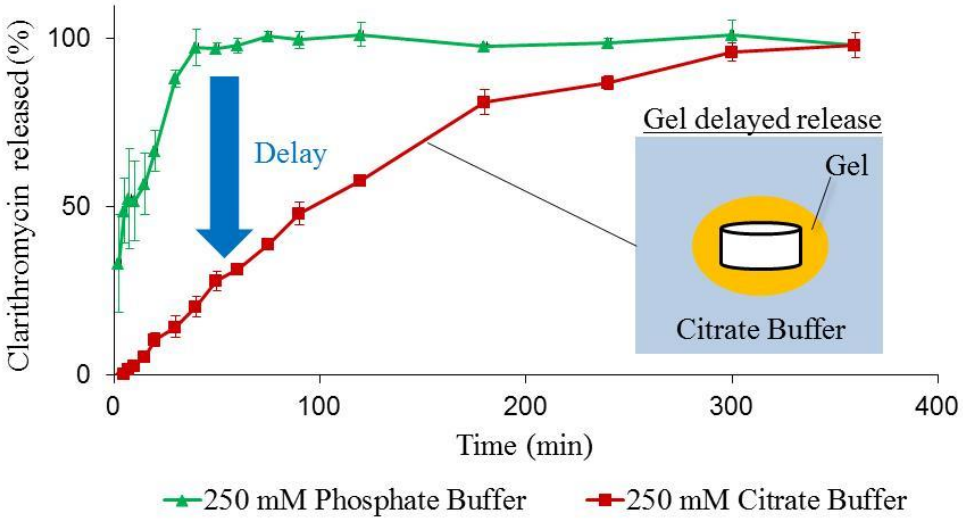
Effect of gel formation on the dissolution behavior of clarithromycin tablets

Koki Inukai[a], Kei Takiyama[a], Shuji Noguchi[a,b], Yasunori Iwao,[a] Shigeru Itai[a,*]

[a]*Department of Pharmaceutical Engineering, Graduate School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan*

[b]*Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*

Abbreviations: CAM, clarithromycin; HPLC, high-performance liquid chromatography; PXRD, powder X-ray diffraction; DSC, differential scanning calorimetry.



Graphic abstract

13

14

Abstract

Clarithromycin (CAM) is a macrolide antibiotic that is widely used at clinical sites. We found that release of CAM is suppressed when tablets of CAM were exposed to an external solvent containing carboxylate buffers such as citrate. The suppressed release of CAM can be attributed to the formation of gels on the tablet surfaces, which inhibits penetration of the solvent into the tablet and thus disintegration of the tablets. Delayed disintegration of the tablets was also observed for commercial tablets. This suggests that taking CAM and carboxylates at the same time might be avoided. The crystal structure of CAM citrate reveals that molecular chains of CAM are cross-linked by hydrogen bond between citrate groups in the crystal. The crystal structure indicates that cross-linked CAM chains of the three-dimensional mesh structure might also be formed in high concentration CAM solutions in the presence of carboxylates, resulting in gel formation.

Keywords: Clarithromycin, Single-crystal X-ray diffraction, Gelation, Carboxylate buffer

1. Introduction

Clarithromycin (CAM) is a 14-membered-ring macrolide antibiotic with a broad antibacterial spectrum, and it is widely used for the clinical treatment of various infectious diseases. It is used, as first-line drug even in today (Judit et al., 2016), with amoxicillin and a proton pump inhibitor to eradicate *Helicobacter pylori*, which was reported to cause stomach cancer.

The dissolution rate of CAM is affected by polymorphic transitions. When a CAM tablet consisting of form I crystals is exposed to an external solution, fine-needle-shaped form IV crystals spontaneously form and cover the tablet surfaces. This coating of form IV crystals prevents the solution from penetrating into the tablet, which inhibits disintegration of the tablet and suppresses release of CAM (Fujiki et al., 2011 and 2015). Noguchi et al. (2014) found that under acidic conditions containing hydrochloride, form II CAM transforms to a chloride salt crystal with a higher dissolution rate via a gel and a metastable crystalline form. In their study, release of CAM was also found to be delayed when a tablet consisting of form II crystals was exposed to an external solvent containing carboxylates. Carboxylates are often contained in foods. For example, vinegar contains approximately 5% acetate (800 mM), and grapefruit juice and orange juice contain approximately 130 and 90 mM citrate, respectively (Penniston et al., 2008). CAM is generally taken after a meal, and its dissolution might be affected by carboxylates contained in food and drink. Floating gastroretentive drug delivery systems of CAM have been reported, which reside in the stomach and release CAM in a sustained manner for efficient eradication of *H. pylori* (Aoki et al., 2015; Rajinikanth et al., 2008), and their function would be also disrupted by carboxylates because the gel formed with carboxylates would change the particle density and suppress the releases of drugs. The suppression of drug releases by gels formed with polymers has been applied to the controlled releases of drugs: for recent example using β-glucans (Xiaoju et al., 2016) and the mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose (Hien et al., 2016). However, controlled

54 release by gels formed with citrate, a low molecular-weight excipient, has not been reported.

55 In this paper, the dissolution behavior of CAM in buffers containing carboxylates is reported,

56 and the possible interaction between CAM and citrate (a carboxylate) is discussed based on the

57 crystal structure of CAM citrate.

58

59 **2. Materials and methods**

60 *2.1. Materials*

61 Form II CAM was purchased from Shiono Chemical Co., Ltd. (Tokyo, Japan). All of the other

62 reagents used were of the highest grade available from commercial sources.

63

64 *2.2. Preparation of CAM tablets*

65 Form II CAM powder 67 wt%, Perfiller 101 32 wt%, and magnesium stearate 1 wt% were

66 mixed with a V-shape rotating mixer at 35 rpm for 5 min. The mixed powder (200 mg) was then

67 tableted by a TabAll N30-EX single-punch tablet machine (Okada Seiko Company, Ltd., Tokyo,

68 Japan) using an 8 mm diameter flat-faced punch with a tableting force of 10 kN.

69

70 *2.3. Disintegration and dissolution testing of tablets*

71 The disintegration tests were performed according to the method described in JP XVII. The

72 times taken for complete disintegration of the tablets were measured using an NT-1HM

73 disintegration tester (Toyama Sangyo Company, Ltd., Osaka, Japan) (n=6). The solvents used were

74 25 and 250 mM sodium phosphate buffer (PB), 25, 50, 75, 100, and 250 mM sodium citrate buffer

75 (CB), and 75, 100, 150, 200, and 250 mM sodium acetate buffer (AB) (37.0 ± 0.5 °C). The pH

76 values of the solvents were adjusted to 5.0, taken the pH value in the stomach after meals or

77 administration of a proton pump inhibitor into consideration.

The dissolutions tests were performed according to the paddle method in JP XVII. The solvents were the same as those used in the disintegration tests and their volumes were 900 mL. The temperature was maintained at 37.0 ± 0.5 °C and the paddle speed was 50 rpm. Aliquots of the solution (1.5 mL) were removed at predetermined time intervals, and then filtered through a 0.20 μm membrane filter. The CAM concentration was quantified by a high-performance liquid chromatography (HPLC) system consisting of a Shimadzu LC-9A pump, a Shimadzu SPD-6A UV spectrophotometric detector, a Shimadzu CTO-6A column oven, a Shimadzu SIL-6B autoinjector, and a Shimadzu Chromatopac C-R7A plus data processor (Shimadzu Corp., Tokyo, Japan). The operating conditions were as follows: an ultraviolet absorption photometer wavelength of 210 nm, a 4.6 mm internal diameter x 15 cm stainless-steel column packed with octadecyl silica (ODS)-80TM (Tosoh Co., Tokyo, Japan), a column temperature of 40 °C, a mixture of 1/15 M potassium dihydrogen phosphate and acetonitrile (13:7) as the mobile phase, and a flow rate of 1 mL/min.

2.4. Dissolution testing by the static disc method

Crystal powder of form II CAM (250 mg) was compressed into 13 mm diameter disks using an oil-press tableting machine (JASCO Corporation, Tokyo, Japan) with a tableting force of 10 kN. The CAM disks were fixed into a cylindrical holder. The surface area of the disk in contact with the dissolution medium was 1.33 cm^2. The holder was placed in a bottle containing 900 mL of the dissolution medium and allowed to sink to the bottom, according to JP XVII. All of the dissolution tests were performed under the sink condition. The medium was stirred with a paddle at 50 rpm according to the paddle method of JP XVII. The solvents were 25 mM PB and 1, 25, or 250 mM CB containing 25 mM PB (37.0 ± 0.5 °C). The solvents were adjusted to pH 5.0. The dissolved CAM concentrations were quantified by HPLC, as described in Section 2.3.

The solvents, as specified in Section 2.3, and excess crystal powder of form II CAM were

added to 2 mL tubes with screw caps. The tubes were mixed upside down in an incubator at 37 ± 0.5 °C. The solutions were filtered after 1 h and diluted ten-fold with the same solvents, and their CAM concentrations were quantified by HPLC, as described at Section 2.3. The measured concentrations were the same as those measured by the same procedure after 1.5 h, confirming that the CAM concentration reached the saturated concentration.

The apparent intrinsic dissolution rate k (cm min^{-1}) was calculated using the following equation:

$$k = KV/(SC_S) \quad (1)$$

where K is the dissolution rate, V is the volume of the dissolution medium, S is the surface area in contact with the dissolution medium, and C_S is the solubility.

2.5. Preparation of CAM carboxylate salts

Crystal powder of form II CAM (250 mg) and distilled water (70 mL) were mixed with a stirring bar in a beaker, and CAM was dissolved by decreasing the pH to 5.0 using 5 M phosphoric acid solution. Undissolved CAM was removed with filter paper. The filtrates were mixed with 105 mL of 3.0 M AB (pH 5.0), 0.7 mL of 1.0 M CB, 12.3 mL of sodium malate buffer, 14 mL of 0.5 M sodium tartrate buffer, or 21 mL of 0.2 M sodium oxalate buffer. The solutions were stirred overnight at room temperature. The precipitates or gel formed were collected using a Buchner funnel and filter paper, and they were washed with distilled water. The collected samples were dried for 2 days at 37 °C.

2.6. X-ray powder diffraction analysis

The powder X-ray diffraction (PXRD) data of the CAM carboxylate salts was collected at beam line BL5S2 of the Aichi Synchrotron Radiation Center, which is equipped with a Debye–Sherrer

camera and a curved imaging plate detector. The salt powders were packed in 0.4 mm diameter Lindemann glass capillaries. The X-ray wavelength was set to 1.000 Å and the temperature was 25 °C.

2.7. Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements of the CAM carboxylate salts were performed using a DSC7020 calorimeter (Hitachi High-Tech, Tokyo, Japan) at a heating rate of 10 °C min^{-1} under 40 mL min^{-1} dry N_2 gas.

2.8. Single-crystal X-ray structure analysis of CAM citrate

Crystal powder of CAM citrate was prepared (see Section 2.5). A CAM citrate solution was made to dissolve this powder and citric acid powder in water, where the amount was controlled by reducing the pH to 3.6 using a pH meter. The beaker containing the saturated solution (about 10 mL) was placed in an enclosed space with calcium chloride. The solution slowly evaporated at room temperature. After 2 weeks, the solution was completely dry, and there were many plate-like crystals at the bottom of the beaker. These crystals were hermetically stored at room temperature.

Single-crystal X-ray diffraction data of CAM citrate was collected at beam line BL2S1 of the Aichi Synchrotron Radiation Center, which is equipped with an oscillation camera and an ADSC Quantum 315r charge-coupled device detector. The wavelength was set to 1.000 Å. During the data collection, the samples were cooled to 100 K using N_2 gas. The crystal parameters, statistics of the X-ray diffraction data collection, and crystallographic refinement data are summarized in Table 1.

The structure solution was performed using SHELXT (Sheldrick, 2015), and the structure was crystallographically refined using SHELXL (Sheldrick, 2015) and shelXle (Hübschle et al., 2011). The atomic coordinates and diffraction data have been deposited in the Cambridge Structural

Database (CCDC number 1465268). The molecular structure and molecular sequence were determined using Mercury (Macrae et al., 2008).

2.8. Disintegration testing of commercial CAM tablets

Disintegration tests were performed according to JP XVII using commercial CAM tablets. The times taken for complete disintegration of the tablets were measured using an NT-1HM disintegration tester (Toyama Sangyo Company Ltd., Osaka, Japan) in triplicate at 37.0 ± 0.5 °C. The solvents used were 25 and 250 mM of pH 5.0 PB and 25, 50, 75, 100, and 250 mM of pH 5.0 CB.

3. Results and discussion

3.1. Disintegration tests

In disintegration tests using PB as the solvent, CAM tablets rapidly disintegrated: the maximum disintegration time was only 0.5 min in 250 mM buffer (Fig. 1). However, for buffers containing carboxylates, the disintegration times increased as the buffer concentration increased: the disintegration times in 250 mM AB and CB were approximately 500- and 300-times longer than that in PB. When CAM tablets were placed in 250 mM pH 5.0 AB, a translucent gel formed on the surface of the CAM tablets, as shown in Fig. 2. A gel also formed when CB was used, although it was less noticeable. The gels formed on the tablet surfaces may inhibit penetration of the solvent into the tablets, which results in inhibition of the disintegration of the tablets.

3.2. Dissolution tests

Dissolution tests were performed using sodium phosphate and carboxylate buffers (Fig. 3). Release of CAM was very rapid in the PB and 100% of CAM was released. In contrast, release of

CAM was suppressed in CB with concentrations higher than 50 mM and in the AB with concentrations higher than 200 mM. Release of CAM was suppressed more as the buffer concentration increased. In the sodium carboxylate buffers, the suppressed release of CAM can be attributed to inhibition of disintegration of the tablets caused by gel formation on the tablet surfaces. In the dissolution tests in the PB, the time to reach 100% CAM dissolution in 250 mM buffer was 20 min longer than that in 25 mM buffer. This may be caused by the salting-out effect.

3.3. Dissolution parameters

The apparent intrinsic dissolution rates were calculated using the solubility of CAM and the dissolution rate from the disk of form II CAM (Table 2). The dissolution rate and solubility using 25 mM CB are more than twice those using 1, or 250 mM CB. The difference in the solubility may be caused by salting-in and salting-out effects. The apparent intrinsic dissolution rate is significantly lower when 250 mM CB was used. This indicates that the decreased dissolution rate in 250 mM CB is not only caused by the decreased solubility. The gel formed on the surface of the disk may have inhibited CAM dissolution from the disk. There are three factors that may inhibit dissolution of CAM: inhibition of disintegration of the tablet, suppression of CAM elution by gel formation, and decrease in the solubility by the salting-out effect. Therefore, foods containing carboxylates, including citrate, may be avoided when taking CAM formulations, especially the floating gastroretentive drug delivery system.

3.4. Evaluation of the physical and chemical properties of CAM carboxylate salts

When sodium carboxylate buffer was added to CAM dissolved in PB, a gel immediately formed and the solution became cloudy. A photograph of the gel collected form the solvent using AB is shown in Fig. 4. A gel was formed using sodium citrate, malate, oxalate, and tartrate buffers.

PXRD profiles of the CAM carboxylate salts are shown in Fig. 5. All of the profiles are different from previously reported profiles of CAM, indicating that these are new crystals of carboxylate salts. The lattice constants and possible space groups of crystals prepared using AB and CB were calculated from the PXRD profiles using EXPO2014 (Table 3). All of the peaks in the PXRD profiles could be indexed with these cell parameters, confirming that each of these crystal powders consisted of a single crystalline phase. The crystal powder prepared using CB was confirmed to be CAM citrate hydrate by single-crystal X-ray structure analysis. Assuming that the crystals prepared using AB are CAM acetate and their space group is monoclinic $P2_1$, its specific volume (volume per unit molecular weight) is 1.44 Å/Da. This value is comparable with the values of previously reported CAM crystals (Noguchi et al., 2014), suggesting that this crystal is CAM acetate or possibly CAM acetate hydrate. The diffraction peaks of the PXRD profiles of crystals prepared using malate, oxalate, and tartrate buffers could not be indexed using a single crystal cell, suggesting that these crystals are mixtures of polymorphs and/or pseudopolymorphs, such as hydrates.

The CAM carboxylate crystals were analyzed by DSC (Fig. 6). The melting points are 226.4 °C for form II, 218.6 °C for the acetate salt, 175.2 °C for the citrate salt, 199.6 °C for the malate salt, 186.5 °C for the tartrate salt, and 191.3 °C the tartrate salt. The differences in the melting points show that these are new crystal forms. All of the melting points of the CAM carboxylate salts are lower than that of form II. Although the melting points of the citrate and acetate salts are sharp endothermic peaks, those of the malate, oxalate and tartrate salts are not. This may be because the citrate and acetate salts are pure crystalline phase and the others are not, as suggested by PXRD analysis.

3.5. Single-crystal X-ray structure analysis of CAM citrate

Single-crystal structure determination of CAM citrate revealed that the unit cell consists of one CAM molecule, one citrate molecule, and five water molecules (Table 1). The occupancies of the four water molecules are less than 1.0.

The numbering of the atoms in the crystal structure is given in Fig. 7(a). A hydrogen-bonded network forms between CAM citrate and the water molecules (Fig. 7(b)). There is also a hydrogen bond between the O9 oxygen atom of the cladinose ring and the O3 oxygen atom of the 14-membered aglycone ring of CAM molecules. The CAM molecules form in head-to-tail chain parallel to the *b* axis. This chain arrangement mediated by O9–O3 hydrogen bonds is also found in the crystal structures of form 0 (Spanton et al., 1999), metastable form I (Noguchi et al., 2012), and the hydrochloride hydrate (Parvez et al., 2000), suggesting that this arrangement is stable for CAM. Hydrogen bonds form between CAM and citrate parallel to the *c* axis between the protonated N1 nitrogen atom of the CAM desosamine ring and the O16 hydroxyl oxygen of citrate, and parallel to the *b* axis between the O13 hydroxyl oxygen atom of the CAM desosamine ring and the O14 carbonyl oxygen atom of citrate. Protonation of N1 is confirmed because the electron density of the hydrogen atom bound to N1 is clearly observed. The molecular chains of CAM are cross-linked by hydrogen bonds with citrate molecules. One of the carboxyl groups of the citrate molecule (O19–C43–O20) is thought to be deprotonated and O20 would have a negative electrostatic charge. This is because the O19–C43 and O20–C43 distances are 1.216 and 1.273 Å, indicating that they are double and single bonds, respectively, and O20 is a hydrogen acceptor for hydrogen atoms attached to the OW1 oxygen atom of a water molecule and the O15 carboxyl oxygen atom of a citrate molecule. The presence of the hydrogen atoms bound to OW1 and O15 is confirmed by the fact that their electron densities are clearly observed. These hydrogen bonds would stabilize the negatively charged O20 oxygen atom. No ionic bond is formed between CAM and citrate molecules, although they are positively and negatively charged, respectively. The other two carboxyl groups of the citrate

molecule (O15–C39–O16 and O17–C44–O18) are thought to be protonated, because the electron densities of hydrogen atoms bound to O15 and O18 are observed.

Although the structural characteristics described above are found in the crystal structure of CAM citrate, they also indicate the structure of the CAM gel formed in the buffer-containing carboxylate buffers. In the CAM citrate crystal, molecular chains of CAM are cross-linked by citrate molecules by a number of hydrogen bonds. These hydrogen bonds would also possibly form in the gel. The molecular chains of CAM might form at the region of high CAM concentration and the chain might be cross-linked by hydrogen bonds when carboxylates, such as citrate, coexist, as observed in the crystal structure. This results in formation of a three-dimensional mesh structure. Water molecules would be trapped in the mesh by formation of hydrogen bonds, as is observed in the crystal structure, and gelation would occur (Fig. 8). Controlled release of other weakly-basic drugs might be possible when the drugs are inclined to form gels with carboxylates as in the case of CAM.

3.6. Disintegration testing of commercial CAM tablets

In disintegration tests using PB as the solvent, commercial CAM tablets disintegrated and the maximum disintegration time was only 10 min (Fig. 9). In disintegration tests using CB as the solvent, the tablets rapidly disintegrated in 25 and 50 mM buffer solutions. However, the disintegration time increased with increasing concentration of the buffer for concentrations higher than 50 mM. The maximum disintegration time was 340.4 min in 250 mM CB. It is assumed that penetration of the solvent into the tablet is suppressed by the gel formed on the tablet surface, as discussed in Section 3.1. These results suggested that the disintegration time of commercial tablets could significantly increase in the presence of carboxylates, for example, by more than 2 h in 100 mM citrate, which is the typical concentration in citrus juices. It is assumed that disintegration and

dissolution of CAM are also delayed with intake of citric acid from foods.

4. Conclusion

Disintegration and dissolution tests using AB and CB showed that dissolution of CAM is suppressed depending on their concentration, because a gel formed on the tablet surfaces would delay disintegration. Disintegration of commercial tablets was also delayed in CB. Hence, foods and drinks with high carboxylate contents, such as grapefruit juice, might be avoided when taking CAM formulations, especially the floating gastroretentive drug delivery system.

Single-crystal X-ray structure analysis of CAM citrate revealed that molecular chains of CAM are cross-linked by hydrogen bonds between citrate molecules in the crystal. It is assumed that these molecular chains of CAM might be also formed in the gel. The molecular chains of CAM might be cross-linked by hydrogen bonds when carboxylates, such as citrate, are present, similar to the crystal structure, resulting in formation of a three-dimensional mesh structure.

Acknowledgments

The synchrotron radiation experiments were performed at beam lines BL5S2 and BL2S1 of the Aichi Synchrotron Radiation Center, Aichi Science & Technology Foundation, Aichi, Japan (approval numbers 201401010, 201403031, and 2015N2011). This work was supported by the Japan Society for the Promotion of Science KAKENHI (grant numbers 26460224, 26460039, and 26460226).

References

Aoki, H., Iwao, Y., Mizoguchi, M., Noguchi, S., Itai, S., 2015. Clarithromycin highly-loaded gastro-floating fine granules prepared by high-shear melt granulation can enhance the efficacy of Helicobacter pylori eradication. Eur. J. Pharm. Sci. 92, 22–27.

Altomare, A. Cuocci, C. Giacovazzo, C. Moliterni, A. Rizzi, R. Corriero N., Falcicchio, A., 2013. EXPO2013: a kit of tools for phasing crystal structures from powder data. J. Appl. Crystallogr. 46, 1231–1235.

Fujiki, S., Iwao, Y., Kobayashi, M., Miyagishima, A., Itai, S., 2011. Stabilization mechanism of clarithromycin tablets under gastric pH condition. Chem. Pharm. Bull. 59, 553–558.

Fujiki, S., Watanabe, N., Iwao, Y., Noguchi, S., Mizoguchi, M., Iwamura, T., Itai, S., 2015. Suppressed release of clarithromycin from tablets by crystalline phase transition of metastable polymorph form I. J. Pharm. Sci. 104, 2641–2644.

Hien, V., N., Van, H., N., Beom, J., L., 2016. Dual release and molecular mechanism of bilayered aceclofenac tablet using polymer mixture. Int. J. Pharm. 515, 233–244.

Hübschle, C.B., Sheldrick, G.M., Dittrich, B., 2011. ShelXle: a Qt graphical user interface for SHELXL. J. Appl. Crystallogr. 44, 1281–1284.

Noguchi, S., Miura, K., Fujiki, S., Iwao, Y., Itai, S., 2012. Clarithromycin form I determined by synchrotron X-ray powder diffraction. Acta Crystallogr. C68, 41–44.

Noguchi, S., Takiyama, K., Fujiki, S., Iwao, Y., Miura, K., Itai, S., 2014. Polymorphic transformation of antibiotic clarithromycin under acidic condition. J. Pharm. Sci. 103, 580–586.

Macrae, C.F., Bruno, I.J., Chisholm, J.A., Edgington, P.R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J., Wood, P.A., 2008. Mercury CSD 2.0 - New Features for the visualization and investigation of crystal structures. J. Appl. Cryst. 41,

466–470.

Parsons, S., Flack, H.D., Wagner, T., 2013. Use of intensity quotients and differences in absolute structure refinement. Acta Crystallogr. B69, 249–259.

Parvez, M., Arayne, M.S., Sabri, R., Sultana, N., 2000. Clarithromycin hydrochloride 3.5-hydrate. Acta Crystallogr. C56, 398–399.

Penniston, K.L., Nakada, S.Y., Holmes, R.P., Assimos, D.G., 2008. Quantitative assessment of citric acid in lemon juice, lime juice, and commercially-available fruit juice products. J. Endourology 22, 567–570.

Rajinikanth, P.S., Mishra, B., 2008. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H. pylori. J. Controlled Release. 125, 33–41.

Sheldrick, G.M., 2015. Crystal structure refinement with *SHELXL*. Acta Crystallogr. C71, 3–8.

Sheldrick, G.M., 2015. *SHELXT* – Integrated space-group and crystal-structure determination. Acta Crystallogr. A71, 3–8.

Spanton, S.G., Henry, R.F., Riley, D.A., Liu, J.-H., 1999. Crystal form O of clarithromycin. US Patent No. 5945405.

Xiaoju, Z., Pengyu, W., Jiong, W., Zhi, L., Xuechuan, H., Yuling, X., Peng, L., Xianming, H., 2016. Hydroxyethyl Pachyman as a novel excipient for sustained-release matrix tablets. Carbohydr. Polym. 154, 1–7.

Judit, A., Gloria, F., Enoc, C., Carlos, A., C., Jose, D., S., Ivan, C., C., Reyes, B., Adolfo, R., 2016. Clarithromycin resistance and prevalence of Helicobacter pylori virulent genotypes in patients from Southern México with chronic gastritis. Infect. Genet. Evol. 44, 190–198.

335 **FIGURE CAPTIONS**

336 **Fig. 1.** Disintegration times in the carboxylate buffers. Each bare represents the mean ± standard
337 deviation (SD) (*n*=6).

338 **Fig 2.** Gel of CAM formed on the form II tablet. The tablet was placed in 250 mM AB and stirred
339 for 5 min at 37.0 °C.

340 **Fig 3.** CAM dissolution test results. Each data represents the mean ± SD (*n*=3).

341 **Fig 4.** Gel formed when CAM powders are mixed with AB.

342 **Fig 5.** PXRD profiles of CAM carboxylate salts. Form II (green), CAM acetate (blue), CAM citrate
343 (red), CAM malate (purple), CAM oxalate (light green), and CAM tartrate (yellow).

344 **Fig 6.** DSC curves of CAM carboxylate salts. Form II (green), CAM acetate (blue), CAM citrate
345 (red), CAM malate (purple), CAM oxalate (light green), and CAM tartrate (yellow).

346 **Fig 7.** (a) Molecular structures of CAM, citrate, and water molecules with the atom-numbering
347 scheme. C, O, and N atoms are shown in grey, red, and light blue, respectively. (b) Crystal structure
348 of CAM citrate. The unit cell is shown as a thin black line. CAM and citrate are shown in light blue
349 and green, respectively. Hydrogen atoms are not shown for clarity. Hydrogen bonds are shown as
350 black dotted lines.
351

352 **Fig 8.** Schematic drawing of the proposed structure of the CAM citrate gel. CAM and citrate are
353 shown as blue and green spheres, respectively. Water molecules except for OW1 are not shown.

354

355 **Fig 9.** Disintegration times of commercial tablets in different concentration buffer solutions. Each

356 column represents the mean ± SD (*n*=3).

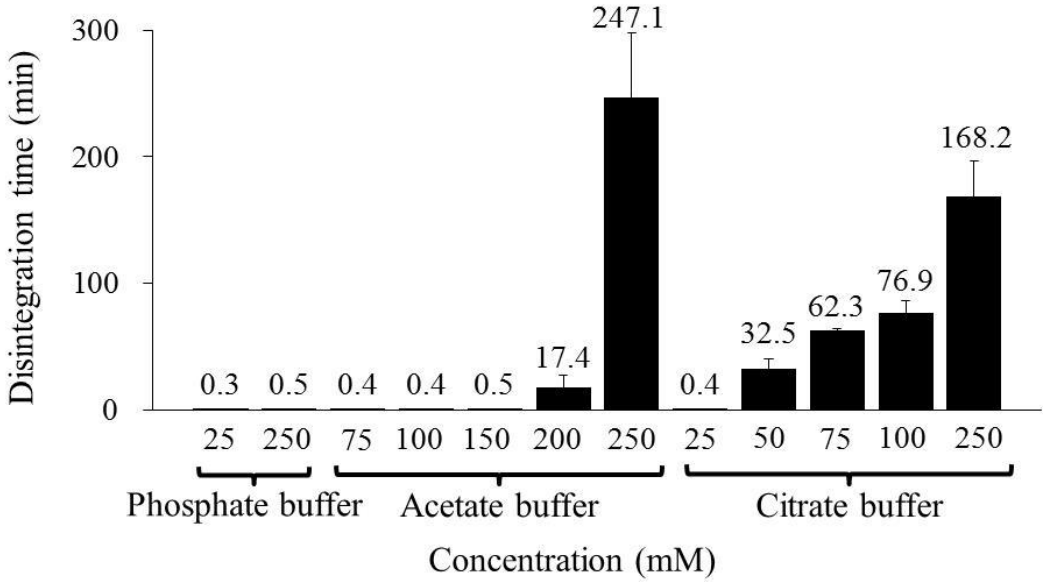


Fig. 1

357

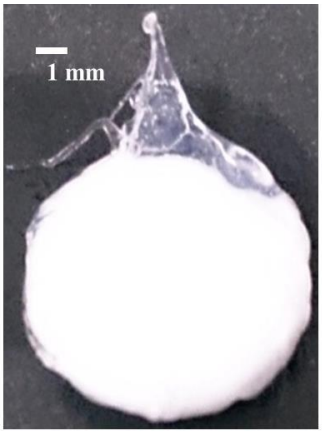


Fig. 2

358

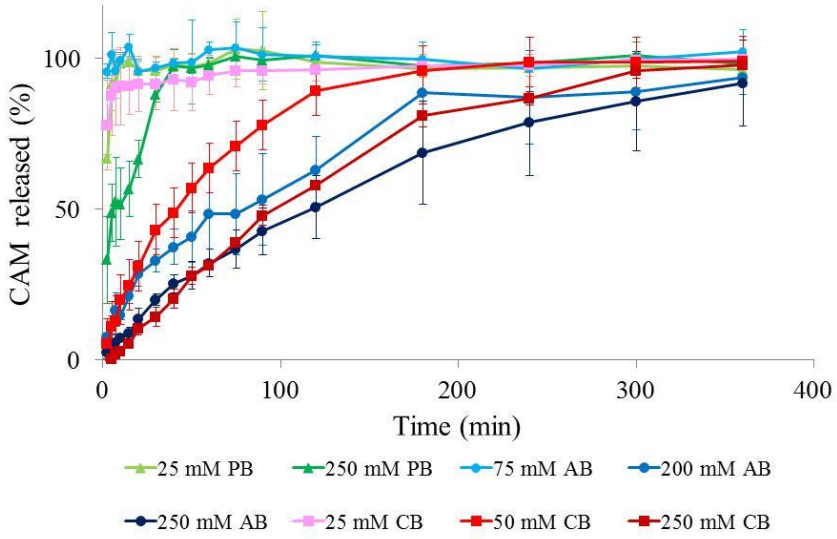


Fig. 3

359

Fig. 4

360

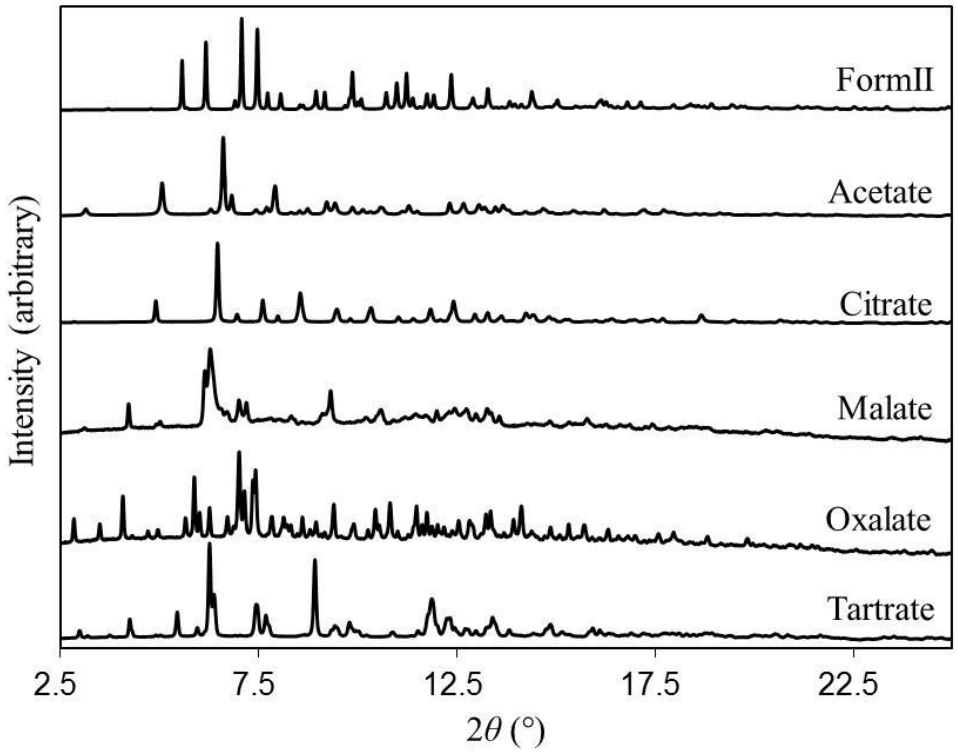


Fig. 5

361

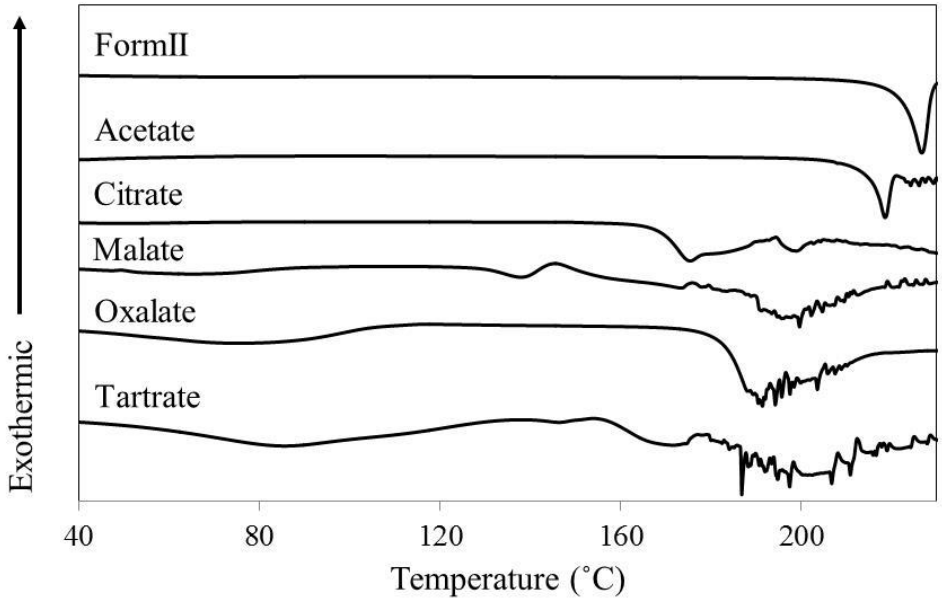


Fig. 6

362

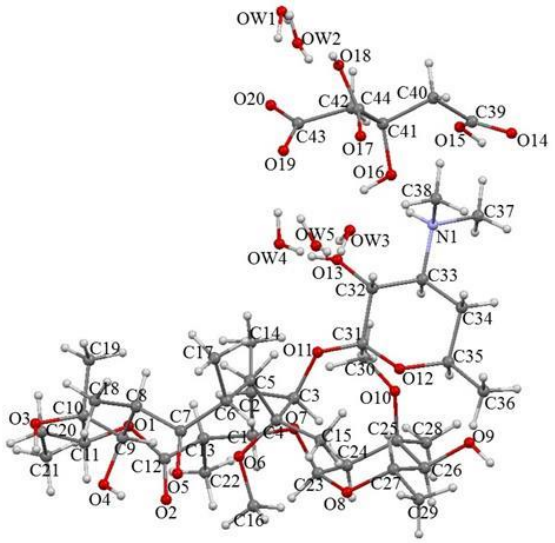

OW1
OW2
O18
O20
C42
C44
C40
C39
C43
C41
O15
O14
O19
O17
O16
C38
C37
OW5
OW3
N1
OW4
O13
C33
C32
C34
C14
C31
C19
C17
O11
C30
C35
C18
C8
C5
C3
O12
O10
C36
O3
C10
C6
C2
O7
C25
C28
O1
C7
C20
C1
C4
C15
O9
C9
C24
C11
C13
O6
C12
C22
C26
C21
O5
C23
C27
O4
O8
O2
C16
C29

Fig. 7 (a)

363

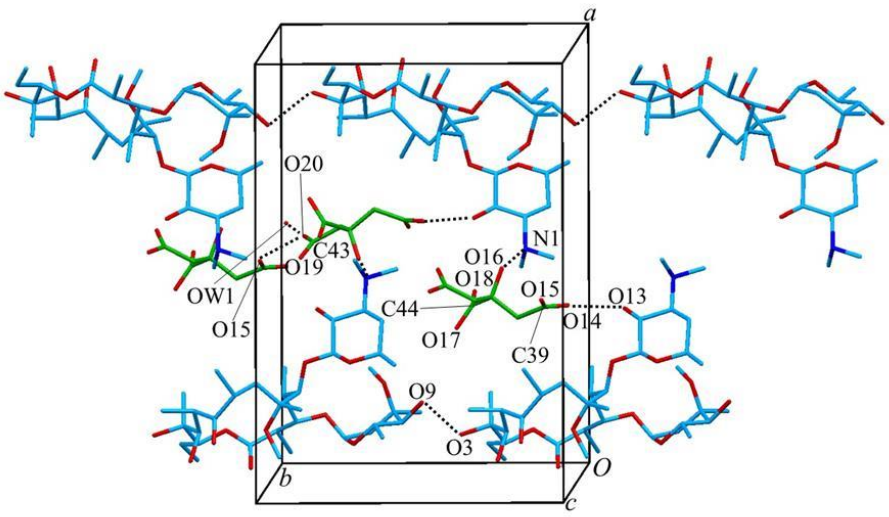


Fig. 7 (b)

364

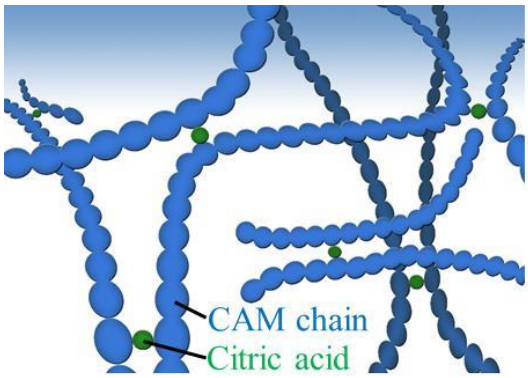


Fig. 8

365

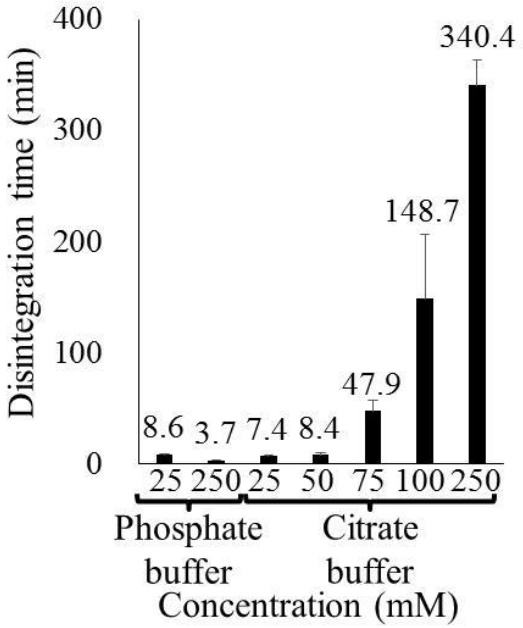

400
300
200
100
0
Disintegration time (min)
340.4
148.7
47.9
8.6
3.7
7.4
8.4
25
250
25
50
75
100
250
Phosphate buffer
Citrate buffer
Concentration (mM)

Fig. 9

366