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# Effect of surfactants or a water soluble polymer on the crystal transition of clarithromycin during a wet granulation process

Kenji Nozawa[a,b], Yasunori Iwao[a], Shuji Noguchi[a], Shigeru Itai[a,*]

[a] Department of Pharmaceutical Engineering, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[b] Pharmaceutical Development Department, Sawai Pharmaceutical Co., Ltd, 2-30, Miyahara 5-chome, Yodogawa-ku, Osaka 532-0003, Japan

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ABSTRACT

To generate products containing a stable form of clarithromycin (CAM) (form II) regardless of the initial crystal form of CAM or type of granulation solvent, the effects of five surfactants, or a water-soluble polymer (macrogol 400) were determined on the crystal transition of CAM. The metastable form (form I) was kneaded with water, after adding surfactants, or a water-soluble polymer. Form II was also kneaded with ethanol, after adding the same additives. The resulting samples were analyzed by powder X-ray diffraction. Form I was completely converted to form II by a wet granulation using water with additives bearing polyoxyethylene chains such as polysorbate 80 (PS80), polyoxyl 40 stearate or macrogol 400. The granulation of the form II using ethanol with these additives did not result in a crystal transition to form I. Furthermore, CAM tablets were manufactured using granules with PS80, and these crystal forms and dissolution behaviors were investigated. As a result, the wet granulation of CAM with PS80 gave CAM tablets containing only form II and PS80 did not have any adverse effects on tablet characteristics. Therefore, these data suggests that the crystal form of CAM can be controlled to be form II using a wet granulation process with additives bearing polyoxyethylene chains regardless of the initial crystal form of CAM or type of granulation solvent.



## 1. Introduction

Clarithromycin (CAM), which is a 14-membered semi-synthetic macrolide antibiotic, is more stable to acidic conditions than erythromycin (Nakagawa et al., 1992) and exhibits a broad range of antimicrobial activities. CAM is widely used for the treatment of a variety of different infections, including *Helicobacter pylori* infection. Several tablet-based and pediatric formulations (i.e., granules for oral suspension) containing CAM have been developed and marketed throughout the world (Yajima et al., 1999, 2002). The total annual sales of generic CAM products in Japan equates to more than 340 million dollar (35 billion yen). It is noteworthy that it has been more than 20 years since branded CAM products were available to buy in Japan.

Nine crystal forms of CAM have been reported in the literature, including form 0 (ethanol solvate) (Spanton et al., 1999), form I (metastable form) (Liu et al., 1999; Noguchi et al., 2012; Tozuka et al., 2002), form II (stable form) (Tozuka et al., 2002; Liu et al., 1998; Suh et al., 2002; Sohn et al., 2000; Tian et al., 2011), form III (acetonitrile solvate) (Liu et al., 2003), form IV (hydrate) (Avrutov et al., 2003; Jacco, 2012), form V (Gruss et al., 2008), a hydrochloride salt (Parvez et al., 2000; Noguchi et al., 2014) and a methanol solvate (Iwasaki et al., 1993). Polymorphic crystals generally exhibit significant differences in their individual physicochemical properties, including their solubility, stability and bioavailability properties. These differences can have a significant impact on the therapeutic properties of medicinal agents, and the selection of the optimal crystal form of a medicinal agent is therefore one of the most important factors governing the development of pharmaceutical formulations. The CAM products currently marketed in Japan are formulated using the most thermodynamically stable from of the CAM crystals, which is form II (Liu et al., 1998; Suh et al., 2002; Tian et al., 2011). The purification of form II is typically achieved by the conversion of crystal form 0 or I to form II using temperatures greater than 80 °C under vacuum conditions (Liu et al., 1999, 1998; Suh et al., 2002; Sohn et al., 2000; Tian et al., 2011). The development of a novel process for the preparation of form II that avoids the use of high temperature conditions could therefore reduce the costs

*Abbreviations:* CAM, clarithromycin; SDS, sodium lauryl sulfate; LCT, soybean lecithin; SFE, sucrose fatty acid ester; PS80, polysorbate 80; POS40, polyoxyl 40 stearate; PEG400, macrogol 400; PXRD, powder X-ray diffraction; L-HPC, low-substituted hydroxypropylcellulose.

* Corresponding author. Fax: +81 54 264 5615.
*E-mail address:* s-itai@u-shizuoka-ken.ac.jp (S. Itai).

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associated with the manufacture of these products, as well as production cost of the active pharmaceutical ingredient.

Concerns remain that form II of CAM could undergo a crystal transition during the manufacturing process to give the metastable form of CAM. Although various pharmaceutical techniques have been used to produce solid dosage forms such as wet granulation, dry granulation and direct tableting, wet granulation may be the most appropriate technique for the CAM formulation process, because this technique can improve the surface condition of CAM with a highly adhesive property. During the wet granulation process, an organic solvent can also be used in addition to water for the formulation of CAM to induce the uniform granulation of CAM powders with a water-insoluble property. However, when the wet granulation of form II CAM powders is performed in the presence of an organic solvent, such as ethanol, the CAM crystals can be converted from form II to form I via form 0 (Spanton et al., 1999). It is therefore critically important to suppress the crystal transition of CAM from form II to any of its other forms and to promote the crystal transition to form II during the wet granulation of CAM in the presence of an organic solvent.

To overcome the problems listed above, we focused on the use of surfactants, because several surfactants have been reported to induce the solution-mediated crystal transition of drug compounds (Roderiguez-Hornedo and Murphy, 2004). In this study, we have established a simple technique to enhance the crystal transition of CAM from form I to form II, whilst preventing the crystal transition of the form II crystals during the pharmaceutical manufacturing process by means of additives bearing polyoxyethylene chains.

## 2. Materials and methods

### 2.1. Materials

Forms I and II of CAM were obtained from Kyonbo pharmaceutical Co., Ltd. (Chungchongnam, Korea) and Ercros Industrial S.A. (Barcelona, Spain), respectively. Sodium lauryl sulfate (SDS), which is an anionic surfactant, was obtained from Sigma–Aldrich (Tokyo, Japan). Soybean lecithin (LCT), which is an amphoteric surfactant, was obtained from Nacalai Tesque (Tokyo, Japan). Sucrose fatty acid ester (SFE), polysorbate 80 (PS 80) and polyoxyl 40 (POS40) stearate, which are non-ionic surfactants, were obtained from Mitsubishi-Kagaku Foods Co. (Tokyo, Japan), Kanto Chemical (Tokyo, Japan) and NOF Co. (Tokyo, Japan), respectively. Macrogol 400 (PEG400), which is a water-soluble polymer, was obtained from NOF Co., Corn starch, which is used as a filler, was obtained from Nihon Shokuhin Kako Co., Ltd. (Tokyo, Japan). Low-substituted hydroxypropyl cellulose (L-HPC; used as a disintegrant) was obtained from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Light anhydrous silicic acid (used as a plasticizer) was supplied by Freund Co., Ltd. (Tokyo, Japan). Magnesium stearate (used as a lubricant) was purchased from Taihei Chemical Industrial Co., Ltd. (Tokyo, Japan). Ethanol (>95%) was obtained from the Japan Synthetic Alcohol Co., Ltd. (Kanagawa, Japan). All of the other reagents used in the current study conformed to the standards defined in the 16th edition of the Japanese Pharmacopoeia (JP16).

### 2.2. Methods

#### 2.2.1. Preparation of wet granules using form I and purified water

Five gram samples of form I were mixed with 0, 0.05, 0.25, 0.5 or 1.0 g of each surfactant or PEG400. The resulting mixtures were then treated with 0.75, 1.5 or 3.0 mL of purified water, before being kneaded for 2 min using a mortar and a pestle at room temperature. The wet granulated powders were subsequently sieved through a 2360-μm screen, and the resulting granules were dried in an oven at 50 °C for 40 min. The dried granules were then sieved through a 1000-μm screen, and the resulting sieved powders were subjected to powder X-ray diffraction (PXRD) analysis.

#### 2.2.2. Preparation of wet granules using form II and ethanol

Five gram samples of form II were mixed with 0 or 0.25 g of each surfactant or PEG400. The resulting mixtures were then treated with 0.75, 1.5 or 3.0 g of ethanol before being kneaded for 2 min at room temperature using a mortar and a pestle to give the corresponding granulated powders, which were sieved and dried according to the procedure described above for the “preparation of wet granulation powders of form I with purified water”.

#### 2.2.3. Preparation of wet granules using form II and purified water or using form I and ethanol

Five gram samples of form II or form I were mixed with 0 or 0.25 g of each surfactant or PEG400. The resulting mixtures containing form II were then treated with 1.5 g of water, and these containing form I were then treated with 1.5 g of ethanol before being kneaded for 2 min at room temperature using a mortar and a pestle. Granulation powders thus prepared were sieved and dried according to the procedure described above for the “preparation of wet granulation powders of form I with purified water”.

### 2.3. PXRD

The crystal forms of the CAM found in the granulation powders and tablets were analyzed using a Bruker PXRD system (Bruker AXS Co., Ltd., Kanagawa, Japan). The granulation powders and tablets were gently ground into fine powders using a mortar and

**Table 1**
Compositions of the CAM tablets.

| Ingredient | | Formulation | | | | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| Granulation | Form II of CAM-intact | 200.0 | – | – | – | 200.0 | 200.0 |
| | Form I of CAM-intact | – | 200.0 | 200.0 | – | – | – |
| | Form I of CAM-hammer milling | – | – | – | 200.0 | – | – |
| | Corn starch | 52.4 | 62.4 | 52.4 | 52.4 | 62.4 | 52.4 |
| | L-HPC | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 |
| | Light anhydrous silicic acid | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| | Polysorbate 80 | 10.0 | – | 10.0 | 10.0 | – | 10.0 |
| | Granulation solvent | Water | Water | Water | Water | Ethanol | Ethanol |
| Before compression | Light anhydrous silicic acid | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |
| | Magnesium stearate | 9.6 | 9.6 | 9.6 | 9.6 | 9.6 | 9.6 |
| Total | | 320.0 | 320.0 | 320.0 | 320.0 | 320.0 | 320.0 |

The each value represents the amount (mg/tablet) of each additives added in CAM tablet.