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Application of ascorbic acid 2-glucoside as a solubilizing agent for clarithromycin: Solubilization and nanoparticle formation

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Abstract

Clarithromycin (CAM) was co-ground with L-ascorbic acid 2-glucoside (AA-2G), a newly developed food additive, to improve the solubility characteristics. The complete solubilizing effect of AA-2G was observed for the ground mixture with 1:1 molar ratio. When ground mixtures of CAM and AA-2G (2:1) were dispersed into water, not only the solubilization of CAM was observed but also nanoparticle formation with a mean particle diameter of 280 nm. The CAM particles obtained in this manner were stable in suspension for at least 7 days. Zeta potential analysis showed that positive charges on the particle surface may be contributing to the stability of the suspension. ^{1}H NMR spectrum of CAM dissolved in a phosphate buffer (pH 5.5) showed a signal derived from the *N*,*N*-dimethylamino group at 2.73 ppm, while that of an equimolar ground mixture of CAM with AA-2G in D_2O (pH 5.5) showed clearly two signals at 2.65 and 2.77 ppm derived from the splitting of the two methyl groups. The ^{13}C NMR spectrum of the equimolar ground mixture dissolved in D_2O exhibited two signals derived from *N*,*N*-dimethyl carbons of desosamine group at 37.2 and 42.3 ppm, whereas unprocessed CAM showed no resonance signal arising from those carbons. Moreover, the carbon resonance at 163 and 173 ppm arising from the ketone group in the CAM lactone ring shifted downfield to 177 and 180 ppm after the co-grinding with AA-2G. The formation of nanoparticles was only observed when CAM was co-ground with AA-2G in the molar ratio of 2:1, which might be attributable to a grinding-induced interaction in the solid-state via the ketone group in lactone ring of CAM.
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Keywords: Clarithromycin; Ascorbic acid 2-glucoside; Solubilization; Nanoparticle; Co-grinding; Poorly water-soluble drug

1. Introduction

Clarithromycin (CAM), a 14-membered macrolide antibiotic, was developed with greatly improved acid stability compared to erythromycin (Nakagawa et al., 1992). CAM possesses potent antibacterial activity against clinically important respiratory pathogens such as penicillin-susceptible and -intermediate pneumococci. CAM has also been used to treat *Helicobacter pylori* infection (Gisbert and Pajares, 2003) and pediatric infections (Fujii et al., 1994). However, like many other macrolide antibiotics, CAM exhibits poor absorption and low bioavailability when administered orally. Because of its very low aqueous solubility (0.342 μg/mL H_2O at 25 °C), it is difficult to achieve an injectable CAM product in a clinically and commercially acceptable formulation.

The bioavailability of poorly water-soluble drugs can generally be improved by formulation techniques such as the preparation of binary systems with a hydrophilic carrier by mixing, melting or solvent methods (Aigner et al., 2002; Hassan et al., 2004). However, these methods can leave residual solvent, cause hydrolysis or bring about thermal decomposition of the pharmaceutically active component. Moreover, these processes are so complicated that good cost-performance cannot be easily accomplished. It has been reported that the solubility of a poorly water-soluble drug can be increased by altering the solvent's ability to solvate the drug, via intermolecular hydrogen bonding with pharmaceutically acceptable excipients, such as benzoate or benzoic acid (Simamora et al., 2001). However, it is necessary to add large amounts of excipients to cause solubilization of the drug. Therefore, a simpler and more practical pharmaceutical

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process has been sought for. The solubility improvement of poorly water-soluble drugs using safety-approved solubilizing agents is a very challenging target.

It has been widely known that ascorbic acid is a useful compound for solubilization in pharmaceutical formulations (Itoh et al., 2003). The molecule also acts an antioxidant, inhibiting oxidation at the cell membrane. The well-known susceptibility of ascorbic acid to thermal and oxidative degradation has led to considerable interest in its derivatives. L-Ascorbic acid 2-glucoside (AA-2G), structurally D-glucopyranosyl bonded to the second position of ascorbic acid, has been developed as one of the L-ascorbic acid derivatives. AA-2G has two beneficial properties; high stability against thermal and oxidative degradation and rapid conversion to ascorbic acid by α-glucosidase in the blood and liver cells (Yamamoto et al., 1990; Matsukawa et al., 2000). AA-2G has been approved as a newly developed food additive. Moreover, it is expected to be used in the development of lipid-soluble vitamins and as the principal component in cosmetic ingredients (Yamamoto et al., 2002). Some ascorbic acid derivatives have also been synthesized to improve drug solubility (Mandai et al., 1992). Variation in the alkyl chain of the fatty acid, which forms the ester linkage to the ascorbic acid can be used to improve surface activity, which would improve the solubilization of pharmaceutically active materials (Bilia et al., 2002).

In this study, we characterized a possible use of AA-2G for a newly developed formulation based on CAM. To clarify the solubilization mechanism, we have investigated the interactions of CAM with AA-2G in aqueous solution by ^{1}H NMR and ^{13}C NMR spectroscopy.

2. Materials and methods

2.1. Materials

Clarithromycin (Fig. 1) was received from Taisho Pharmaceutical Co., Ltd., Japan. L-Ascorbic acid 2-glucoside, L-tartaric acid, maleic acid, potassium dihydrogenphosphate and potassium hydroxide were of reagent grade and purchased from Wako Pure Chemical Industries, Ltd., Japan. All other chemicals used were of reagent grade. Clarithromycin (2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-5-(3,4,6-trideoxy-3-dimethylamino-β-D-xylo-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxopentadecan-13-olide) is an antibiotic approved for the treatment of common bacterial infections in non-immunocompromised individuals.

2.2. Methods

2.2.1. Preparation of physical mixture and ground mixture

CAM and AA-2G were physically mixed at a molar ratio of 2:1 or 1:1 in a glass vial using a vortex mixer. Ground mixtures were prepared by grinding in a vibration mill (CMT TI-200, Tochigi, Japan) for 30 min.

2.2.2. Powder X-ray diffraction (PXRD) measurement

Powder X-ray diffraction measurements were performed on a Rigaku Miniflex powder X-ray diffractometer (Rigaku, Japan). The measurement conditions were as follows: 30 kV voltage, 15 mA current, a scanning speed of 4° min^{-1} and a radiation source of CuKα.

2.2.3. Particle size analysis

The ground mixture was dispersed in distilled water and the suspension was sonicated for 2 min. The particle size was measured by the light-scattering method using a Microtrac FRA® (Nikkiso, Japan; measurement range, 0.1–700 μm) and by the dynamic light-scattering method using a Microtrac UPA® (Nikkiso, Japan; measurement range, 0.003–6 μm).

2.2.4. FT-IR spectroscopy

Infrared (IR) spectra were obtained with a Fourier transform JASCO 230 (FT)-IR spectrometer (JASCO Corporation, Japan). The samples were ground with potassium bromide and compressed to obtain disks, and the spectra were recorded at resolution of 4 cm^{-1}.

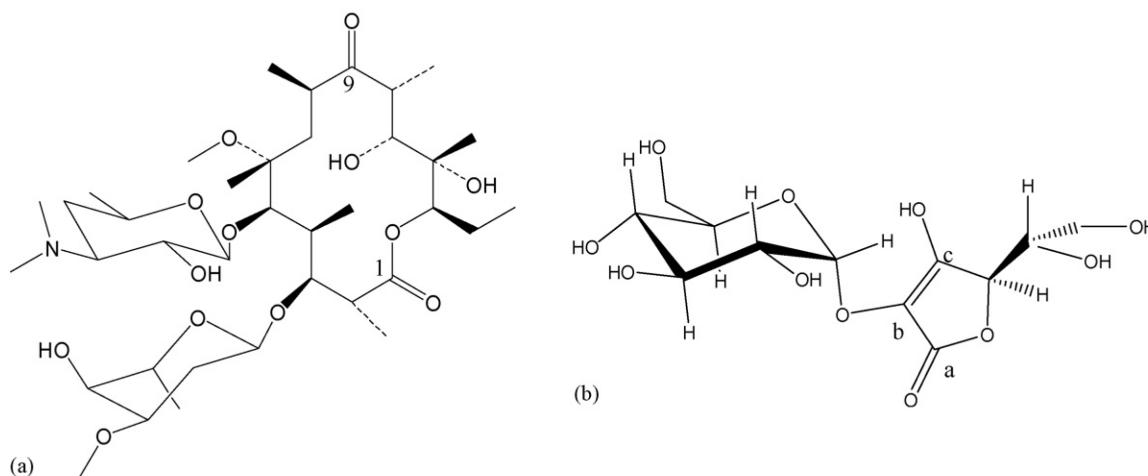

Fig. 1. Chemical structures of (a) clarithromycin (CAM) and (b) L-ascorbic acid 2-glucoside (AA-2G).

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