Suppressed release of clarithromycin from tablets by crystalline phase transition of metastable polymorph form I

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Abbreviations: API, active pharmaceutical ingredient; CAM, clarithromycin; JP, Japanese Pharmacopoeia; L-HPC, low-substituted hydroxypropyl cellulose; MCC, microcrystalline cellulose; CS, colloidal silica; Mg-St, magnesium stearate; PXRD, powder X-ray diffraction.

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 due to the slow penetration of a buffer 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 exposure to the buffer. These crystals were identified as form IV crystals by powder X-ray diffraction. The phenomenon that release of CAM 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.

INTRODUCTION

Clarithromycin (CAM; MW 748.0; pK_a = 8.5) is a fourteen-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[1]. In addition, several gastroretentive dosage forms of CAM have recently been developed to enhance the eradication efficacy of CAM towards *H. pylori* in the stomach[2,3]. 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 capecitabine from a formulation containing the amorphous form was suppressed compared with its release from a formulation containing the stable crystalline form.[4] This suppression was attributed to a phase transition of the drug to a gel when exposed to an external solution. A similar suppression process had also been reported for the release of CAM under acidic condition.[5] Taken together, 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 pseudo-polymorphic solvate forms of CAM have been reported in the literature[7–15]. Form II is 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[17]. Although form I has been fully characterized by crystallographic analysis[18], 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

CAM (purity > 99%) was purchased from Shiono Chemicals (Tokyo, Japan). Microcrystalline cellulose CEOLUS® PH101 (MCC), low-substituted hydroxypropyl cellulose LH-21 (L-HPC) and colloidal silica AEROSIL® 200 (CS) were kindly provided by Asahi Kasei (Tokyo, Japan), Shin-Etsu Chemical Co. Ltd (Tokyo, Japan) and Nippon Aerosil Co., 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 hours 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 hours, 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 hours.

Recipes of CAM tablets are summarized in Table 1. CAM, MCC, L-HPC and CS, total 10 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 Co., Ltd, Tokyo, Japan) using a flat-faced punch 8 mm in diameter and a tableting force of 10 kN.

Powders of CAM (250 mg) were compressed into discs of 13 mm in diameter using an oil-press tableting machine (JASCO Corporation, Tokyo, Japan) with a tableting 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 Pharmacopoeia XVI (JP XVI). The dissolution media was 900 mL of 50 mM sodium potassium phosphate buffer pH6.5 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[6].

Solubility Measurement

Excess powders of forms I, II or VI were mixed with phosphate buffer pH 6.5, 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 hours. 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 hours and the values at 1.5 hour 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 phosphate buffer pH 6.5 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.

Disintegration Test

Disintegration tests were performed according to the method described in the JP XVI. The times taken for the complete disintegration of the tablets in phosphate buffer pH 6.5 at 37.0 ± 0.5°C were measured using an NT-1HM disintegration tester (Toyama Sangyo Co. Ltd., Osaka, Japan). Tablets with retarded disintegration (recipe I-3 in Table 1) were removed from the disintegration test buffer after 15 min, and their surfaces were immediately scraped and analyzed by PXRD using a Mini Flex II X-ray diffractometer (Rigaku Corporation, Tokyo, Japan. Their surfaces were also investigated by scanning electron microscopy (SEM) using a JSM-5310LV (JEOL Ltd, Tokyo, Japan) after drying for 24 hours and sputter-coated with platinum. As comparison, the morphology of form I powders following their contact with the phosphate buffer were observed using an optical microscope.

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. 1(a)). In contrast, the

dissolution rate of form I was 553 mg mL^{-1} min^{-1}, which was approximately 10-fold higher than those of form II, 54.4 mg mL^{-1} min^{-1}, and form IV, 56.8 mg mL^{-1} min^{-1} (Fig. 1(b)). 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 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 (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 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 (Fig. 2(a) and (b)). The needle-shaped microcrystals were also observed immediately when form I crystals were in contact with the phosphate buffer (Fig. 2(c) and (d)). PXRD profile of the surface of the form I tablet exposed to the phosphate buffer contained diffraction peaks characteristic of form IV (Fig. 2(e)). 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 disc used in the static disc method, the dissolution rate from form I disc was much higher than that of

form IV, suggesting that the decrease in the dissolution rate caused by the formation of form IV on the surface of form I disc was minor. Because form I tablets contained insoluble and slightly swellable MCC, the stirring of the solution at the close proximity of the tablet surface might be less efficient than that at the surface of static discs without MCC. This would have resulted in the less disruption of the layer of saturated CAM solution 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 following mechanism (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 tablet. At the same time, crystal nuclei of form IV would form all over the surface of tablet through the pseudo-polymorphic 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 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.

CONCLUSION

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.

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TABLE

Table 1. Recipes for the CAM tablets, and results of disintegration test and liquid penetration test

Recipe	Amount of API and excipients per tablet (mg)							Disintegration time (min) [a]	Liquid penetration rate (μL/min) [a]
	CAM		MCC	L-HPC	CS	Mg-St	Total		
I-1	Form I	200	94	0	3	3	300	> 480	
I-2	Form I	200	91	3	3	3	300	> 480	
I-3	Form I	200	85	9	3	3	300	> 480	1.0 ± 0.1
I-4	Form I	200	79	15	3	3	300	> 480	
II-1	Form II	200	94	0	3	3	300	17.9 ± 4.5	
II-2	Form II	200	91	3	3	3	300	4.3 ± 1.5	
II-3	Form II	200	85	9	3	3	300	1.3 ± 0.2	22.9 ± 5.3
II-4	Form II	200	79	15	3	3	300	1.3 ± 0.1	
IV	Form IV	200	85	9	3	3	300	3.5± 0.2	22.5 ± 2.4

[a] Each value represents the mean ± S.D. (n=3–6).

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FIGURE CAPTIONS

Figure 1. Dissolution profiles of CAM, (a) from tablets and (b) from static discs. Each point represents the mean ± S.D. (*n*=3).

Figure 2. (a) SEM images of the surface of form I tablet (recipe I-3) under dry condition and (b) after the exposure to phosphate buffer pH 6.5. (c) Form I crystals under dry condition and (d) 3 s after exposure to the phosphate buffer. (e) Powder X-ray diffraction 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).

Figure 3. Schematic diagram of the inhibition mechanism of solution penetration into form I tablets.

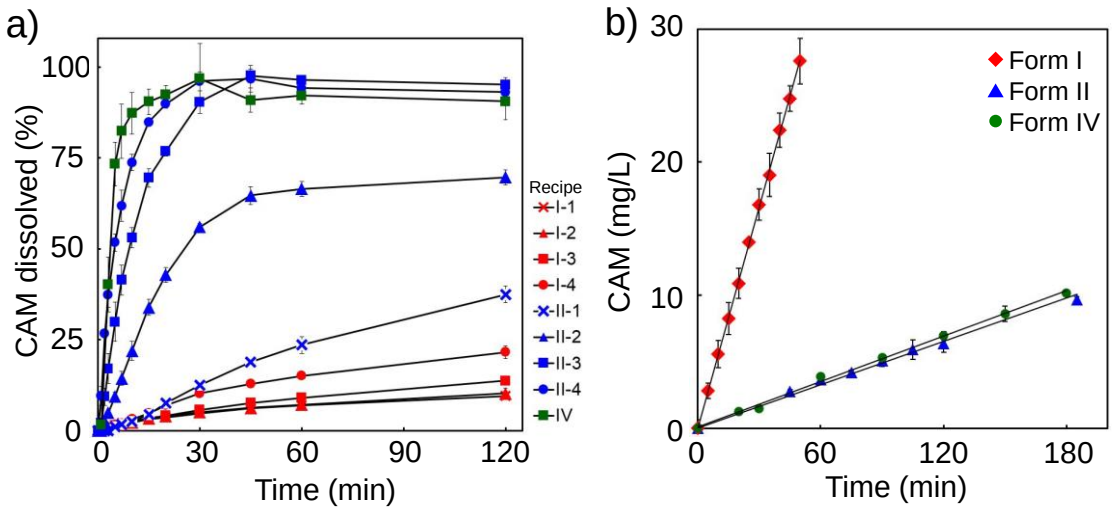
a)
CAM dissolved (%)
100
75
50
25
0
0
30
60
90
120
Time (min)
Recipe
I-1
I-2
I-3
I-4
II-1
II-2
II-3
II-4
IV
b)
CAM (mg/L)
30
20
10
0
0
60
120
180
Time (min)
Form I
Form II
Form IV

Fig. 1

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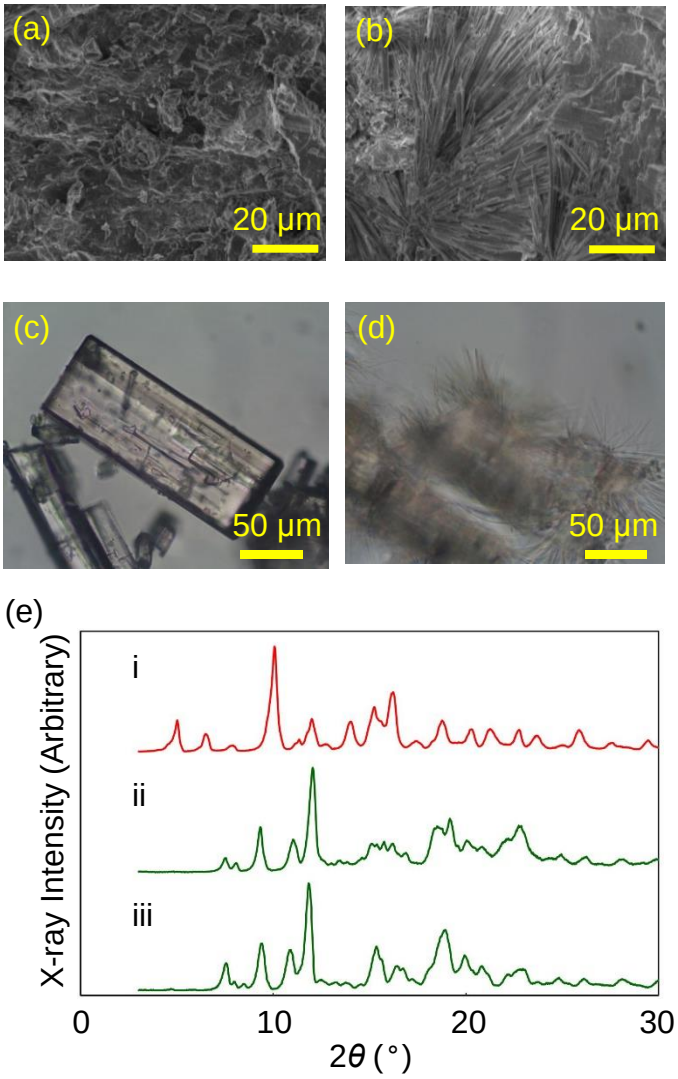
(a)
20 μm
(b)
20 μm
(c)
50 μm
(d)
50 μm
(e)
X-ray Intensity (Arbitrary)
i
ii
iii
0
10
20
30
2θ (°)

Fig. 2

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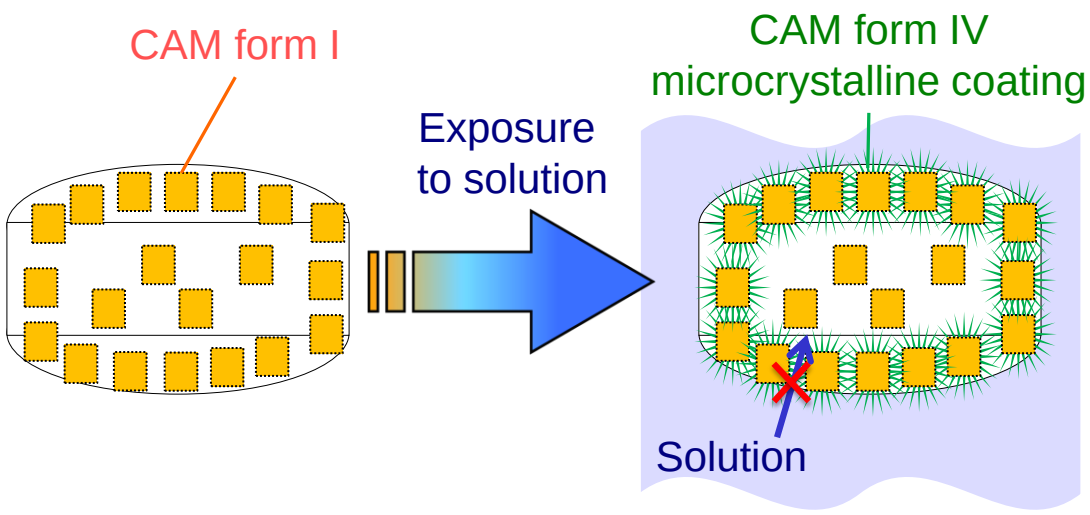
CAM form I
Exposure
to solution
CAM form IV
microcrystalline coating
Solution

Fig. 3

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