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A study of the differences between two amorphous spray-dried samples of cefditoren pivoxil which exhibited different physical stabilities

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Abstract

The objective of this study was to investigate the reasons for the difference in physical stability of two amorphous cefditoren pivoxil samples that had been prepared using spray drying at inlet-air temperatures of 40 °C (SD-A) and 100 °C (SD-B). The two samples appeared amorphous by powder X-ray diffraction and had indistinguishable glass transition temperatures. Despite the fact that glass transition is often regarded as an indicator of the stability of amorphous forms, crystallisation was observed for SD-A, but not for SD-B, during storage at 60 °C and 81% relative humidity (RH). Gravimetric water sorption data demonstrated very similar water sorption until high RH values, at which point SD-A sorbed more water than did SD-B. The values of the dispersive, acidic (K_A) and basic (K_D) components of surface energy of the spray-dried samples were obtained using inverse gas chromatography (IGC), in the dry state and after equilibration with different RH environments. The data showed that the two amorphous samples had different surface properties and that the effect of sorbed water on these samples was also different. It is concluded that the two samples did not have long-range order, but had differences in the orientation of molecules at the surface, which were significant enough to alter the stability when the samples were stressed with water vapour and high temperature storage. IGC proved a valuable tool with which to study changes in the surface properties of amorphous materials.

Keywords: Amorphous; Cefditoren pivoxil; Inverse gas chromatography; Molecular mobility; Physicochemical stability; Surface energy

1. Introduction

Amorphous materials are thermodynamically unstable and therefore show some tendency to crystallise

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spontaneously. The transition from the amorphous to the crystalline form will depend on the molecular mobility, which is related to the glass transition temperature (T_g). Many amorphous materials are plasticised by sorbed water. Once incorporated into the amorphous region, water can increase the free volume and lead to enhance molecular mobility within the amorphous material, causing crystallisation.

Inverse gas chromatography (IGC) can give information on the relative exposure of particular functional groups on the surface of solid materials, due to electron acceptor and donor properties. Grimsey et al. (2002) have demonstrated that the acidic and basic parameters of saccharides determined by IGC, reflect the concentration of hydroxyl groups exposed on their surface. Furthermore, IGC can be used to determine the electron acceptor and donor properties on the surface of solid materials at various relative humidities (RHs), to explore the extent of the interaction between the surface and water. Sunkersett et al. (2001) have demonstrated that the specific energies of adsorption of polar probes ($-\Delta G_A^{SP}$) for paracetamol and carbamazepine change as RH is raised and the particular interaction sites of water molecules on the surface have been identified using a combination of IGC and molecular modelling.

In this study, it is hypothesised that changes in molecular mobility of amorphous materials, which will be enhanced by water sorption, will bring about changes in concentrations of the functional groups expressed on the solid surface.

Two amorphous forms of cefditoren pivoxil, an oral cephalosporin antibiotic, were prepared using spray drying at different inlet-air temperatures, and then differences in their crystallisation behaviour during storage at 60 °C and 81% RH were investigated using powder X-ray diffractometry. The objective of the study was to investigate the reasons for the observed differences in the physicochemical stability.

2. Materials and methods

2.1. Materials

Crystalline cefditoren pivoxil was synthesised at Meiji Seika Kaisha Ltd. (Japan).

2.2. Preparation of spray-dried solids

Three hundred grams of cefditoren pivoxil was dissolved in 18 l dichloromethane. The solution was spray-dried using an L-8 spray-drier (Ogawara, Japan) with inlet-air temperatures of either 40 or 100 °C. The supply rate of the solution was 100 ml/min. The rotation speed of the atomizer was 15,000 rpm.

2.3. Physicochemical stability study under high relative humidity

The spray-dried samples (150 mg) were stored at 60 °C and 81% RH (saturated solution of potassium chloride) for eight weeks. The changes in crystallinity were evaluated using powder X-ray diffraction.

2.4. Powder X-ray diffraction

Powder X-ray diffraction patterns were obtained using an X-ray diffractometer (model RINT 2200, Rigaku, Japan) by using a scintillation counter, Cu Kα radiation (40 kV, 20 mA), and a symmetrical reflection goniometer at a scanning speed 4°/min between $2\theta = 5$ and 40°.

2.5. Inverse gas chromatography

Experiments were performed using IGC (Surface Measurement System Ltd., UK). Approximately 600 mg of spray-dried samples were packed into the silanised glass column (Surface Measurement System Ltd., UK) of size 6 mm o.d., 3 mm i.d. and 300 mm long by vertical tapping. Progress was monitored visually whilst tapping for at least 15 min. Tapping continued until there were no visible cracks, hollows or channels in the body of the powder. Both ends of the columns were loosely stopped with silanised glass wool. The conditioning of the column packed with the sample powder was carried out at 303 K. The RH was initially 0% and was increased at increments of 10% up to 90% and then was decreased at decreases of 10% to 0%, the equilibration time at each RH was 40 min, which gave rise to a flat response on the thermal conductivity meter, indicating equilibration. Methane was used for the inert reference, *n*-decane, *n*-nonane, *n*-octane, *n*-heptane and *n*-hexane were used to determine the dispersive surface energies, acetone and ethyl acetate were employed to probe the acidic nature of the surface, and chloroform was employed to determine the basic nature of the surface. The gas flow rate used was 10 ml/min. Each probe was injected three times to give a measure of the reproducibility.

2.6. Determination of dispersive surface energies

The retention times for a homologous series of alkane probes were used to calculate the dispersive surface energies of spray-dried samples. The equations for this analysis have been firmly established for some time (Condor and Young, 1979) and have been reproduced recently by Columbano et al. (2003). Data were treated exactly as described by Planinšek and Buckton (2003) with dispersive energies calculated from the gradient of a plot of $RT \ln V_N^\circ$ versus $a(\gamma_L^D)^{1/2}$, where R is the gas constant, T the absolute temperature, V_N° the net retention volume, a the surface area of the probe molecule and γ_L^D is the dispersive surface energy of the probe. The values of a and γ_L^D were obtained from the literatures (Schultz et al., 1987; Nardin and Papirer, 1990).

2.7. Determination of acidic and basic parameters

The retention behaviour of polar probes on the $RT \ln V_N^\circ$ versus $a(\gamma_L^D)^{1/2}$ plot, results in responses that are located above the line drawn through the alkane probe results. The vertical distance between the data points of the polar probes and the alkane line gives the specific energy of adsorption ($-\Delta G^{AB}$). According to the Gutmann (1978), acid–base concept, liquids are characterised as an electron donor or base number (DN) and an electron acceptor or acid number (AN). AN was corrected to take into account dispersive contributions by Riddle and Fowkes (1990) to give AN*. The value of $-\Delta G^{AB}$ has been related to the acidic or electron accepting parameter (K_A) and the basic or electron-donating parameter (K_D) as described in Eq. (1):

$$-\Delta G^{AB} = K_A \mathrm{DN} + K_D \mathrm{AN}^* \tag{1}$$

By measuring the value of $-\Delta G^{AB}$ for polar probes, a linear plot of $-\Delta G^{AB}/\mathrm{AN}^*$ versus $\mathrm{DN}/\mathrm{AN}^*$ was obtained. The values of K_A and K_D of spray-dried samples were determined from the gradient and intercept of the line, respectively. The values of DN and AN* were obtained from the literature (Gutmann, 1978; Riddle and Fowkes, 1990).

2.8. Differential scanning calorimetry (DSC)

The DSC study was performed using a DSC 7 (Perkin-Elmer, USA) under a nitrogen gas flow using aluminum pans with non-hermetically sealed lid and a heating rate of 10 °C/min. The sample weights in the study were about 5 mg. For the calibration of enthalpy determination, indium of 99.99% purity was used. The onset temperature of the baseline shift in the DSC trace was determined as a glass transition temperature.

2.9. Water vapour sorption and desorption analysis

A microbalance system (model SGA-100, VTI, USA) was used for determination of water vapour sorption and desorption isotherms at 30 °C. Spray-dried samples (50 mg) were placed on the microbalance pan and were dried at 60 °C until equilibrium was reached (i.e. the weight change for 5 min was less than 0.01%). The RH was initially 0% and was increased at increments of 5% up to 95% and then was decreased at decreases of 5% down to 5% RH.

3. Results and discussion

3.1. Physical stability study under high relative humidity and temperature

Two spray-dried cefditoren pivoxil samples that were prepared using spray drying at inlet-air temperatures of 40 and 100 °C, were designated as SD-A and SD-B, respectively. The powder X-ray diffraction patterns of the spray-dried cefditoren pivoxil stored at 60 °C and 81% RH are shown in Fig. 1. Both the initial samples showed halo patterns and were consequently regarded to be amorphous. The patterns of SD-A showed sharp diffraction peaks, due to some crystal formation after four weeks' storage. The extent of crystallinity was largely unchanged following storage from four to eight weeks. The SD-B sample showed a halo pattern even after storage for eight weeks, with no signs of crystallisation, consequently the two spray-dried samples had very different physical stability.

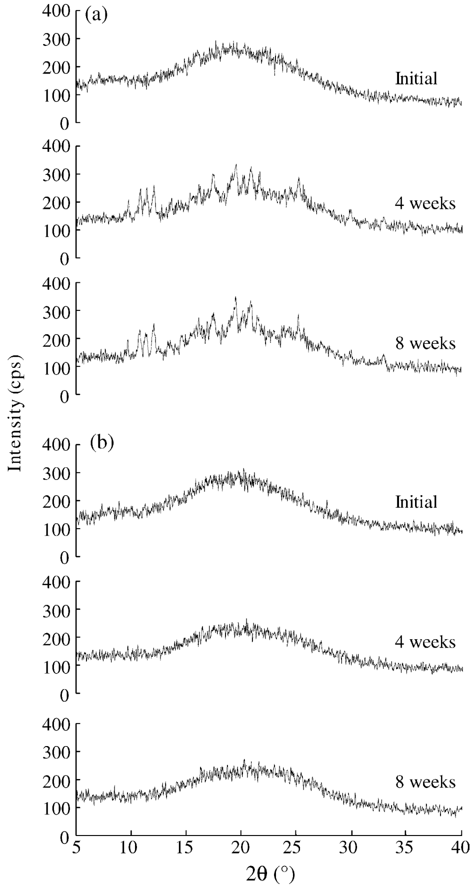

Fig. 1. Powder X-ray diffraction patterns of spray-dried cefditoren pivoxil stored at 60 °C and 81% RH: (a) SD-A and (b) SD-B.

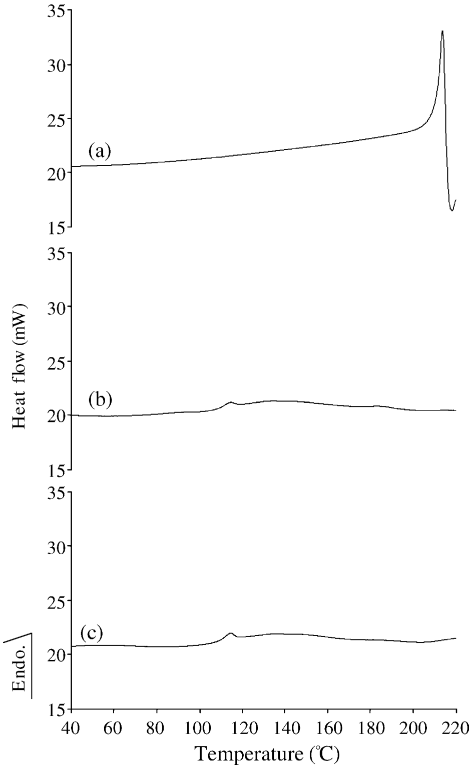

Fig. 2. DSC traces of crystalline and spray-dried cefditoren pivoxil: (a) cefditoren pivoxil crystal, (b) SD-A and (c) SD-B.

One possible reason for changes in stability could be retention of dichloromethane (the solvent used in spray drying). The amount of dichloromethane remaining in SD-A and SD-B was determined by gas chromatography as 157 and 382 ppm, respectively, and the remaining levels were acceptably low. As SD-B was more physically stable and had marginally more retained solvent it can be concluded that the differences in stability was not a consequence of any plasticising effect of residual organic solvent.

3.2. Physicochemical stability study under dry conditions

The DSC traces of crystalline and dry spray-dried cefditoren pivoxil are shown in Fig. 2. An endothermic event (melt) at 210 °C followed by an exothermic peak (decomposition) was observed for the crystalline cefditoren pivoxil. An exothermic event due to crystallisation has previously been observed at 142 °C for partially amorphous cefditoren pivoxil prepared by grinding (Ohta et al., 1999); however, this was not seen for these spray-dried samples. For the spray-dried material, the only thermal event was the glass transition (SD-A and SD-B being 107.4 and 107.6 °C, respectively). Consequently, both of the spray-dried samples were physically stable during the heating in the DSC, with no tendency to crystallise. This indicates an absence of crystalline seeds (no melt observed, and unlike the milled material which was largely amorphous, but which retained seeds, there was no crystallisation response).

The combination of X-ray and DSC data is indicative of two spray-dried samples that are amorphous, with no detectable crystallinity and with essentially the same glass transition temperature, but which have unexplained differences in stability.

3.3. Water vapour sorption and desorption isotherms

The water vapour sorption and desorption isotherms of spray-dried cefditoren pivoxil at 30 °C are shown in Fig. 3. The sorption data are similar until high RH values after which there is a greater extent of sorption for SD-A. The percentage of mass increase at 95% RH (whilst greater for SD-A) was ca. 3% for both samples; this is much lower than the uptake seen for more hydrophilic amorphous samples (often around 20% uptake). Hysteresis between sorption and desorption processes was found for both of the spray-dried samples, and the area enclosed between sorption and desorption events for SD-A was greater than that for SD-B. It is reasonable to conclude that the extent of water sorption is large enough to indicate that some sorption has occurred, but sufficiently low to indicate limited access of water vapour into the amorphous mass.

It has been demonstrated that the area enclosed between sorption and desorption events and the amount of water sorbed at 95% RH become greater with increasing amorphous content of cefditoren pivoxil (Ohta et al., 2000). The results presented here for water sorption would therefore suggested that the crystallinity of SD-A was lower than that of SD-B, however this is not in keeping with the X-ray and DSC data. It follows that either the water sorption is better suited to detecting changes in crystallinity, or more likely that the different amorphous forms have different morphologies, giving rise to changes in the ability for water to absorb.

3.4. Changes in dispersive surface energy with varying relative humidity

The changes in dispersive surface energy ($\gamma_{\mathrm{S}}^{\mathrm{D}}$) of spray-dried cefditoren pivoxil with varying RH at 303 K are shown in Fig. 4. It can be seen in Fig. 4 that when dry and when sorbing at low RH there are differences in dispersive energy between samples A and B, but that at higher RH the measured values are similar. This is indicative of a difference in surface nature for the dry material, due to the orientation of molecules at the particle surface. The values of $\gamma_{\mathrm{S}}^{\mathrm{D}}$ during the water desorption process were smaller than those in the water vapour sorption process for both of the spray-dried samples. We have demonstrated that the presence of sorbed water decreases the value of $\gamma_{\mathrm{S}}^{\mathrm{D}}$ for an amorphous cefditoren pivoxil prepared by grinding, which is believed to be due to water shielding the highly energetic interaction sites from organic probes (Ohta and Buckton, 2004). Since the amount of water present at any RH in the desorption process was greater than that in the sorption process for both of the spray-dried samples as shown in Fig. 3, the reduction in the value of $\gamma_{\mathrm{S}}^{\mathrm{D}}$ could also be the result of water blocking sorption sites on the surface. The extent of depression of the values of $\gamma_{\mathrm{S}}^{\mathrm{D}}$ in the desorption process compared with the

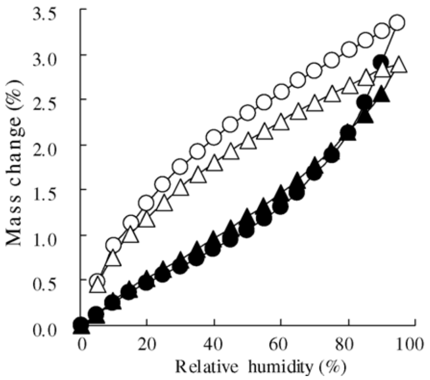

Fig. 3. Water vapour sorption and desorption isotherms of spray-dried cefditoren pivoxil at 30 °C: (●) SD-A (sorption), (○) SD-A (desorption), (▲) SD-B (sorption), (△) SD-B (desorption).

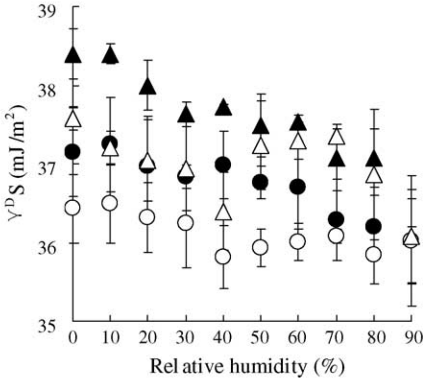

Fig. 4. Changes in dispersive surface energy of spray-dried cefditoren pivoxil with varying relative humidity at 303 K: (●) SD-A (sorption), (○) SD-A (desorption), (▲) SD-B (sorption), (△) SD-B (desorption).

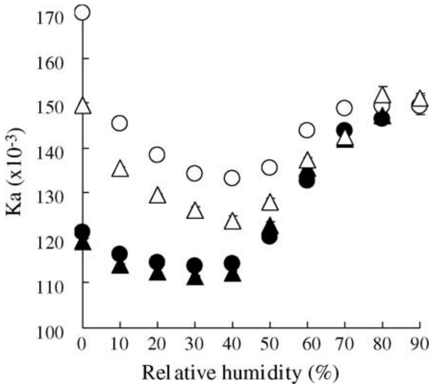

Fig. 5. Changes in acidic parameter of spray-dried cefditoren pivoxil with varying relative humidity at 303 K: (●) SD-A (sorption), (○) SD-A (desorption), (▲) SD-B (sorption), (△) SD-B (desorption).

sorption process for SD-A was similar to that for SD-B. The changes in the values of γ_S^D with varying RH could not thus give an explanation for the difference in the physicochemical stabilities of the two amorphous cefditoren pivoxil samples.

3.5. Changes in acidic and basic parameters with varying relative humidity

The changes in acidic (K_A) and basic (K_D) parameters of spray-dried cefditoren pivoxil with varying RH at 303 K are shown in Figs. 5 and 6, respectively. Hysteresis of the value of K_A and K_D between the water vapour sorption and desorption processes was found for both of the spray-dried samples, and the area enclosed between the sorption and desorption events for SD-A was greater than that for SD-B. The values of K_A and K_D in the water vapour desorption process for both of the spray-dried samples were greater than those in the water vapour sorption process in contrast with the values of γ_S^D, so that the phenomena cannot be explained by the blocking effect of the sorbed water. Indeed, this is indicative of greater affinity of the probe, either due to interactions with the sorbed water or due to accessibility of different sites as a consequence of water exerting a plasticising effect. The differences between SD-A and SD-B in the dry state and during sorption are minor ones, consequently this does not in itself provide an explanation of the differences between these two materials.

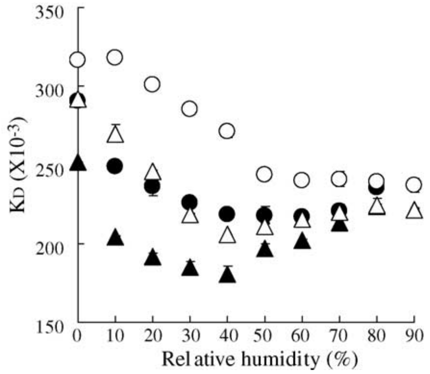

Fig. 6. Changes in basic parameter of spray-dried cefditoren pivoxil with varying relative humidity at 303 K: (●) SD-A (sorption), (○) SD-A (desorption), (▲) SD-B (sorption), (△) SD-B (desorption).

Applying a BET (Brunauer et al., 1938) approach, as reported by Teng et al. (1991) (even though BET defines adsorption and this clearly involves some absorption) to the water vapour sorption isotherms in Fig. 3, the inflection point that would be indicative of “monolayer formation” (ca. 40% RH) is in a similar position to the jump in K_A values (Fig. 5). This indicates that the increase in the value of K_A and K_D for both of the spray-dried samples above 50% RH resulted from enhancing the interaction between probes and water molecules because of the progressive buildup of “more loosely bound” water molecules on the powder.

3.6. Changes in ratio of basic to acidic parameter with varying relative humidity

The changes in the ratio of basic to acidic parameter (K_D/K_A) of spray-dried cefditoren pivoxil with varying RH at 303 K are shown in Fig. 7. The values of K_D/K_A of SD-A and SD-B at 0% RH in the water vapour sorption process were 2.39 and 2.11, respectively.

Previously, we have shown that the value of K_D/K_A can be used to quantify the crystallinity of a cefditoren pivoxil sample that had been made amorphous through milling (Ohta and Buckton, 2004), due to a reorientation of the functional groups at the surface as the material became increasingly amorphous. The data in Fig. 7 could therefore either reflect differences in crystallinity between SD-A and SD-B, corresponding to the results derived from the water vapour sorption and desorption isotherms, or again simply reflect that these two amorphous samples have been formed with quite

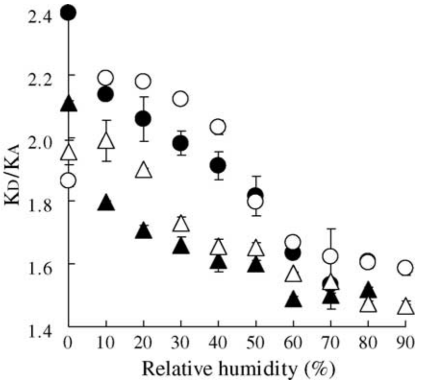

Fig. 7. Changes in ratio of basic to acidic parameter of spray-dried cefditoren pivoxil with varying relative humidity at 303 K: (●) SD-A (sorption), (○) SD-A (desorption), (▲) SD-B (sorption), (△) SD-B (desorption).

different molecular orientations at the particle surface. Based on the X-ray and DSC data, which show lack of crystallinity, the second option is more probable.

The values of K_D/K_A of SD-A and SD-B at 0% RH after the water sorption–desorption cycle were both lower than the values for the original dry materials (Fig. 7), suggesting that the samples had relaxed and reorientated during the experiment. The fact that the difference was greater for SD-A demonstrated that this sample showed a greater tendency to change during the experiment. The relaxation of both forms indicates that the two spray-dried materials will both gradually relax to the stable crystalline state. This is taken to imply that the presence of two different properties as a consequence of processing is simply a consequence of different extents of disruption of the molecules, rather than what is now often described as “polyamorphism” i.e. we do not believe that two discreet energetic states exist, but rather we believe that a continuum of energy states is possible as the different levels of disruption revert to the state form.

The values of K_D/K_A for both of the spray-dried samples showed a general decrease as RH was increased in the water vapour sorption process, with the most dramatic fall being between 0 and 10% RH. The drop in K_D/K_A can be attributed to water preferentially shielding the carbonyl groups that have electron-donating nature (this has previously been discussed for the surface of amorphous cefditoren pivoxil prepared by grinding (Ohta and Buckton, 2004)). Since water molecules would be sorbed to the most hydrophilic sites at the initial RH increment, it seems reasonable to suppose that the most hydrophilic sorption sites on the surface of spray-dried cefditoren pivoxil are the exposed carbonyl groups.

The values of K_D/K_A for both of the spray-dried samples were seen an increase as RH was dropped from 90% to 10%, followed by a fall on reducing the RH from 0% to 10% during the water vapour desorption process. The large decrease on removing the water to 0% RH reflects a change in packing as the water is removed.

4. Conclusions

Two spray-dried samples, differing in the parameters used during drying, were seen to have very different physical stability, whilst both seemingly being amorphous and dry.

The two samples showed different water sorption and desorption properties, reflecting physical differences in the particles. SD-A was able to sorb more water than SD-B at high RH, despite the fact that the major part of the sorption isotherm was very similar.

The two samples had differences in γ_S^D (with SD-A having a lower dispersive surface energy), K_D (where SD-A showed a stronger interaction with the polar probe) and to some extent with K_A (but only really on the desorption cycle). IGC has clearly shown differences in surface properties, and also provided information on how those differences change with RH. These differences show that the SD-A and SD-B amorphous particles both lack long-range order, but clearly have different local order of molecules at their surfaces, which gives rise to a substantial change in stability.

IGC can be sensitive tools for studies of the surface nature of amorphous samples, this could be of considerable use in the identification of batch-to-batch variability.

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