Colloids and Surfaces B: Biointerfaces 76 (2010) 158–163

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Improvement of theophylline anhydrate stability at high humidity by surface-physicochemical modification

Makoto Otsuka[a,*], Mika Ishii[b]

[a] Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, 1-1-20 Shinmachi, Nishi-Tokyo, 202-8585, Japan
[b] Kobe Pharmaceutical University, Motoyama-Kitamachi, Kobe, 658-0001, Japan

ARTICLE INFO

Article history:
Received 20 August 2009
Received in revised form 17 October 2009
Accepted 18 October 2009
Available online 27 October 2009

Keywords:
Theophylline
Anhydride
Surface-modification
Stability
Hydration kinetic analysis
Dissolution kinetics

ABSTRACT

To improve the stability of theophylline anhydrate (THA) at high humidity and temperature, the surface of THA was modified by adsorption of n-butanol and phase transformation kinetics and dissolution kinetics were investigated. Hydration kinetics was evaluated using differential scanning calorimetry. The samples were stored in various saturated salt solutions at 30, 40 and 50 °C. A dissolution test was performed in distilled water at 37 °C, 100 rpm. Hydration of THA and surface-modified THA (STHA) at various levels of RH at 40 °C followed a two-dimensional growth of nuclei equation (Avrami equation) including an induction period (IP). The IP of STHA was significantly longer ($p < 0.05$) than that of THA at each RH, but the k of STHA was not significantly different ($p > 0.05$) from that at each relative humidity (RH). The IP of STMA was significantly longer at 40 and 50 °C, 93% RH ($p < 0.05$) than at 30 °C, but there was no significant difference between 40 and 50 °C. The k of THA and STHA increased with the increase in storage temperature at 30–50 °C. Arrhenius plots of the k of THA and STHA showed a straight line. The activation energy of hydration of THA and STHA was 17.60 ± 1.38 and 28.92 ± 5.56 J/mol, respectively. Dissolution of THA and STHA followed the Hixson–Crowell equation, and the dissolution rate constant, K', was 0.0306 ± 0.0041 and $0.0269 \pm 0.0034\ \mathrm{mg}^{1/3}\ \mathrm{s}^{-1}$ ($n = 3$), respectively.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Hygroscopicity is an important characteristic of bulk powders of pharmaceuticals, since the properties of pharmaceutical preparations affect drug stability through water content during manufacturing and storage. The affinity for pharmaceuticals to adsorb water vapor is generally referred to as hygroscopicity. Since adsorption is not favored in terms of entropy, the water–solid interaction must provide a sufficient driving force with respect to enthalpy, if such sorption is to occur. Many investigators [1,2] have reported the moisture sorption kinetics for pure and/or mixtures of water-soluble pharmaceuticals under conditions of relatively high humidity. The interaction of water with pharmaceuticals plays an important role in many aspects of drug development, from synthetic design and dosage form to effective product packaging and drug bioavailability. The U.S. Food and Drug Administration reported that the *in vitro* dissolution rate of a commercial carbamazepine preparation that had been exposed to 97% relative humidity for 2 weeks decreased by up to one third [3]. Gouda et al. [4] and Ebian et al. [5,6] reported that the dissolution rate and bioavailability of commercial nitrofurantoin tablets in humans decreased after 1–8 weeks of storage at different relative humidity at higher temperature. The *in vitro* dissolution rate decreased especially dramatically after storage at 100% relative humidity [5,6] due to phase transformation [7]. In order to supply safe and effective pharmaceuticals, it is important to obtain a stable bulk powder. Previously [7–9], to improve the stability of a nitrofurantoin and/or carbamazepine bulk powder at high humidity, the anhydrate crystal was modified at the surface by hydrophobic treatment with alcohol vapors, and the transformation kinetics at high humidity was investigated using differential scanning calorimetry and X-ray powder diffractometry. The results indicated that the surface-modified anhydrates were more stable at high humidity than the intact samples. In this study, to improve the stability of a theophylline bulk powder at high humidity and temperature, theophylline anhydrate crystals were modified by hydrophobic treatment and phase transformation kinetics and dissolution kinetics were investigated.

2. Experimental

2.1. Materials

Theophylline anhydrate (THA) was obtained from Shizuoka Caffeine Co., Ltd. (Shizuoka, Japan). Theophylline monohydrate (THM)

---

[*] Corresponding author. Tel.: +81 42 468 8658; fax: +81 42 468 8658.
E-mail address: motsuka@musashino-u.ac.jp (M. Otsuka).

0927-7765/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.colsurfb.2009.10.026

was obtained by recrystallization from distilled water as reported [7–9]. All other chemicals were of analytical grade.

2.2. Preparation of the surface-modified sample powder

The surface-modification apparatus was placed in a thermobath at 60 °C as reported [10]. The anhydrate sample powder (5 g) was dried in a test tube for 2 h in a vacuum, and then alcoholic vapor was introduced for 15 h at 60 °C.

2.3. X-ray powder diffraction analysis

X-ray powder diffraction profiles were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu Co., Kyoto, Japan). The operating conditions were as follows: target, Cu; filter, Ni; voltage 20 kV, current, 5 mA; receiving slit, 0.1 mm; time constant, 1 s; counting range, 1 kcps; scanning speed, 1 °/min.

2.4. FT-IR measurement

The sample powder was obtained by dispersion of a 5 w/w% sample powder in KBr powder. FT-IR spectra were obtained by powder-diffuse reflectance on an FT-infrared spectrophotometer (Type Spectra One, PerkinElmer Co., Yokohama, Japan) under the following conditions: number of scans per sample, 64; resolution, 8 cm^{-1}, and range; 450–4000 cm^{-1}. FT-IR powder-diffused reflectance spectra were transformed into absorption spectra by using the Kubelka–Munk equation.

2.5. Thermal analysis

Differential scanning calorimetry (DSC) was performed with a type 3100 instrument (Mac Science Co., Tokyo). The operating conditions in the open-pan system were as follows: sample weight, 5 mg; heating rate, 10 °C/min; N_2 gas flow rate, 30 ml/min.

2.6. Measurement of the monohydrate content of the sample powder

Standard samples were obtained by physically mixing the THA and THM crystals. DSC curves of these standard samples were measured in triplicate. The monohydrate content of each sample was evaluated based on the latent heat due to dehydration at around 40–80 °C. The calibration curve gave a good linear correlation between monohydrate content and latent heat, and the standard deviation of the data was within 5%.

2.7. Storage conditions

The samples were stored in 150-ml plastic bottles with caps that also contained 40 ml of various kinds of saturated salt solutions and were kept at 30, 40 and 50 ± 1 °C. Storage conditions for DSC were as follows: Sample powder (500 mg) was put in a 10-ml glass bottle, and stored in a plastic bottle. After mixing of the sample powder, about 30 mg was taken out at a suitable time to immediately measure a DSC curve.

2.8. Dissolution test

A sample containing 20 mg of THA powder was introduced into 900-ml of distilled water in a covered 1000-ml round-bottomed flask. The flask was fixed on the sample holder in a thermostatically regulated water bath maintained at 37 ± 0.5 °C, and stirred by a paddle at 0 rpm (static condition) and 100 rpm (dynamic condition). Aliquots (5 ml) of the sample were withdrawn at appropriate times with a syringe. The sample was filtered through a 0.8-μm membrane filter and diluted with the dissolution medium for photometric analysis (UV 160A, Shimadzu Co.) at 270 nm. The loss in volume was compensated for by the addition of dissolution medium maintained at the same temperature.

3. Results and discussion

3.1. Physiochemical properties of THA modified by n-butanol

Figs. 1 and 2 show X-ray diffractogams and FT-IR spectra of THA and surface-modified THA (STHA). The X-ray diffraction profiles and FT-IR spectra of THA were identified using data reported [11] for THA. STHA exhibited almost the same X-ray diffraction profile and FT-IR spectrum as the intact THA. Since the absorption peak due to n-butanol did not appear in the FT-IR spectrum of STHA, and after heating at 150 °C in a vacuum for 10 h, the weight of STHA was unchanged, these results indicated that the adsorbed amount of alcohol was negligible. The X-ray diffraction result also suggested that the crystalline characteristics of THA were not affected by surface-modifications using the adsorption of n-butanol. The crystalline structure of THA was not changed by the surface-modification treatment, and it appeared that a very small amount of alcohol formed an alcoholic monolayer on the surface of anhydrate crystals as reported previously.

3.2. Stability of THA and STHA at high humidity

Fig. 3 shows the effect of humidity on the water content of THA at 40 °C. After 1 week of storage, THA absorbed a small amount of water at 79 and 82% RH, and 1 mol of water at more than 82% RH. After 1 month, THA had absorbed 0.25 and 1 mol of water at 79 and 82% RH. The X-ray diffraction profile of THA at more than 79% RH indicated that it transformed into THM, but did not show any diffraction peak due to THM after storage at less than 76% RH for 3 months. In the present study, therefore, hydration kinetic processes

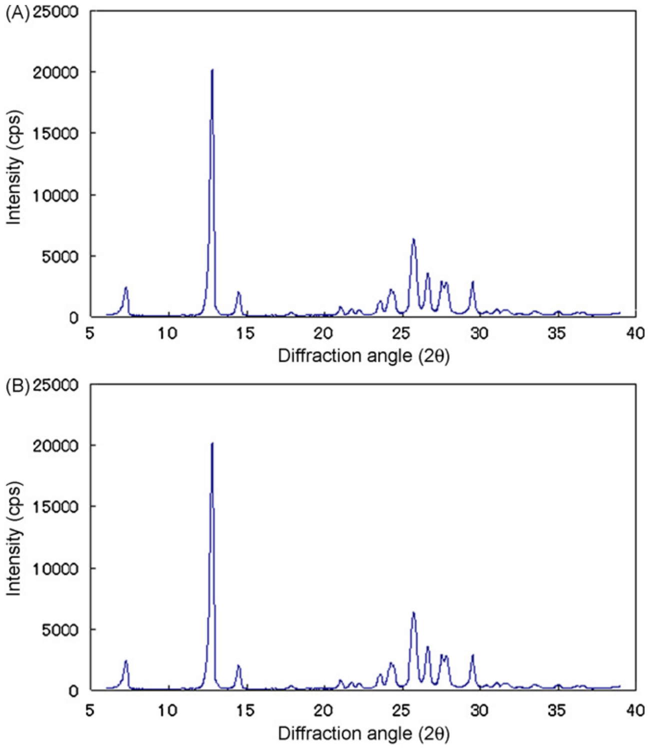

Fig. 1. Effect of the surface-modification on powder X-ray diffraction profiles of THA. (A) THA, (B) STHA.

Download English Version:

https://daneshyari.com/en/article/602010

Download Persian Version:

https://daneshyari.com/article/602010

Daneshyari.com