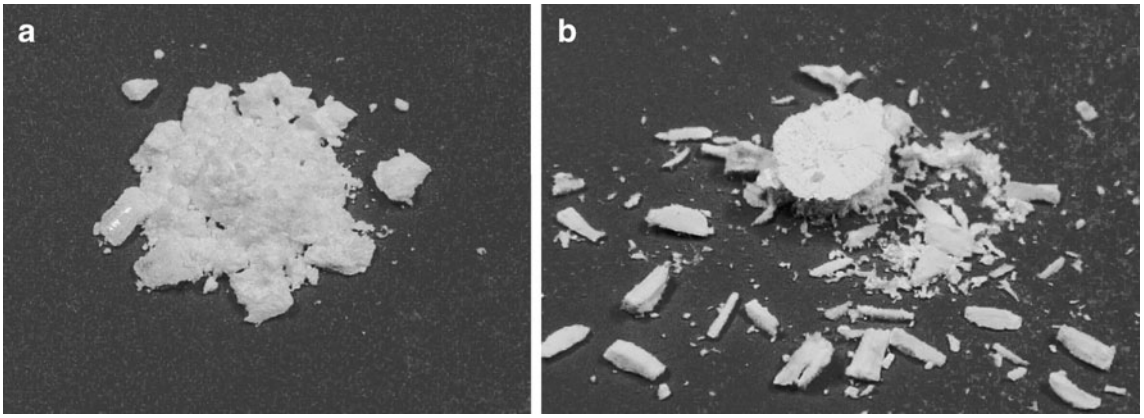


**Fig. 9** The tablets of paracetamol after testing the crushing force (the force is applied along the axis of the tablet): (**a**) a tablet prepared from commercial sample (sample 1); (**b**) tablet prepared from sample 2.

2.39 MPa) (15). In contrast to the tablets prepared from the commercial monoclinic paracetamol (sample 1), the tablet prepared from the sample 2 was crushed into well-defined fragments preserving the hardness of the initial tablet (Fig. 9).

Compactability of paracetamol sample 2 is even better as compared with that of paracetamol-II. Diffraction experiments have shown that the paracetamol sample 2 does not transform into the orthorhombic polymorph on tabletting, i.e. an improvement in the compactability of paracetamol sample 2 is not related to obtaining another polymorph (Fig. 10). Compactability can be sensitive to particle rheology and surface interactions more than to the internal crystal structure. For example, even sand can become compressible if the particles are covered with a thin PVP layer (41).

When considering the size and shape of particles comprising the agglomerates of sample 2 (Fig. 4), it is worth noting a rather narrow particle size distribution and shape uniformity (planar particles), in contrast to the commercial paracetamol sample 1, which is an aggregate of irregularly shaped crystallite fragments (platelets and blocks) with sizes from 10 to 100 μm and larger. The particle shapes in sample 2 are also more favorable for tabletting (42) than those in the commercial sample 1. In addition, a better compactability of paracetamol sample 2, as compared to commercial sample 1, can be attributed to a certain increase in specific surface area. The specific surface areas of the paracetamol sample 2 and the raw material (sample 1) were $0.57 \pm 0.06$ and $0.13 \pm 0.01$ $m^2/g$, respectively.

The images of the cleavage surfaces (parallel to the planar surface) obtained with a scanning electron microscope (Fig. 11) have revealed that compression results in ordering of planar paracetamol particles of sample 2, so that the normal to the best developed face coincides with the force direction. If we had flat single crystals, this ordering would result in a preferred orientation seen from X-ray powder diffraction patterns. However, our experiments have shown that there is no preferred orientation in

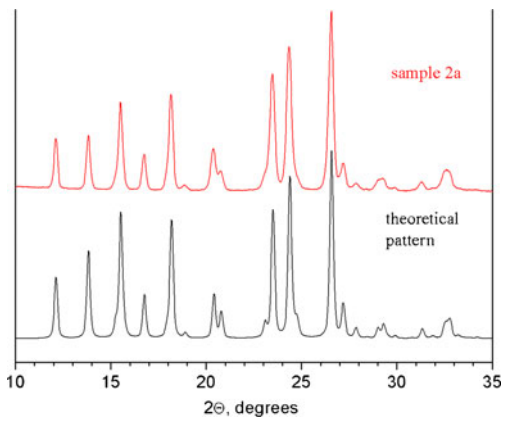


**Fig. 10** X-ray powder diffraction pattern of paracetamol sample 2a *vs.* theoretical pattern for pure monoclinic paracetamol calculated from single-crystal diffraction data (HXACAN01, (2)).

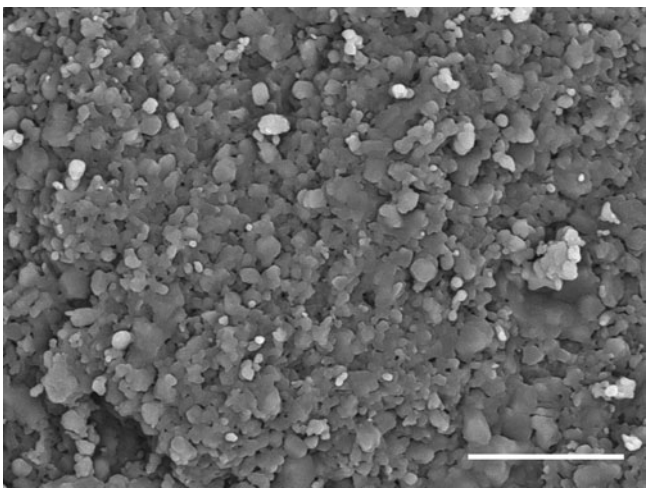

**Fig. 11** SEM image of the cleavage surface of a tablet (sample 2a) prepared by compression of the paracetamol sample 2, in a plane parallel to the base. Bar equal to 15 μm.

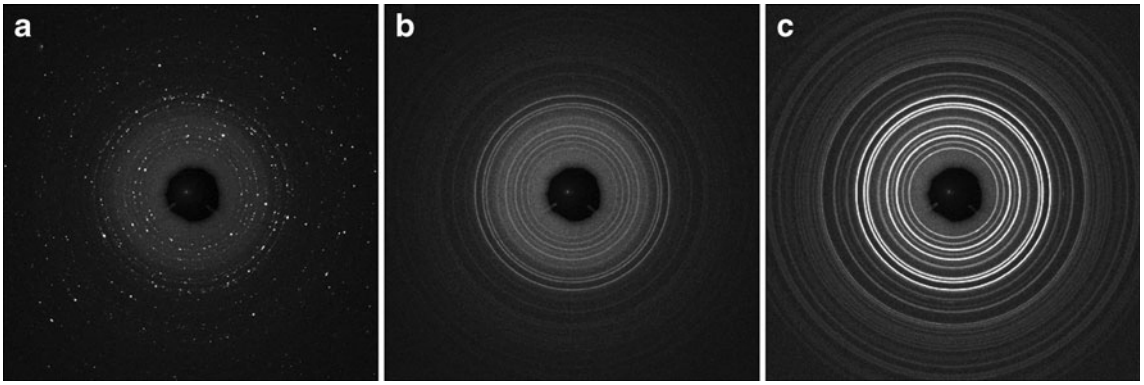


**Fig. 12** Diffraction patterns confirming the absence of the preferred orientation of the crystallites in the paracetamol sample 2a. (**a**) diffraction pattern from the raw material (sample 1); (**b**, **c**) diffraction patterns from the samples before (sample 2) (**b**) and after (sample 2a) (**c**) tabletting (primary beam is normal to the tablet plane).

the samples (Figs. 10, and 12), and this suggests that the flat particles are polycrystalline with a random orientation of the crystallites within a particle.

The authors of (4), who studied the direct compression of paracetamol-II, have noted that the "crystals folded under compression pressure." SEM images of the cleavage surfaces of tablets prepared from paracetamol-II published in (4) are similar to those obtained in our work for paracetamol-I. At the same time, in the SEM images of the cleavage surfaces of the tablets prepared from paracetamol-I in (4), one can clearly see that the crystals of paracetamol have crushed on compression, and the fragments are packed rather independently from each other. This was interpreted by the authors of (4) as a manifestation of the weakness of the interactions between the particles in the sample, the reason for the tablets sticking to the punch and for the fragmentation of the tablets (Fig. 7 a, b).

Diffraction experiments have revealed no preferred orientation of crystallites in the fine paracetamol sample 2 even after its compression into a tablet (sample 2a), in contrast to the commercial paracetamol (sample 1) (Figs. 10, and 12). Clearly distinguishable difference in the intensities of the diffraction patterns recorded before and after compression is explained by more than three-fold difference between the

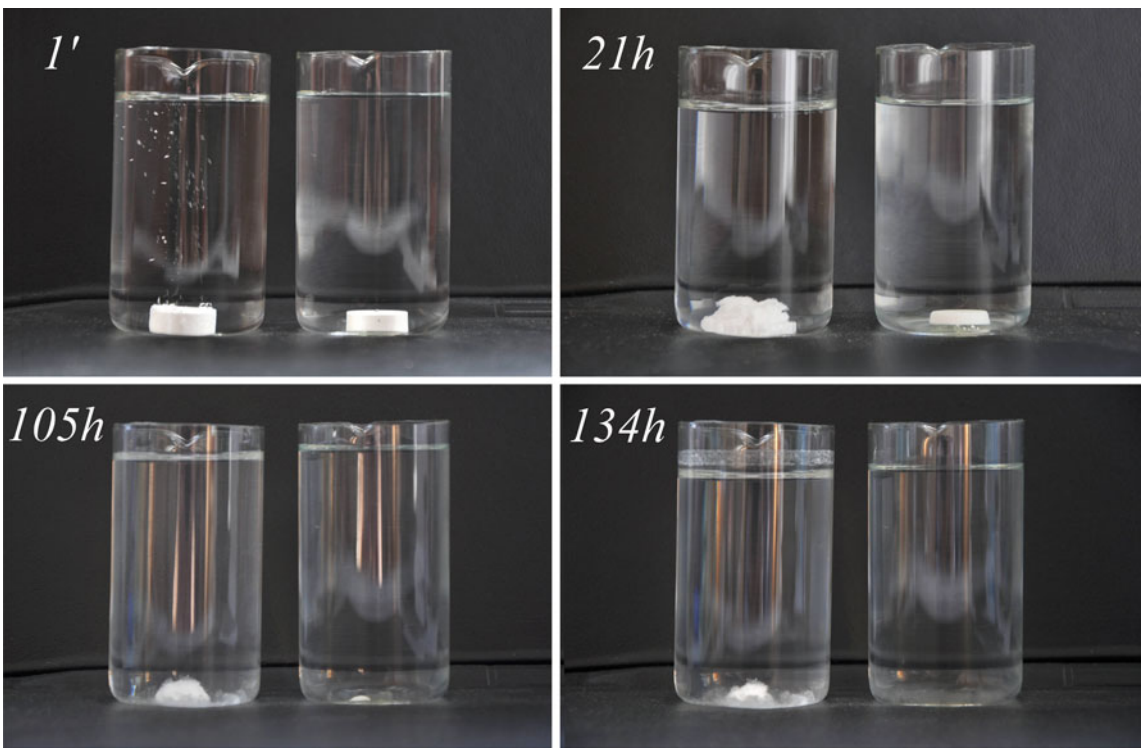


**Fig. 13** Dissolution of paracetamol tablets in water at 22°C: left bottle—commercial tablet, right bottle—sample 2a.

bulk density of the ultrafine paracetamol sample 2 (the sample was not additionally compacted before the diffraction experiment) and the density of the prepared tablet.

### Dissolution Studies

Although the tablets prepared from sample 2 without any excipients are mechanically very robust, they are well-soluble in water even without preliminary tablet fragmentation and stirring of the solution. Even a mere visual observation a) of a paracetamol tablet containig excipients as bought in a pharmacy and b) of a tablet prepared from sample 2 prepared by direct compression without any additives left in pure water for a few days has revealed a better dissolution behavior of the latter (Fig. 13). As one can see, the tablet sample 2a is completely dissolved, as expected, while the additives enhancing the compactability and improving the rheological properties slow down the tablet dissolution.

## CONCLUSIONS

Summing up, the proposed method of obtaining fine paracetamol powder by freeze-drying of its acetone-water solutions gives samples of the stable monoclinic polymorph I, which are suitable for direct compression without any excipients, stable on storage, mechanically robust, and, at the same time, well-soluble. Paracetamol is an inexpensive drug; therefore, the proposed method for this API may not yield economic advantage. Rather, paracetamol serves as a model compound to demonstrate a method that can be used to prepare new, improved forms of other molecular solids for pharmaceutical applications. In particular, one can produce fine particles of APIs for aerosols and suspensions in this way. Instead of trial-and-error method, detailed X-ray diffraction analysis at low temperatures and reduced pressures *in situ* and SEM of the solid products are more efficient to optimize experimental conditions of obtaining the desirable product.

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