Suppressed Release of Clarithromycin from Tablets by Crystalline Phase Transition of Metastable Polymorph Form I

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ABSTRACT: The pharmaceutical properties of clarithromycin (CAM) tablets containing the metastable form I of crystalline CAM were investigated. Although the dissolution rate of form I was higher than that of stable form II, the release of CAM from form I tablet was delayed. Disintegration test and liquid penetration test showed that the disintegration of the tablet delayed because of the slow penetration of an external solution into form I tablet. Investigation by scanning electron microscopy revealed that the surface of form I tablet was covered with fine needle-shaped crystals following an exposure to the external solution. These crystals were identified as form IV crystals by powder X-ray diffraction. The phenomenon that CAM releases from tablet was inhibited by fine crystals spontaneously formed on the tablet surface could be applied to the design of sustained-release formulation systems with high CAM contents by minimizing the amount of functional excipients.

Keywords: polymorphism; hydration; tablet; sustained release; controlled release; transition; pseudopolymorphism

INTRODUCTION

Clarithromycin (CAM; molecular weight 748.0; pKa = 8.5) is a 14-membered macrolide antibiotic of a broad spectrum against various bacteria. CAM is widely used for the clinical treatment of various infectious diseases and the eradication of Helicobacter pylori. CAM is commercially available in various dosage forms, including tablets and a dry syrup. In addition, several gastroretentive dosage forms of CAM have recently been developed to enhance the eradication efficacy of CAM toward H. pylori in the stomach. However, concerns have been raised regarding the volumes of these dosage forms, which contained large amounts of excipients for their necessary functionalities. Patients would find large dosage forms difficult to swallow, which could reduce patient compliance.

Several novel functional dosage forms have been designed that use not excipients but amorphous or metastable crystalline forms of the active pharmaceutical ingredients (APIs). The use of the amorphous form of an API can not only lead to improve the solubility properties of poorly soluble APIs, but can also control the release rate of API from dosage form. For a recent example, the release of the capetabine from a formulation containing the amorphous form was suppressed compared with its release from a formulation containing the stable crystalline form. This suppression was attributed to a phase transition of the drug to a gel when exposed to an external solution. The report implies that specific strategies could be designed for the sustained release of APIs from formulations containing high API and minimum contents of special functional excipients.

Numerous polymorphic crystalline forms and pseudopolymorphic solvate forms of CAM have been reported (summarized in the literature). Form II is the most stable and is used clinically in formulations. Metastable form I can be obtained by the vacuum drying of ethanol solvate form 0 and readily converted to hydrate form IV under high-humidity conditions. Although form I has been fully characterized by crystallographic analysis, the pharmaceutical properties of formulations containing form I remain unclear. In this study, the pharmaceutical properties of tablets containing form I have been compared with those of tablets containing form II, to examine the possibility of developing a novel sustained-release strategy of CAM using form I.

MATERIALS AND METHODS

Materials

Clarithromycin (purity >99%) was purchased from Shiono Chemicals (Tokyo, Japan). Microcrystalline cellulose (MCC; CEOLUS® PH101), low-substituted hydroxypropyl cellulose (L-HPC; LH-21), and colloidal silica (CS; AEROSIL® 200) were kindly provided by Asahi Kasei (Tokyo, Japan), Shin-Etsu Chemical Company Ltd. (Tokyo, Japan), and Nippon Aerosil Company, Ltd. (Tokyo, Japan), respectively. All of the regents used were of the highest grade commercially available.

Preparation of CAM Tablets and Discs

Form 0 was prepared by the recrystallization of CAM from ethanol. Form I was prepared by vacuum drying form 0 for 24 h at 25°C, followed by the sieving through a 177-μm mesh. Form II was prepared by heating form 0 at 150°C for 1.5 h, followed by the sieving through a 177-μm mesh. Form IV was prepared by storing form I hermetically with saturated...
potassium sulfate solution (relative humidity 97%) at 25°C for 24 h.

Recipes of CAM tablets are summarized in Table 1. CAM, MCC, L-HPC, and CS, total 10.0 g, were put into a polyethylene bag and mixed by shaking for 10 min. Magnesium stearate (Mg-St) was added into the bag and mixed for a further 2 min. The mixed powders were then tableted by a TabAll N30-EX single-punch tablet machine (Okada Seiko Company Ltd., Tokyo, Japan) using an 8 mm in diameter flat-faced punch and a tabletting force of 10 kN.

Powders of CAM (250 mg) were compressed into discs of 13 mm in diameter using an oil-press tabletting machine (JASCO Corporation, Tokyo, Japan) with a tabletting force of 10 kN. The discs were fixed into cylindrical holders made of polyvinyl chloride and used to determine the dissolution rates using the static disc method.

### Dissolution Test of Tablets and Discs

Dissolution tests were performed according to the paddle method described in the Japanese Pharmacopeia XVI (JP XVI). The dissolution medium was 900 mL of 50 mM sodium potassium phosphate buffer (pH 6.5) according to JP XVI. Temperature was kept at 37.0 ± 0.5°C, and a paddle speed was 50 rpm. Aliquots of the dissolution medium were removed at predetermined time intervals. Each aliquot was then filtered through a 0.20 μm membrane filter, and CAM concentration was quantified by HPLC.8

### Solubility Measurement

Excess powders of forms I, II, or VI were mixed with pH 6.5 phosphate buffer in triplicates, and shaken at 37.0 ± 0.5°C. Aliquots of forms II and IV mixtures were removed after 1.0 and 1.5 h. For form I, aliquots were removed every 30 s for 2 min, and then at 5, 10, and 30 min. These removed aliquots were immediately filtered and diluted by 10-fold with the mobile phase, and quantified by HPLC. Dissolved CAM concentrations of forms II and IV samples were comparable at 1.0 and 1.5 h, and the values at 1.5 h were regarded as their solubilities. The highest concentration of form I was found in the solution at 60 s, and it was regarded as the solubility of form I.

### Measurement of Liquid Penetration Rates

Liquid penetration time was determined by measuring the time required for 10 μL of pH 6.5 phosphate buffer to be completely absorbed into a tablet after being placed onto the tablet surface. The liquid penetration rate (μL/min) was calculated by dividing the volume of the buffer by the penetration time.

### Results and Discussion

The dissolution test showed that almost 100% of the CAM had been released from forms II and IV tablets containing L-HPC larger than 9 mg (recipes II-3, 4, and IV) after 30 min, whereas only 10% of the CAM had been released from form I tablet (recipe I-4) at the same time period, even though L-HPC was included as much as 5% (w/w) (Fig. 1a). In contrast, the dissolution rate of form I was 553 mg mL−1 −1, which was approximately 10-fold higher than those of form II, 54.4 mg mL−1 −1, and form IV, 56.8 mg mL−1 −1 (Fig. 1b). The solubility of form I, 11.7 ± 0.1 mg mL−1, was highest among three crystal forms, and the solubility of form IV, 1.49 ± 0.05 mg mL−1, was slightly higher than that of form II, 1.13 ± 0.05 mg mL−1, in spite that form IV is a hydrate crystal. These results indicated the release of CAM from form I tablet was suppressed compared with the release from forms II and IV tablets. Disintegration test showed that the suppressed release of CAM from form I tablet was caused by the retarded disintegration of the tablet despite the inclusion of disintegrant L-HPC (Table 1).

L-HPC accelerates the disintegration of tablets by swelling, so an external solution must penetrate the tablets so that it can contact with the L-HPC. The liquid penetration rate of form I tablet was much slower than those of forms II and IV tablets.

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**Table 1. Recipes for the CAM Tablets, and Results of Disintegration Test and Liquid Penetration Test**

<table>
<thead>
<tr>
<th>Recipe</th>
<th>Amount of API and Excipients per Tablet (mg)</th>
<th>Disintegration Time (min)</th>
<th>Liquid Penetration Rate (μL min−1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>Form I 200, MCC 94, L-HPC 0, CS 3, Mg-St 3</td>
<td>&gt;480</td>
<td></td>
</tr>
<tr>
<td>I-2</td>
<td>Form I 200, MCC 91, L-HPC 3, CS 3, Mg-St 3</td>
<td>&gt;480</td>
<td></td>
</tr>
<tr>
<td>I-3</td>
<td>Form I 200, MCC 85, L-HPC 9, CS 3, Mg-St 3</td>
<td>&gt;480</td>
<td></td>
</tr>
<tr>
<td>I-4</td>
<td>Form I 200, MCC 79, L-HPC 15, CS 3, Mg-St 3</td>
<td>&gt;480</td>
<td></td>
</tr>
<tr>
<td>II-1</td>
<td>Form II 200, MCC 94, L-HPC 0, CS 3, Mg-St 3</td>
<td>17.9 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>II-2</td>
<td>Form II 200, MCC 91, L-HPC 3, CS 3, Mg-St 3</td>
<td>4.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>II-3</td>
<td>Form II 200, MCC 85, L-HPC 9, CS 3, Mg-St 3</td>
<td>1.3 ± 0.2</td>
<td>22.9 ± 5.3</td>
</tr>
<tr>
<td>II-4</td>
<td>Form II 200, MCC 79, L-HPC 15, CS 3, Mg-St 3</td>
<td>1.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Form IV 200, MCC 85, L-HPC 9, CS 3, Mg-St 3</td>
<td>3.5 ± 0.2</td>
<td>22.5 ± 2.4</td>
</tr>
</tbody>
</table>

*Each value represents the mean ± SD (n = 3–6).
Figure 1. Dissolution profiles of CAM (a) from tablets and (b) from static discs. Each point represents the mean ± SD (n = 3).

(Table 1), suggesting that the suppression of liquid penetration into form I tablet caused the suppression of CAM release from the tablet.

The liquid penetration into form I tablets was presumed to be suppressed by morphological or polymorphic changes in the structure of form I. SEM investigation revealed that after an exposure to phosphate buffer, needle-shaped crystals of approximately 1 μm thick and 20 μm long had covered the surface of form I tablet of recipe I-3 (Figs. 2a and 2b). The needle-shaped microcrystals were also observed immediately when form I crystals were in contact with the phosphate buffer (Figs. 2c and 2d). PXRD profile of the surface of the form I tablet exposed to the phosphate buffer contained diffraction peaks, a characteristic of form IV (Fig. 2e). This indicated that the needle-shaped crystals that appeared on the surface of the form I tablet were form IV crystals.

Although the formation of form IV crystals should have also occurred in form I discs used in the static disc method, the dissolution rate from form I discs was much higher than that of form IV. Because the dissolution process of CAM from the discs did not involve the disc disintegration, this suggested that the decrease in the dissolution rate caused by the formation of form IV crystals on the surface of form I discs was minor, and that the CAM release from form I tablets was suppressed mainly by the retarded disintegration of the tablets. Formation of form IV crystals on the tablet surfaces might be possibly promoted by the excipients, L-HPC, MCC, and CS: the stirring of the solution at the tablet surface would be less efficient because of these swellable excipients, resulting in the less disruption of the saturated CAM-solution layer and the efficient growth of form IV crystals at the tablet surface.

Taken together, these results implied that the suppression of CAM release from form I tablet was caused by the mechanism given below (Fig. 3). Form I crystals on the tablet surface would rapidly dissolve when the tablet was exposed to an external solution, which would lead to the formation of a thin layer of saturated CAM solution in close proximity of the surface of the tablet. At the same time, crystal nuclei of form IV would form all over the surface of tablet through the pseudopolymorphic transition of form I because the surface of tablet in this case would effectively mimic that of a highly humid environment. Because the solubility of form IV is much lower than that of form I, the crystal nuclei of form IV would then grow into needle-shaped microcrystals in the saturated CAM

Figure 2. (a) Scanning electron microscopy images of the surface of form I tablet (recipe I-3) under dry condition and (b) after the exposure to pH 6.5 phosphate buffer. (c) Form I crystals under dry condition and (d) 3 s after exposure to the phosphate buffer. (e) PXRD profiles of form I crystals (i), surface of the tablet (recipe I-3) after exposure to the phosphate buffer (ii), and form IV crystals (iii).
solution covering the surface of tablet, and these form IV microcrystals would ultimately grow to cover the surface of tablet and prevent the solution from penetrating into the tablet.

CONCLUSIONS

When a CAM tablet consisting of form I crystals was exposed to external solution, fine-needle-shaped form IV crystals formed spontaneously and covered the tablet surface. This coating of form IV crystals prevented the solution from penetrating into the tablet, which retard the disintegration of tablet and suppress the release of CAM. This phenomenon could potentially be applied to the design of new sustained-release strategies for the formulation of smaller tablets or tablets containing high CAM contents because no additional excipients would be required to provide the sustained-release strategies.

REFERENCES


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