Polymorphic Transformation of Antibiotic Clarithromycin Under Acidic Condition

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Received 29 July 2013; revised 16 October 2013; accepted 3 December 2013

Published online 20 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23825

ABSTRACT: Clarithromycin (CAM) is a 14-membered semisynthetic macrolide antibiotic used to treat the infection of various bacteria including *Helicobacter pylori*. The polymorphic transformation of CAM form II crystals under acidic conditions is, however, still unclear, and was investigated using X-ray powder diffraction method. Gel of CAM, which was immediately formed by mixing form II crystals with the hydrochloric acid solution, transformed at first to unstable form A crystals and then to form B crystals. Both forms A and B crystals are hydrochloride salts. Analyses using Hancock–Sharp equation revealed that the mechanism of form B formation was three-dimensional growth of nuclei. The rate constant of the transformation indicated that the times for 95% of form A transforming to form B at 37°C are 0.69, 1.90, and 3.79 h at pH 1.5, 2.5, and 3.4, respectively. These suggest that the transformation from form II to form B via gel and form A could occur on the surface of form II formulation of prolonged gastric residence time, in the case that the pH in stomach stays low. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:580–586, 2014
Keywords: clarithromycin; polymorphism; transformation; X-ray powder diffractometry; Dissolution rate; Stability

INTRODUCTION

Clarithromycin (CAM; $C_{38}H_{69}NO_{13}$; molecular weight 748.0; Fig. 1) is a 14-membered semisynthetic macrolide antibiotic used to treat the infection of various bacteria. CAM, using together with amoxicillin and proton pump inhibitor (PPI), is recommended as the first-line treatment choice to eradicate *Helicobacter pylori*,[1] which is one of the etiologic factor of gastric carcinoma in human stomach.[2] Eight crystal forms of CAM are reported so far: form 0 (ethanol solvate),[3] form I,[4] form II,[5] form III (acetonitrile solvate),[6] form IV (hydrate),[7] form V,[8] the hydrochloride salt,[9] and the methanol solvate.[10] Of these crystal forms, most stable form II is applied for clinical use in tablet[11] and dry syrup formulations.[12] At pH lower than 3.0, dissolved CAM is unstable and its cladinose ring is eliminated from 14-membered aglycone ring through an acid-catalyzed hydrolysis.[13] The hydrolyzed CAM has no antibacterial activity,[14] and this is the reason why CAM is used together with PPI for the eradication of *H. pylori*. In spite of this instability, CAM in tablet formulation is stable even in an acidic solution such as gastric fluid, and can be administered orally for the treatments of infectious disease caused by chlamydia, mycoplasma, and so on, without an enteric coating. Under the acidic solution lower than pH 1.5, CAM form II crystals rapidly transform to a transparent gel, and the gel formed on the tablet surface prevents the acidic solution from soaking into the tablets. This results in the protection of CAM in tablet from the inactivation through the hydrolysis, and in the retardation of the elution of CAM and disintegration of the tablets.[15] It is unknown, however, whether the further polymorphic transformation of the gel occurs or not when the gel is exposed to the acidic solution for a longer time. Information on the polymorphic transformation of CAM under acidic condition is necessary to design new CAM formulations that stay prolonged time in stomach, as the fluctuation of pH in stomach would be possible in case of insufficient effects of PPI, not taking the PPI or changes in the physical condition of patients. The CAM formulation of prolonged gastric residence time is thought to be effective for the eradication of *H. pylori*, as the bacteria reside mainly in the gastric mucosa.[16,17] In this study, we have investigated the polymorphic transformation of CAM form II under acidic conditions of hydrochloric acid solution using X-ray powder diffraction method, and found for the first time that the gel of CAM transform finally to the hydrochloride salt crystal via labile intermediate crystal. We report here the analyses of the transformation reaction mechanism and the rate constants using Hancock–Sharp equation,[18,19] which describes the kinetics of isothermal solid-state reactions, and the dissolution behavior of the hydrochloride salt crystal.

METHODS

Materials

Bulk CAM form II powders, purity larger than 99%, were purchased from Shiono Chemical Company Ltd. (Tokyo, Japan). All reagents used were of the highest grade available from commercial sources.

Preparation of Gel and form A Crystals

Method for preparing the gel of CAM is described elsewhere.[20] In short, 1.8 g of CAM form II powder was mixed with 25 mL of 0.1 M hydrochloric acid solution using a mortar and a pestle at room temperature. CAM form II powders transformed to viscous gel immediately after mixing is completed, as observed on the surface of form II tablets in hydrochloric acid solution.[15] The gel transformed completely to fluent and glossy suspension

Abbreviations used: CAM, clarithromycin; PPI, proton pump inhibitor.

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Journal of Pharmaceutical Sciences, Vol. 103, 580–586 (2014)
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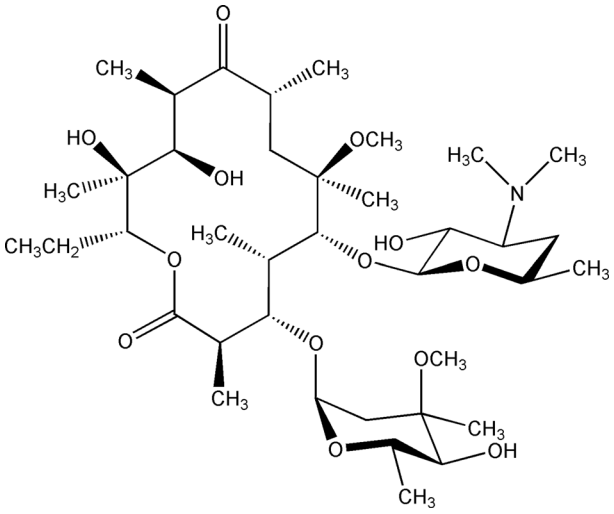

Figure 1. Chemical structure of CAM.

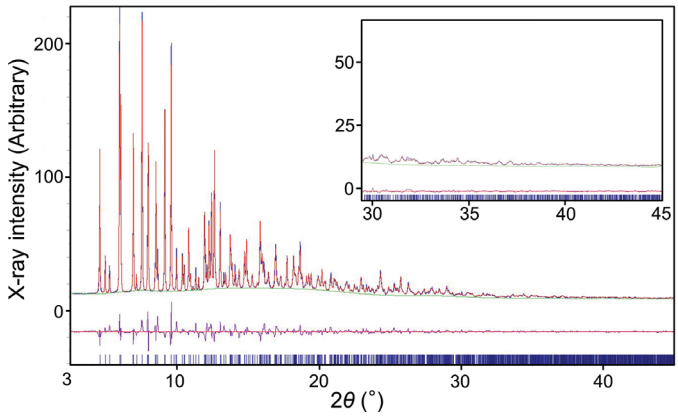

Figure 2. Final Rietveld plot of form B. The experimental, calculated and difference diffraction profiles, and the background profile are drawn with blue, red, purple, and light green lines, respectively. Vertical navy bars at the bottom correspond to the positions of the Bragg peaks.

of fine needle crystals, named form A, within 10 min. The form A crystal suspension was transferred to 50 mL centrifuge tube, and the crystals were collected by centrifugation at 7,200×*g* and 4°C for 5 min. Form A crystals thus collected were washed with 2 mL of ice-cold distilled water three to four times until pH of the wash water became 3.4 or higher. Form A crystals were stable at least 12 h when stored in wet state at 4°C. Form A was transformed to another crystal form, named form B, within 4 h by storing at 37°C under wet condition.

X-ray Powder Diffraction Analysis

Form A crystals were washed and suspended in hydrochloric acid solution of pH 1.5, 2.5, or 3.4. The suspended crystals were packed with the solution in Lindemann glass capillaries of 0.4 mm diameter by centrifugation at 180×*g* and 4°C for 1 min, and subjected to the X-ray powder diffraction studies. X-ray powder diffraction data were collected at SPring-8 BL19B2, which is equipped with Debye–Sherrer camera and a curved imaging plate detector.[21,22] The wavelength was set at 0.9996 Å to reduce the background counts. The time intervals of the diffraction data measurements for form A crystals in pH 1.5, 2.5, and 3.4 solutions were 10, 10, and 20 min, respectively, and the exposure time for each measurement was 5 min. During the data collection, the samples were kept at 37°C using N_2 gas flow, and rotated at 1 rpm/min to reduce the possible preferential orientation. Powder diffraction data of form B, form II, and gel were collected at 25°C.

Cell parameters of forms A and B were determined from X-ray powder diffraction data using N-TREOR09[23] implemented in EXPO2013, the update version of EXPO2009.[24] Rietveld refinement of form B crystal structure was performed using DASH[25] and EXPO2013. The crystal structure of CAM hydrochloride salt[8] was used as a starting model. Hydrogen atoms were generated at their theoretical positions using Jmol[26] at the final refinement stage, and were refined as riding. Positional RMS difference of nonhydrogen atoms is a low value of 0.090 Å^2. Crystallographic data are summarized in Table 1, together with Rietveld refinement statistics. Final Rietveld plot of form B is shown in Figure 2.

Kinetic Analysis of Transformation from Form A to Form B Using Hancock–Sharp Equation

The ratio of form B crystal formed in the form A crystal suspension was estimated from the integrated observed intensities of the reflections (2 0 0) and (1 1 1) at 2θ = 5.80°–6.10°. Hancock–Sharp Eq. (1) was fitted to the ratio to determine the mechanism of the formation of form B crystals:

$$\ln\{-\ln(1-\alpha)\} = \ln B + m \ln t \quad (1)$$

$$\alpha = I(t)/I_{\max} \quad (2)$$

where $I(t)$ is the summed observed intensities of (2 0 0) and (1 1 1) reflections of form B at time t, α is the fraction of form A transformed to form B, and m, B, and $I_{\max}$ were parameters determined by nonlinear least-square fitting. Rate constants for the formation of form B were calculated by nonlinear fitting of the data to Avrami–Erofeev equation for the three-dimensional growth of nuclei:

$$-\ln(1-\alpha) = (kt)^3 \quad (3)$$

All the calculations for nonlinear least-square fitting were performed using GraFit (Erithacus Software, Surrey, UK).

Elemental Analysis of Form A Crystal

Form A crystals washed with distilled water were dried under vacuum overnight. Elemental analyses for carbon, hydrogen, and nitrogen of the dried sample were carried out using CHN CORDER MT-5 (Yanako New Science Inc., Kyoto, Japan). Chloride ions in the dried sample were quantified using Mohr method.[27]

Dissolution Test of CAM Forms B and II by Static Disk Method

Crystal powders of CAM form II or form B, 250 mg, were compressed into disks of 13 mm diameter using oil-press tableting machine (JASCO Corporation, Tokyo, Japan) at the tableting force of 10 kN. The CAM disks were fixed into the cylindrical holder. The surface area of the disk in contact with the dissolution medium is 1.33 cm^2. The holder was sunk into the bottom

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