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EFFECT OF GRINDING ON THE DEHYDRATION BEHAVIOR OF NEDOCROMIL SODIUM HYDRATES

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Nedocromil sodium has a number of known hydrate states, a monohydrate, a trihydrate and a heptahemihydrate, including an amorphous state. Effect of grinding on the hydration states of nedocromil sodium crystals was studied. After grinding the trihydrate, heptahemihydrate was observed in the ground sample, even though, the water content in the ground sample was not sufficient to cover the heptahemihydrate's hydration level. On the other hand, in the ground heptahemihydrate, trihydrate was existed. Apparent activation energies (ΔE) for hydrates, monohydrate→anhydrate, trihydrate→monohydrate and heptahemihydrate→amorphous(anhydrate), were calculated using TG data. ΔE for the dehydration of heptahemihydrate was significantly lower than that of other hydrates. Obtained ΔE data explained the inter-conversion behavior of nedocromil sodium induced by grinding.

Keywords: *activation energy, nedocromil sodium, pharmaceutical hydrate, TG-DTA, XRD-DSC*

Introduction

The common crystalline forms found for a given drug substance are polymorphs and solvates. Solvates are crystalline solid adducts containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug. Hydrates are formed when water is the solvent of crystallization [1]. In hydrates, water occupies definite positions in the crystal lattice, usually by forming hydrogen bond(s) and/or coordinate covalent bond(s) with the anhydrate drug molecules.

The sodium salt of nedocromil (9-ethyl-4,6-dioxo-10-propyl-4H,6H-pyrano[3,2-g]quinoline-2,8-dicarboxylate), has been shown to inhibit the activity of inflammatory cells associated with asthma. The effect that nedocromil sodium has on sensory nerves indicates that it may be effective for the treatment of asthmatic cough, inhibiting early and late-phase asthmatic reactions following allergen exposure and exercise [2]. Nedocromil sodium has a number of known hydrate states including an amorphous phase, which contains variable amounts of water [3–8], a monohydrate, a trihydrate and a heptahemihydrate. It is the monohydrate form of this drug, obtained by dehydration of the trihydrate, which is administered as a dry powder inhalation [9, 10].

In the manufacturing process for the pharmaceutical products, there are many processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating or spray-drying. Especially, the physical manipulation, such as grinding, of a pharmaceutical compound may exert a substantial influence on its solid-state properties. As the compounds change hydration states, substantial modifications in pharmaceutically important properties can occur. The crystallinity and hence entropy is affected, influencing the solubility, dissolution rate, stability, and bio-availability of the drug. For example, desolvated solvates are occasionally produced during the drying process. Dehydrated hydrates are less ordered than their crystalline counterparts and are difficult to characterize, because analytical studies indicate that they are anhydrated compounds when they have the structure of the hydrated crystal form from which they were derived. Evaluation methods which are sensitive for detecting the physical and chemical changes that may take place in a heated sample are required. Thermal methods can be used to evaluate the desirable characteristics of pharmaceutical compounds [11]. The aim of this study is to clarify the effect of grinding on the hydration states of nedocromil sodium using thermal analysis.

Experimental

Materials

Nedocromil sodium was supplied from Rhone-Poulenc Rorer. Hydrates having different hydration level were prepared under the appropriate humidity [3–8]. The water content of the sample was determined by Karl Fischer titrimetry using a Hiranuma Aquacounter AQV-6.

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Grinding method

Samples were ground for a definite interval using the vibrating mill (TI-100, CMT). 2 g of sample and the rod that increased grinding efficiency were placed in the cell. After grinding the samples for 60 min, the temperature of cell was about 40°C, and the humidity inside was about 30% RH.

Methods

Water vapor adsorption isotherm measurement

Dynamic vapor sorption analyzer (DVS) was used for the measurement of water uptake of sample at various relative humidity (RH) values. Sample (5–10 mg) was placed into the sample cup. Sample mass was measured every 2 min by the microbalance and the humidity was automatically regulated from 0% RH to 100% RH at 25°C. The mass stability criterion employed for equilibrium was that the maximum mass change (% min^{-1}) for each measurement was less than 0.02%.

TG-DTA measurement

Thermo plus TG8120 was used for the evaluation of the mass loss due to the dehydration of samples. Samples in open pans were heated at various heating rates under nitrogen gas purge.

XRD-DSC measurement

XRD-DSC II was used for the measurement of the change in the crystalline state of samples. Samples were placed in open aluminum sample pans whose size was 7 mm×7 mm×0.25 mm. The inside of the DSC unit was purged by nitrogen gas. The heating rate of DSC run was 1°C min^{-1} and X-ray diffraction was measured simultaneously.

Determination of apparent activation energy

The value of apparent activation energy (ΔE) was calculated from the TG data associated the change in the temperature at maximum reaction rate based on the differential kinetic data recorded under various heating rate [12, 13]. If the mass decreases to a given fraction at the temperature, T_1, for the heating rate of φ_1, at T_2 for φ_2, and so on, the following equation can be obtained:

$$\log\varphi_1+0.4567\frac{\Delta E}{RT_1}=\log\varphi_2+0.4567\frac{\Delta E}{RT_2}=\cdots$$

Thus the plots of $\log\varphi$ *vs*. the reciprocal absolute temperature gives a straight line, the slope of which gives the active energy.

Results and discussion

Hydration and dehydration behavior of nedocromil sodium

When nedocromil sodium trihydrate was stored under the dry nitrogen stream for 3 h at 25°C, the trihydrate was transformed to the monohydrate, which contained 4.2% water. Figure 1a shows the water vapor adsorption isotherm for the monohydrate derived from the trihydrate. When the dried monohydrate equilibrated at 10% RH≤90% RH, on the hydration process, nedocromil sodium exists as the trihydrate (Fig. 1a). On the dehydration process, nedocromil sodium exists as the heptahemihydrate at the range from 95% RH to 10% RH. This result suggested that the activation energy barrier for the conversion from the heptahemihydrate to the trihydrate in this RH region is too high to be easily overcome at 25°C. By storage at 0% RH for 5 h, the heptahemihydrate was changed to the amorphous state, which was confirmed by the XRD measurement. Obtained amorphous contains the 3.5% water, which value was less than that in the original monohydrate (4.2%). The water uptake behavior for the amorphous derived from heptahemihydrate was shown in Fig. 1b. On hydration at increasing RH, the amorphous form takes up water and is converted to the trihydrate at 45% RH. Dehydration behavior was same as shown in Fig. 1a.

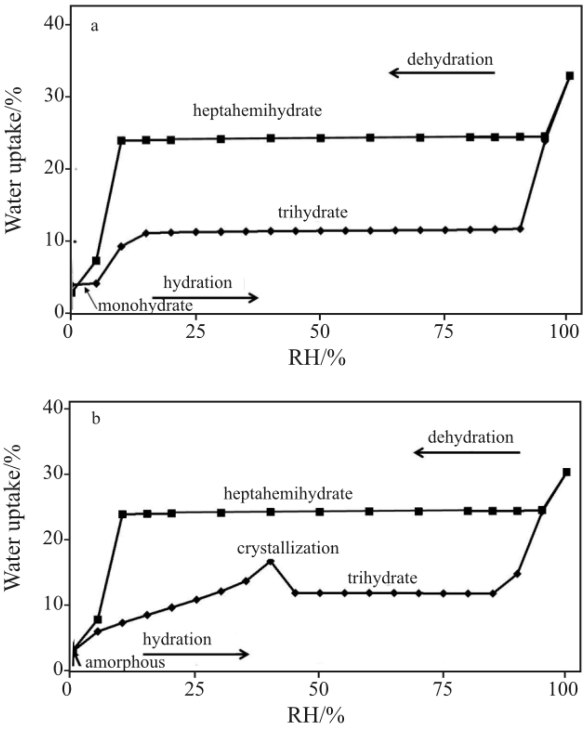


Fig. 1 Water vapor adsorption isotherm for a – monohydrate derived from trihydrate at 25°C and b – amorphous derived from heptahemihydrate at 25°C

Effect of grinding on the molecular state of nedocromil sodium hydrates

Figure 2 shows the XRD-DSC data of heptahemihydrate and trihydrate. On the DSC curve of heptahemihydrate (Fig. 2a), endothermic peak was observed at 50 and 320°C. By comparison of corresponding XRD pattern, the peak at 50°C was due to the dehydration and amorphization of heptahemihydrate, and the peak at 320°C was due to the decomposition of nedocromil sodium. On the other hand, trihydrate showed two endothermic peaks on the DSC curve (Fig. 2b). The endothermic peak at 70°C was identified as the conversion from trihydrate to monohydrate, and the peak at 180°C was due to the conversion from monohydrate to crystalline anhydrate. In this case, the amorphization of nedocromil sodium was not observed. Figure 3a shows the XRD-DSC data of heptahemihydrate ground for 60 min. In the XRD pattern at 40°C (bottom pattern), the diffraction peak, shown as circle, due to the trihydate was observed at 9° (2θ). On the DSC curve of ground heptahemihydrate, an endothermic peak was observed at 70°C which was due to the conversion from trihydrate to monohydrate and

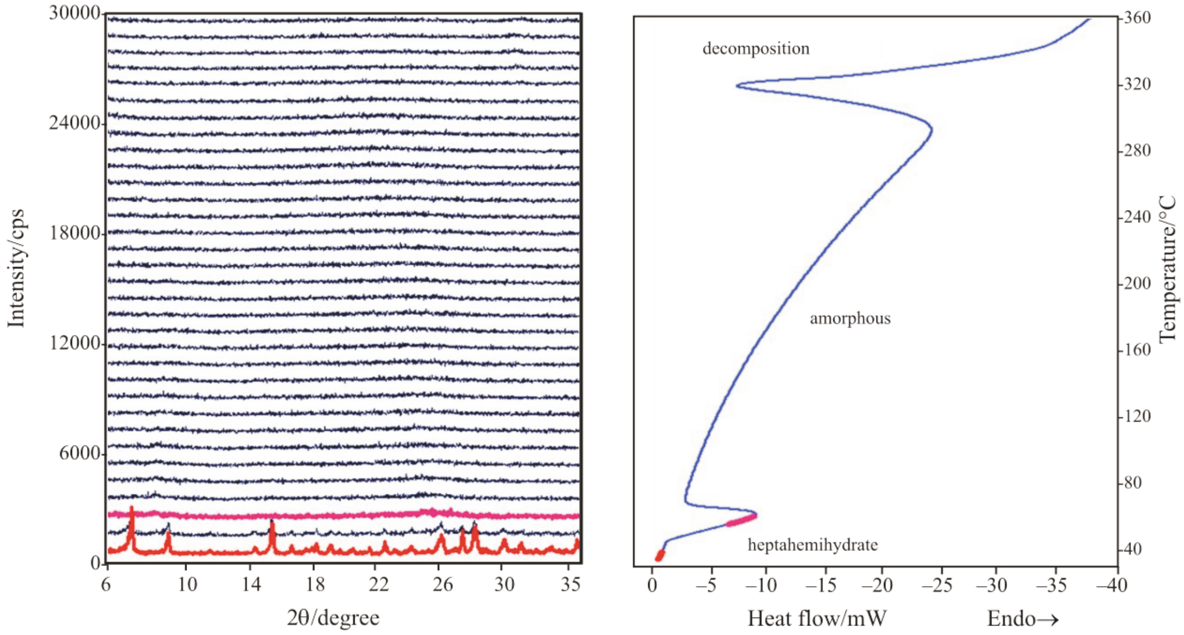


Fig. 2a XRD-DSC data for heptahemihydrate

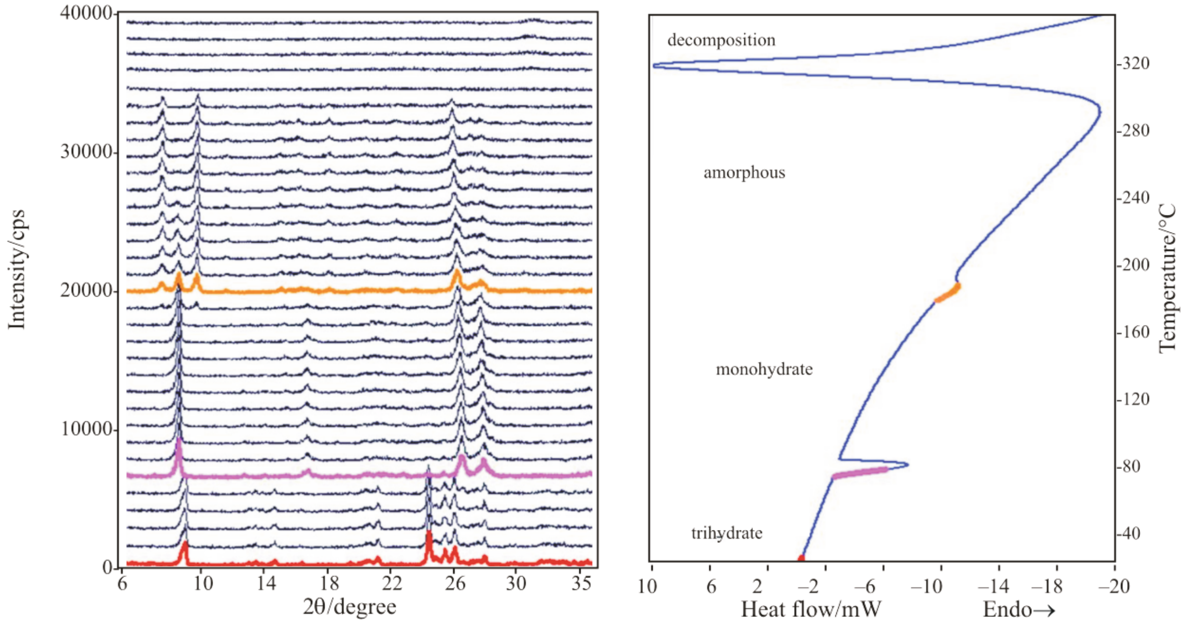


Fig. 2b XRD-DSC data for trihydrate

not observed in the DSC curve of original heptahemihydrate. These results suggested that the conversion from heptahemihydrate to trihydrate was occurred by grinding. Figure 3b also shows the effect of grinding on the molecular state of trihydrate. The XRD pattern of ground trihydrate at 25°C showed the diffraction peak at 7° (2θ), shown as circle, due to the heptahemihydrate, and this peak was disappeared after heating at 50°C. DSC data also supported the existence of heptahemihydrate, because the endothermic peak due to the dehydration of heptahemihydrate, which was not observed in the original DSC curve for trihydrate, was observed 50°C. These results revealed the fact that heptahemihydrate was generated by grinding, despite the water content in the ground trihydrate (10%) was not sufficient to cover the heptahemihydrate's hydration level (26%). The effect of grinding on the inter-conversions of the various phases of nedocromil sodium is summarized in Scheme 1. After grinding the trihydrate, there would be three components, original trihydrate, crystallized heptahemihydrate, and amorphous that contained very little water. On the other hand, in the ground heptahemihydrate, original heptahemihydrate, converted

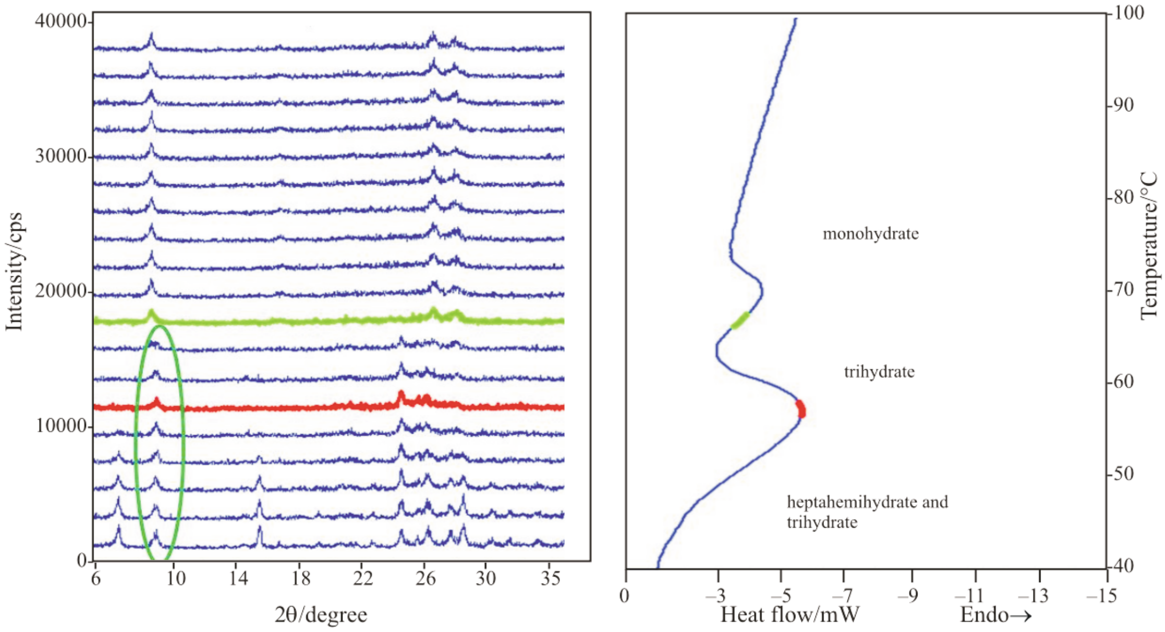


Fig. 3a XRD-DSC data for heptahemihydrate ground for 60 min

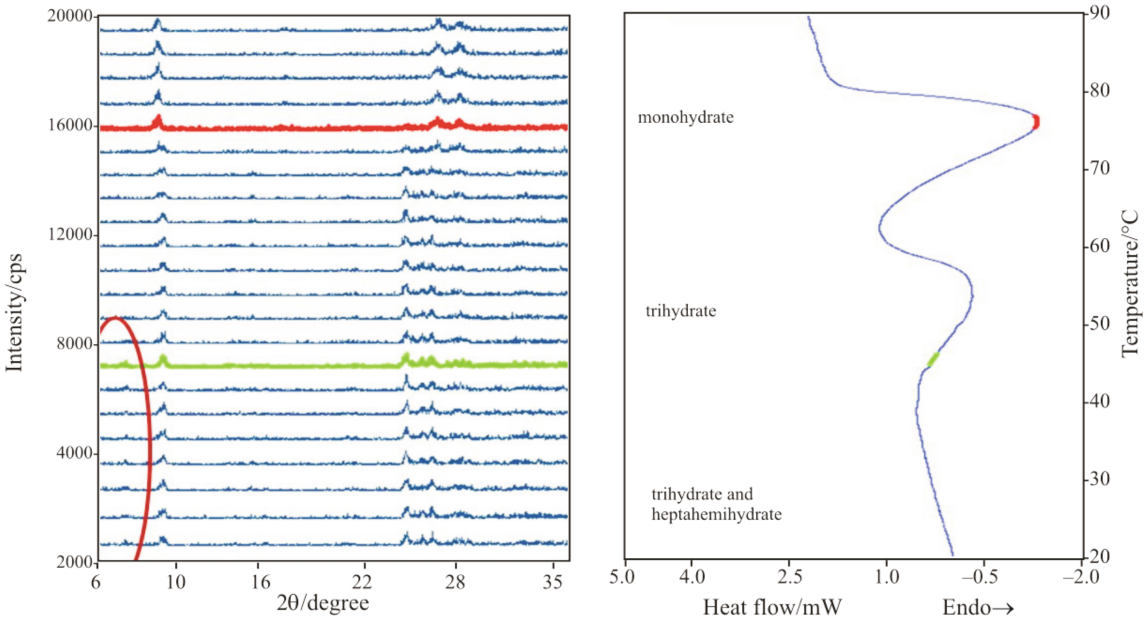
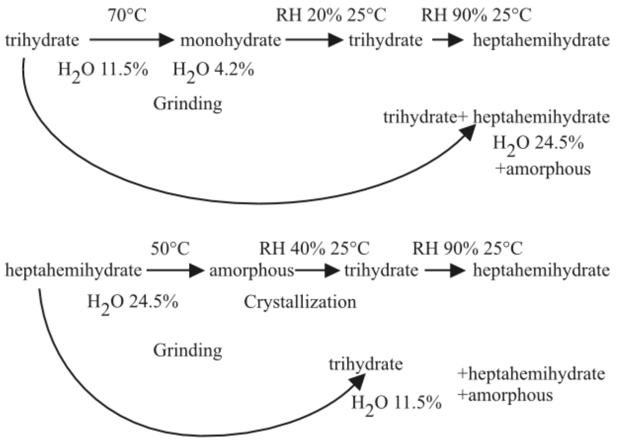


Fig. 3b XRD-DSC data for trihydrate ground for 30 min



Scheme 1 Effect of grinding on the transformation behavior of nedocromil sodium trihydrate and heptahemihydrate

trihydrate, the small amount of amorphous, and excess water would be existed.

Molecular states of ground nedocromil sodium hydrates

Figure 4 shows the TG-DTA curves for trihydrate and heptahemihydrate. TG curve (Fig. 4a) shows two dehydration steps at the two temperatures (70 and 180°C) with water stoichiometries corresponding to about 2 and 1 mol, respectively. This result suggested that there were different water molecules having higher and lower binding energy in the crystal lattice of trihydrate. TG curve of the heptahemihydrate (Fig. 4b) shows a single dehydration step which corresponded to 7.5 water molecules. This result was consistent with the result of the XRD-DSC measurement (Fig. 2a).

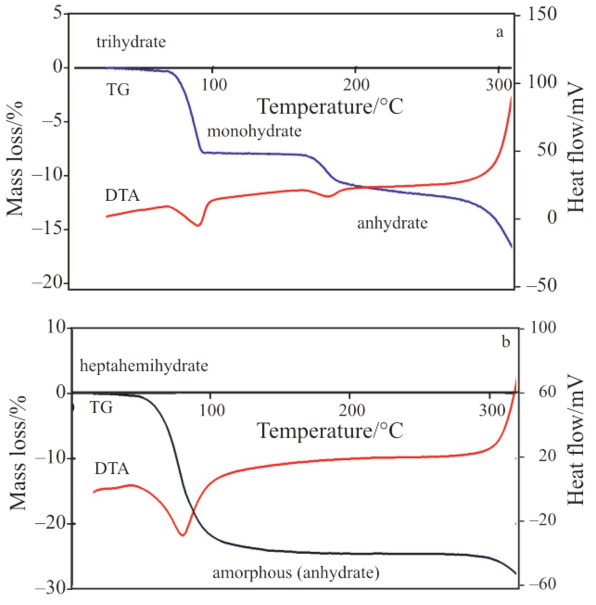


Fig. 4 TG-DTA curves for a – trihydrate and b – heptahemihydrate

Figure 5 shows the $\log\varphi$ *vs*. 1000/T plot for the dehydration process of each hydrate. The values of $\log\varphi$ for hydrates were well correlated with 1000/T. Obtained apparent activation energies (ΔE) were shown in Fig. 6. ΔE for the second dehydration step, monohydrate→anhydrate (409.6 kJ mol^{-1}), was higher than that of the first step, trihydrate→monohydrate (247.2 kJ mol^{-1}), indicated that the last water molecule, which was present as an isolated water molecules, was more tightly bound. However, the ΔE for the dehydration step, heptahemihydrate→amorphous(anhydrate) was obtained as 122.8 kJ mol^{-1}, which was significantly lower than that of other hydrates. From the crystal structure data of heptahemihydrate [4], all the water molecules in the heptahemihydrate are linked together to form continuous water channels, along both the *a*- and *c*-axes. This may explain why the water is dehydrated in single step. Scheme 2 shows the conversion for various solid forms of nedocromil sodium. When heptahemihydrate was ground for enough time, the crystal structure of heptahemihydrate was converted to that of trihydrate, in other words, heptahemihydrate crystals were destroyed, at the same time, trihydrate crystallized. However, inter-conversion from trihydrate to mono- or anhydrate was not occurred, because of the higher activation energy for dehydration,

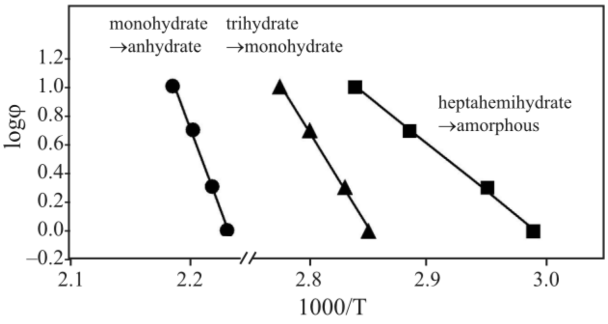


Fig. 5 Plots ($\log\varphi$ *vs*. 1000/T) for the dehydration process of hydrates

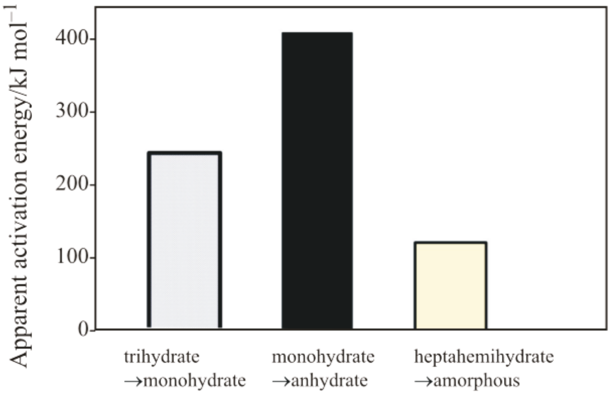
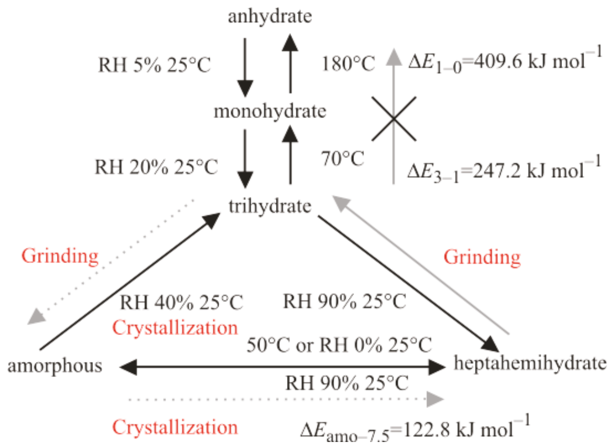


Fig. 6 Apparent activation energy of dehydration process for hydrates



Scheme 2 Conversion scheme for various forms of nedocromil sodium

trihydrate→monohydrate and monohydrate→anhydrate. In contrast, when trihydrate was ground for enough time, the crystal structure of trihydrate was completely destroyed, as a result, the ground sample was amorphized. Subsequently, some fraction of the amorphous may absorb the isolated water from hydrate's crystalline lattice, and crystallize as heptahemihydrate. Water uptake data as shown in Fig. 1b supported the high hygroscopicity of amorphous that can contain twice amount of water compare to the trihydrate at 40% RH, 25°C. Because of the low ΔE of dehydration for heptahemihydrate, amorphous fraction may easily crystallize. Therefore, heptahemihydrate was formed in the ground trihydate.

Conclusions

By grinding, the hydration level of nedocromil sodium was significantly changed. When trihydrate was ground for 30 min, heptahemihydrate was generated, even though, the water content in the ground sample was not sufficient to cover the heptahemihydrate's hydration level. These results suggested that the ground sample was inhomogeneous, and the water existed as crystalline water, adsorbed water, and bulk water in the ground sample. XRD-DSC and TG-DTA were useful to characterize the molecular state and hydration level of nedocromil sodium, and the apparent activation energy of dehydration for hydrates which were determined from the TG data successfully explained the inter-conversion behavior of nedocromil sodium induced by grinding.

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