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Polymorphism of Clarithromycin

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It is well recognized that physicochemical properties of drugs are affected by the type of polymorphic crystalline form of drugs. Clarithromycin is known to exist in at least three polymorphic crystalline forms. Since conventional means to obtain the most thermodynamically stable form (Form II) for the antibiotics is known to be associated with a low purity of the stable form, we developed a novel method to improve the purity of the crystalline form by a modification of the preparation process. The new method involved a simple recrystallization of clarithromycin in solvents having 5-12 carbon atoms (e.g., hexane and heptane) or ethers with 4-10 carbon atoms (e.g., isopropyl ether) and, thus, less likely to be associated with the problem in purity of resulting crystal. Differential scanning calorimetry and powder X-ray diffraction were used to compare the crystalline form of the resultant powder with Form II crystal prepared by the conventional method. The crystal prepared by the new method was identical to Form II crystal of the conventional method as evidenced by the lack of the exothermic peak near 110°C in differential calorimetry scan, indicating that Form II crystal could be readily prepared by the new process. Therefore, these data indicated that the improvement in the purity of the Form II crystal for clarithromycin as well as a significant cost reduction is likely by the novel method.

Key words: Polymorphism, Clarithromycin, 6-O-methylerythromycin A, Crystal form

INTRODUCTION

A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state(Haleblian *et al.*, 1969). The pharmaceutical importance of this phenomenon lies in the fact that different polymorphic phases exhibit unique physicochemical properties include solubility/dissolution rates which can influence bioavailability (Aguiar *et al.*, 1967 and Sohn, 1995), solid-state stability (Sohn, 1991 and Matsumoto *et al.*, 1991).

The presence of this phenomenon in pharmaceuticals is particularly common and a recent report lists over 500 examples of pharmaceuticals that exhibit polymorphism (Grunenburg, 1997). Various techniques are currently utilized to characterize polymorphs including powder X-ray diffraction(PXRD), hot-stage microscopy(HSM), differential scanning calorimetry(DSC), Fourier transform infrared (FT-IR) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, and thermogravimetric analysis (TGA). (Burger, 1982, Henck *et al.*, 1997 and Singh *et al.*, 1998).

6-O-methylerythromycin A(clarithromycin) is a semisynthetic macrolide antibiotic which exhibits broad-spectrum antibacterial activity and is a useful therapy for infections of the upper respiratory tract in children and adults.

Polymorphism of clarithromycin has been reported in patents (Liu *et al.*, 1998, Liu *et al.*, 1998 and Spanton *et al.*, 1998) and three crystal modifications of clarithromycin, "Form I", "Form II", and "Form O" were characterized.

Drugs currently on the market are formulated from the thermodynamically more stable Form II.

In this study, a new preparation method of Form II of clarithromycin was studied.

MATERIALS AND METHODS

Materials

The 6-O-methylerythromycin A was provided from Dong-A Pharmaceutical Co. Ltd.

Other extra pure chemicals were purchased from a reagent commercial company.

Preparation of polymorphs

The compounds examined and the various forms

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obtained are listed below.

Form I

Clarithromycin was recrystallized from solvent (ethanol, tetrahydrofuran, isopropanol, and isopropyl acetate) and the recrystallized product was dried in a vacuum oven (40-45°C) to give Form I.

Form II

(1) Clarithromycin Form I was placed in a vial and heated in vacuum oven (100-110°C) for 18 hours to give Form II.

(2) A suspension of clarithromycin in solvent (acetone, heptane, toluene, tert-butyl ether, N, N-dimethylformamide, ethyl acetate, xylene) was heated at reflux for 15 minutes. The hot solution was filtered and solid was removed. The filter flask was rinsed with acetone. The combined filtrate and rinse was warmed to reflux and acetone was added to dissolve all remaining solid. The solution was cooled to ambient temperature and then in an ice-water bath. The resulting solid was filtered and dried overnight in a vacuum oven to give Form II.

Form O

A mixture of clarithromycin and solvent (ethanol, isopropyl acetate, tetrahydrofuran, and isopropanol) was warmed to reflux and the insoluble material was removed by filtration. The filtrate was transferred to a clean flask and heated to reflux. The clear solution was allowed to cool to ambient temperature and then was further cooled in an ice bath.

The new preparation method of Form II

A mixture of clarithromycin and tetrahydrofuran was stirred and solvent was added and the insoluble material was removed by filtration. The filtrate was washed with solvent and transferred to a clean flask. The recrystallized product was dried in a vacuum oven (40-45°C) to give Form II.

Solvent means hydrocarbon of from 5 to 12 carbon atoms (for example hexane, heptane), or ether of from 4 to 10 carbon atoms (for example isopropylether).

Differential Scanning Calorimetry (DSC)

A Mettler differential scanning calorimeter (Switzerland) equipped with a data station (Thermal analyst 90, Mettler, Switzerland) was used to determine the DSC curves representing the rates of heat uptake with respect to temperature. The solid sample (2 mg) was weighed into aluminum pan and heated with a rate 10°C/min to 300°C.

Powder X-ray Diffraction (PXRD)

The PXRD patterns of polymorphic forms of the clarithromycin were determined using a diffractometer (Rigaku, Japan). Each sample was scanned with the diffraction angle, 2θ, increasing from $5° < 2\theta < 35°$.

RESULTS AND DISCUSSION

Polymorphism of 6-O-methylerythromycin A (clarithromycin) have been reported in patents (Liu *et al.*, 1998, Liu *et al.*, 1998 and Spanton *et al.*, 1998) and three crystal modifications of clarithromycin, "Form I", "Form II", and "Form O" were characterized. Differential scanning calorimetry (DSC) and X-ray powder diffraction (PXRD) analysis are used to characterize polymorphism.

Based on the results obtained from powder X-ray diffraction analysis (λ=1.5418Å) and DSC, Form I (Fig. 1 and 2), Form II (Fig. 3 and 4) were characterized. Form O was a solvate having the structure wherein solvating molecule was selected from the group consisting of ethanol, isopropyl acetate, isopropanol and tetrahydrofuran (Spanton, 1998).

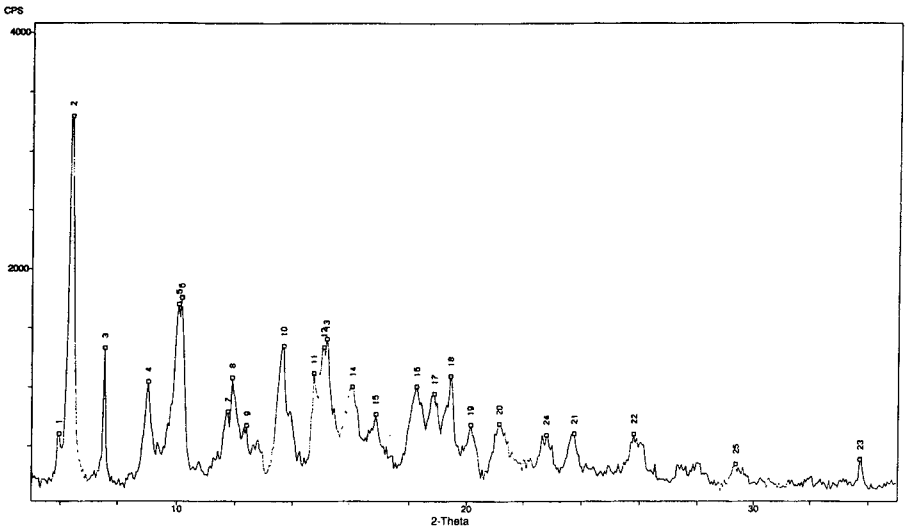

Fig. 1. PXRD pattern of clarithromycin Form I

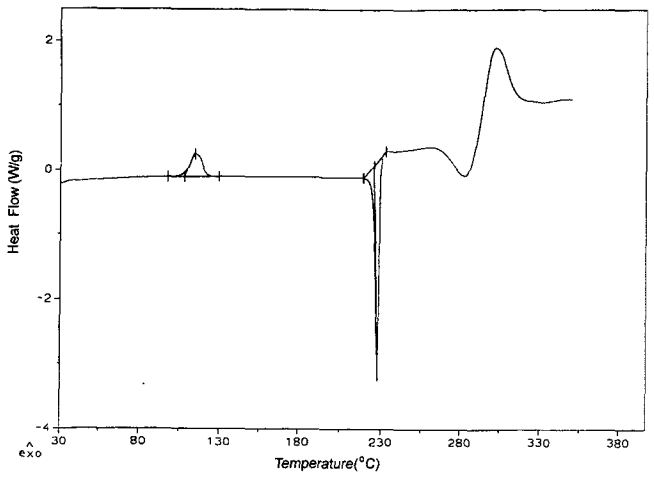

Fig. 2. DSC-thermogram of clarithromycin Form I

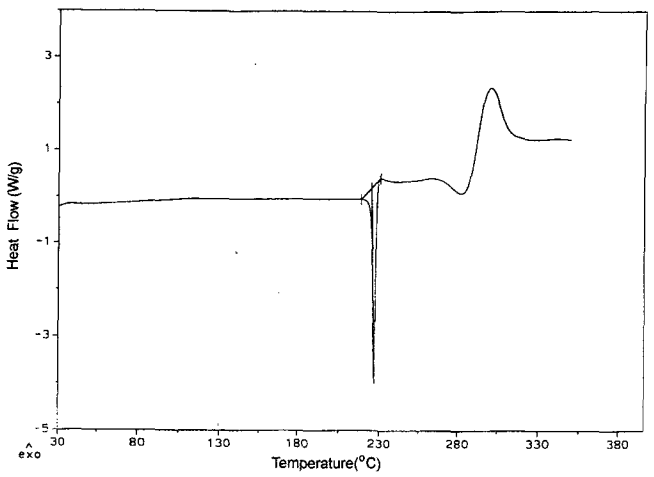

Fig. 4. DSC-thermogram of clarithromycin Form II

Because Form II is more stable than Form I and Form O, preparation of clarithromycin requires converting the Form I crystals to Form II and typically this is done by heating Form I crystals under vacuum at a temperature of greater than 80°C. Therefore, a process for the preparation of Form II which does not require the high temperature treatment would result in substantial processing cost savings. The patent method is follows, a suspension of clarithromycin in solvent (acetone, heptane, toluene, tert-butyl ether, N, N-dimethylformamide, ethyl acetate, xylene) was heated at reflux for 15 min. The hot solution was filtered and solid was removed. This method has a drawback, that is, during the filtration of hot solution, the rapid temperature fall was caused and this is the main reason of low purity of Form II. Therefore, a new preparation method of Form II was studied. The powder X-ray diffraction analysis (Fig. 5) and DSC data (Fig. 6) reveal that the crystals obtained by the new preparation method are identical to Form II.

In general, a number of techniques are used in the study of polymorphism of crystals. For example, hot-stage microscopy (HSM), differential scanning calorimetry (DSC), Fourier transform infrared (FT-IR) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, and thermogravimetric analysis (TGA), was typically employed (Burger, 1982). In this study, crystalline forms of clarithromycin from various production method were determined by DSC and PXRD. It is generally accepted that PXRD analysis is the method of choice for polymorphism study since the diffraction pattern provides information regarding the crystalline nature of the sample. The PXRD pattern obtained for the powder obtained from the new method (Fig. 5) appears qualitatively closer to that of the Form II crystal (Fig. 3) than that of Form I (Fig. 1). In addition, the lack of the exothermic peak near 110°C of the new method and the Form II crystal clearly

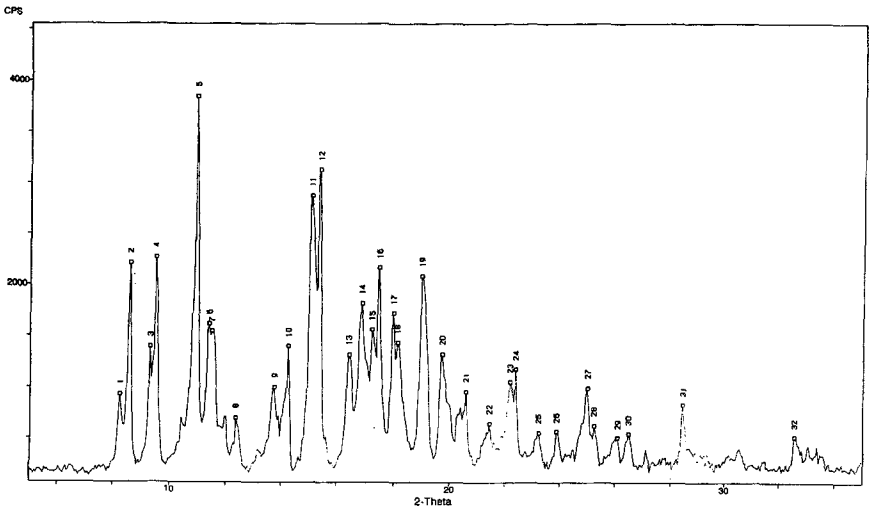

Fig. 3. PXRD pattern of clarithromycin Form II

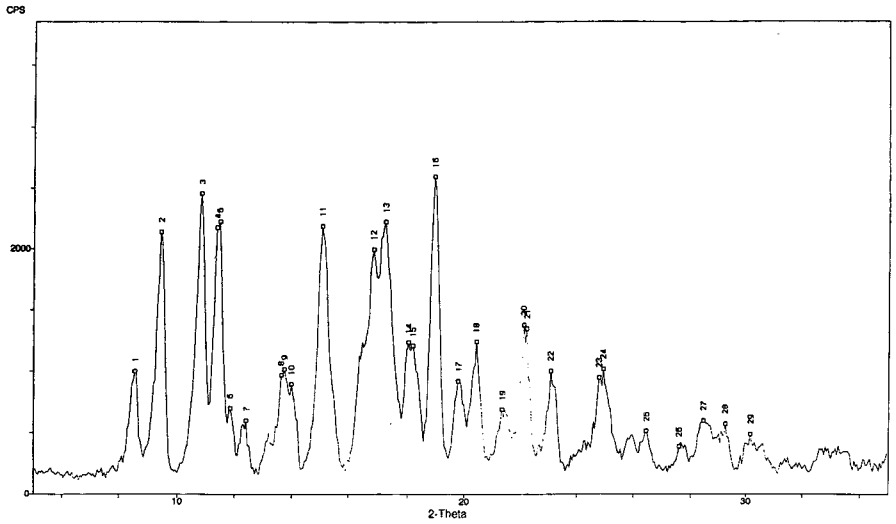

Fig. 5. PXRD pattern of the clarithromycin crystals obtained by the new preparation method

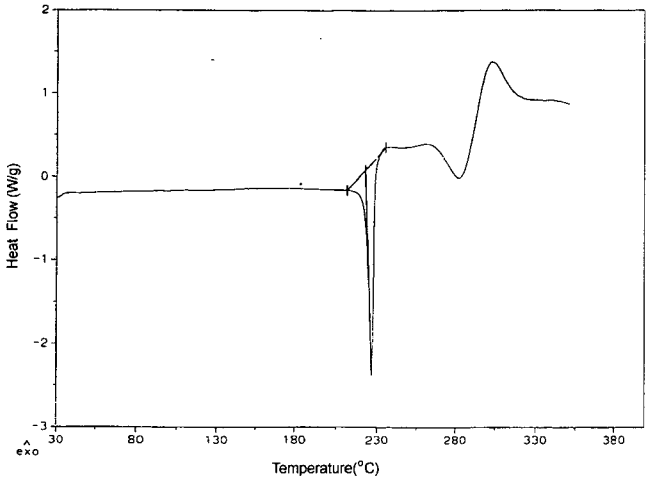

Fig. 6. DSC-thermogram of the clarithromycin crystals obtained by the new preparation method

indicates that the crystalline form of the powder obtained by the new method is most likely to be the Form II. Therefore, these physicochemical data indicated that Form II crystal could be readily prepared by the new process.

In summary, a novel method to generate Form II crystal of clarithromycin was developed. The new method is significantly simpler in the preparation than the conventional method. Since the complexity of crystallization process is known to be the primary reason for the low percentage of Form II crystal of the conventional method, the simple recrystallization process that is involved in the improved method is likely to increase the fraction of Form II crystal in the product. In addition, the simplicity of the method may result in a reduction in the production cost for clarithromycin formulation. Therefore, the new method may be practically applicable with a significant improvement both in the cost and quality of the formulation.

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