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THE DEHYDRATION BEHAVIOR OF NAFAGREL HYDROCHLORIDE HYDRATES

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Nafagrel hydrochloride has two kinds of stable pseudopolymorphs such as hemihydrate and monohydrate. The dehydration of crystal water of these hydrates took place in one step under nitrogen gas atmosphere, whereas the two dehydration steps could be detected for the monohydrate under self-generated atmosphere such as the quasi-sealed and/or the completely sealed systems. These observations indicated that the crystal water of the monohydrate consisted of two different crystal waters.

Prediction of the stability for the hydrates using the kinetic parameters indicated that the dehydration of the monohydrate occurred faster than that of the hemihydrate.

Keywords: nafagrel hydrochloride, phase stability, pseudopolymorphs

Introduction

Nafagrel ((±)-6-(1-imidazolylmethyl)-5, 6, 7, 8-tetrahydronaphthalene)-2-carboxylic acid) hydrochloride is a newly thromboxane A_2 synthetase inhibitor [1]. This compound has two kinds of stable pseudopolymorphs such as the hemihydrate and the monohydrate, which were stable under ca. 20% relative humidity (RH) to ca. 70% RH at room temperature. It is important to select the more physically stable form for the bulk substance between both the hydrates, because of trouble-free processing and optimum formulation. The present study was conducted to clarify the phase stabilities of the hemihydrate and the monohydrate by thermal analysis.

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It is considered that the dehydration behavior depends on the presence or absence of the water vapor. It was reported that the influence of the water vapor could be examined under the self-generated atmosphere by using the quasi-sealed pan [2]. In order to estimate the influence of water vapor, the dehydration behavior was studied under self-generated atmosphere such as the quasi-sealed and completely sealed systems.

Experimental

Materials

Nafagrel hydrochloride hemihydrate and Nafagrel hydrochloride monohydrate were of pharmaceutical grade synthesized in our laboratory.

Thermal analysis

Differential scanning calorimetry (DSC), and thermogravimetry and differential thermal analysis (TG–DTA) were carried out with a SEIKO SSC/580 DSC 10 model and a SEIKO SSC/580 TG-DTA 20 model, respectively. The operating conditions were as follows: temperature range, room temperature to ca. 200°C; sample weight, ca. 10 mg; heating rate, 1, 5, 7 and 10 deg·min^{-1}; N_2 gas flow rate, 100 ml·min^{-1}.

Quasi-sealing

Aluminium cover was placed on the aluminium pan without sealing. This pan had a leak between pan and cover.

Completely sealing

Silver cell and silver cover were completely sealed with pressing. The critical explosion pressure had been certified to be above 50 atm.

Result and discussion

Open system

The TG–DTA of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate was examined using the open pan. Typical DTA and TG

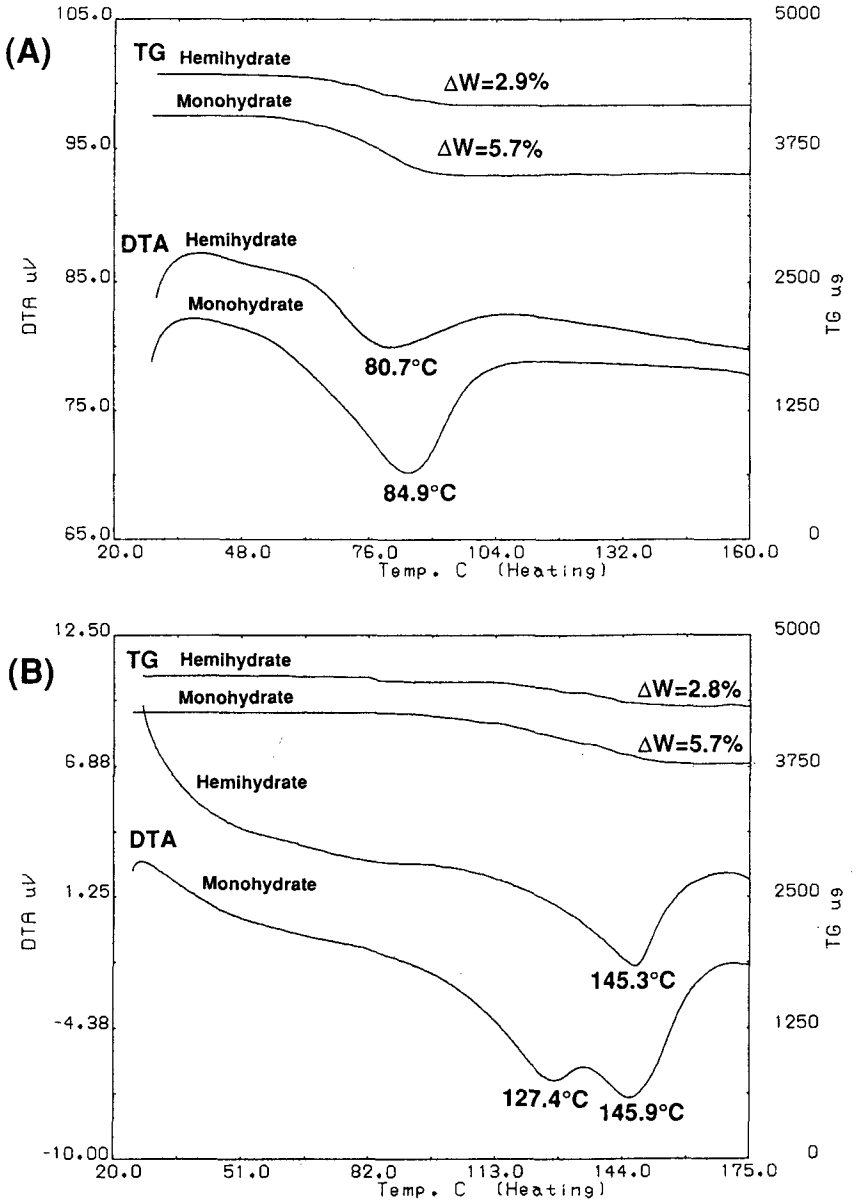

Fig. 1 TG and DTA curves of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate under open system (A) and quasi-sealed system (B). Heating rate: 10 deg·min^{-1}; Atmosphere; N_2 gas 100 ml·min^{-1}

curves of the hemihydrate and the monohydrate are shown in Fig. 1 (A). The DTA curve of the hemihydrate showed an endothermic peak at 80.7°C with a 2.9% loss of weight on the TG curve. This peak was due to the dehydration of 1/2 mol/mol of crystal water (Calcd. 2.98%).

The DTA curve of the monohydrate showed an endothermic peak at 84.9°C with a 5.7% loss of weight on the TG curve. This peak was due to the dehydration of 1 mol/mol of crystal water (Calcd. 5.80%).

Quasi-sealed system

The TG and DTA curves were recorded by the use of the quasi-sealed pan. The results of TG–DTA for the hemihydrate were similar to those of the open system, though the temperature of the dehydration shifted higher than those for the open system. That is, the peak at 145.3°C with a 2.8% loss of weight on the TG curve was due to the dehydration of 1/2 mol/mol of crystal water (Calcd. 2.98%).

On the other hand, the results of TG–DTA for the monohydrate shown in Fig. 1 (B) were apparently different from those for the open system. The DTA peak due to the dehydration was divided into two peaks at 127.4° and 145.9°C, and concerning the TG curve the turning point was observed about middle of the TG descent (5.7% weight loss). Therefore the dehydration may be considered to be composed of two reaction steps as follows:

First step (first weight loss: 2.8%):

$$\text{Nafagrel·HCl·H}_2\text{O} \rightarrow \text{Nafagrel·HCl·1/2H}_2\text{O} + \text{1/2H}_2\text{O}$$

Second step (total weight loss: 5.8%):

$$\text{Nafagrel·HCl·1/2H}_2\text{O} \rightarrow \text{Nafagrel·HCl} + \text{1/2H}_2\text{O}$$

Completely sealed system

In order to clarify the dehydration behavior in the atmosphere containing much water vapor, DSC measurements were run using the completely sealed cell in a temperature range from room temperature to ca. 200°C.

The DSC curves are shown in Fig. 2. The results of DSC for the completely sealed system showed one endothermic peak for the hemihydrate and two endothermic peaks for the monohydrate. These DSC curves corresponded to the DTA curves obtained under the quasi-sealed system. Table 1 shows the peak temperatures and the enthalpy changes for the dehydrations of the hemihydrate and the monohydrate. The peak temperature and the enthalpy change for the hemihydrate were higher than those for the first step of dehydration of the

monohydrate. These observations indicated that the crystal water of the monohydrate consisted of two different crystal waters.

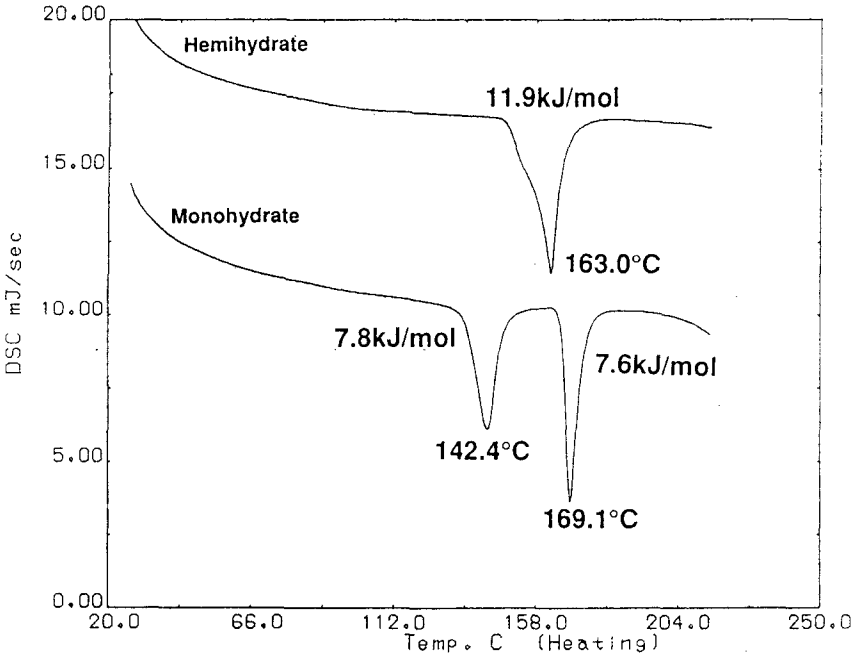

Fig. 2 DSC curves of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate under completely sealed system. Heating rate: 5 deg·min^{-1}; Atmosphere: N_2 gas 100 ml·min^{-1}

Table 1 Peak temperatures and enthalpy changes measured by DSC at various heating rates for the dehydration of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate

Heating rate /	Hemihydrate		Monohydrate			
			1st dehydration		2nd dehydration	
deg·min^{-1}	Peak temp. / °C	ΔH / kJ·mol^{-1}	Peak temp. / °C	ΔH / kJ·mol^{-1}	Peak temp. / °C	ΔH / kJ·mol^{-1}
1	158.1	11.83	134.7	7.24	167.9	8.20
5	163.0	11.92	142.4	7.77	169.1	7.61
7	164.8	11.86	144.8	8.55	169.0	8.39
10	166.9	11.98	147.2	7.33	169.9	8.14

Kinetics and mechanisms

Figure 3 shows the variation of activation energies E for the dehydration with the fraction reacted α, calculated by the Ozawa method [3] for the open system. The E values were much higher at smaller α than those at larger α. Such variation in the E values determined from the Ozawa method implies that nonisothermal dehydration of the material consists of two unit processes or more, and that the kinetic mechanism changes as reaction advances. We assumed that the changes of the kinetic mechanism were due to the destruction of the lattice by the rapid dehydration.

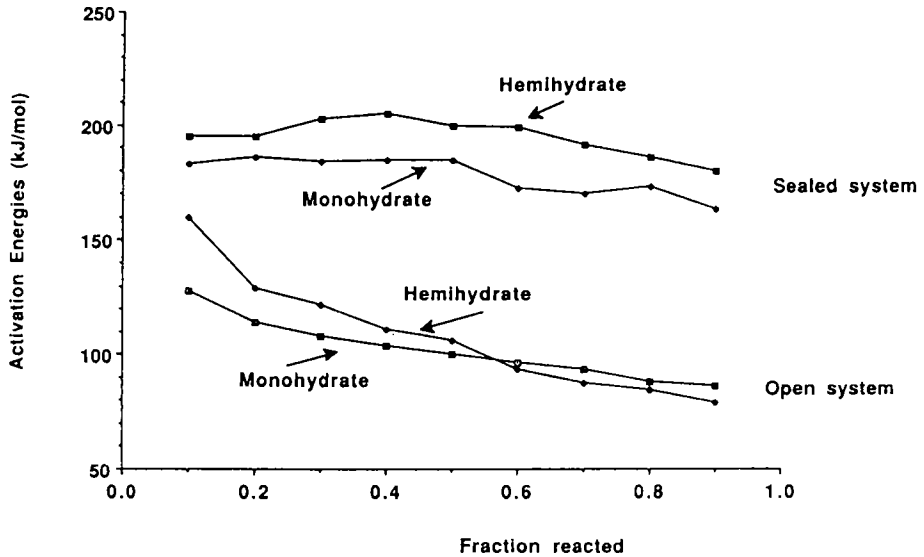

Fig. 3 Activation energies, E at various fractions reacted, α calculated by the Ozawa method for the dehydration of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate under open system and completely sealed system

Figure 3 also shows the variation of the E values for the dehydration under the completely sealed system. The variations of the E values were lower compared with those for the open system. The mean E values for the hemihydrate and the monohydrate were 195.4 and 178.2 kJ/mol, respectively. These activation energies were extended to determine the reaction mechanisms according to the Ozawa method, through use of Eq. (1)

$$g(\alpha) = A\,\theta \tag{1}$$

Table 2 Kinetic parameters, E and A, and function $g(\alpha)$, derived from kinetic analyses of DSC curves for the nonisothermal dehydration of nafagrel hydrochloride hemihydrate and nafagrel hydrochloride monohydrate

Compound	Reaction	$g(\alpha)$	E / kJ·mol^{-1}	A / hr^{-1}
Nafagrel·HCl· ½H_2O	Nafagrel·HCl· ½H_2O →Nafagrel·HCl + ½H_2O↑	$[-\ln(1-\alpha)]^{1/2}$	195.4	$1.0 \cdot 10^{25}$
Nafagrel·HCl·H_2O	Nafagrel·HCl·H_2O → Nafagrel·HCl· ½H_2O + ½H_2O↑	$[-\ln(1-\alpha)]^{1/3}$	178.2	$9.4 \cdot 10^{23}$

where A is the preexponential factor in Arrhenius equation and θ is the reduced time [4]. The $g(\alpha)$ is a function depending on the reaction mechanism. Many theoretical model functions have been proposed for the $g(\alpha)$ [5]. The kinetic mechanism of the dehydration was judged on the basis of the correlation of Eq. (1). Table 2 summarized the kinetic parameters of the dehydration reactions of the hemihydrate and the monohydrate. It was proved that the dehydration of the hemihydrate and the monohydrate proceeded by the mechanism of two-dimensional growth of nuclei for the former and three-dimensional growth of nuclei for the latter. The half lives were calculated using the kinetic parameters in the Table 2 to be ca. 17000 h for the hemihydrate and ca. 530 h for the first step of the monohydrate at 75°C.

On the basis of the above results, we concluded that the hemihydrate was more suitable for the bulk substance than the monohydrate.

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Zusammenfassung — Nafagrel Hydrochlorid besitzt zwei Arten von stabilen pseudopolymorphen Erscheinungsformen: Halbhydrat und Monohydrat. Die Dehydratation des Kristallwassers dieser Komplexe erfolgt in Stickstoffatmosphäre in zwei Schritten, während für das Monohydrat in selbstgenerierter Atmosphäre (in halb- oder vollständig geschlossenem System) zwei Dehydratationsschritte beobachtet werden konnten. Diese Beobachtungen zeigen, daß das Kristallwasser des Monohydrates aus zwei verschiedenen Arten von Kristallwasser besteht.
Eine Voraussage der Stabilität der Hydrate unter Anwendung der kinetischen Parameter zeigt, daß die Dehydratation des Monohydrates schneller verläuft als die des Halbhydrates.