Polymorphism and pseudopolymorphism of Clarithromycin

Mari-Alet de Jager

B. Pharm

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Supervisor: Prof. W. Liebenberg
Co-supervisor: Mnr. M. Brits

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Abstract

Clarithromycin is a 14-membered-ring, macrolide antibiotic, a derivative of erythromycin, that is commonly used for the treatment of chronic, obstructive upper - and lower respiratory -, skin - and soft tissue -, as well as for gastric (duodenal ulcers caused by *H. pylori*) infections.

During this study, polymorphic and pseudopolymorphic forms were evaluated, identified and characterised, using normal spectral and thermal methods, such as x-ray powder diffractometry, infrared spectroscopy, differential scanning calorimetry, thermogravimetrical analysis and thermal microscopy.

Literature described Form 0, a solvate; Form I, a metastable polymorph; Form II, the thermodynamically more stable polymorph; Form III, a solvate (from acetonitrile) and Form IV, an amorph.

Various solvents were used for slow recrystallisation of clarithromycin. The thermodynamically more stable Form II was prepared from acetone, methanol, benzene, dimethylformamide and tetrahydrofuran. Recrystallisations from acetonitrile produced Form II, and not Form III as reported in the literature. Two new forms, i.e. an ethyl acetate (Form V) and a chloroform solvate (Form VI) were prepared.

Recrystallisation from both ethanol and iso-propanol produced Forms 0 and II. Although Form 0 desolvated prior to analysis, thus no longer contained the recrystallisation solvent, these crystals retained the structure of the solvated Form 0.

Form 0 was recrystallised from n-propanol, n-butanol, dioxane and dichloromethane.

Forms 0, I, III, V and VI all transformed into the thermodynamically more stable Form II, after storage at room conditions.

The dissolution results, relating to chloroform recrystallisation, showed that desolvation can improve the dissolution rate, since the chloroform solvate had a poor dissolution performance (61% after 30 minutes), whilst the desolvated form was almost completely dissolved within 30 minutes (96%), in the 0.1 M sodium acetate buffer.

Uittreksel

Klaritromisien is 'n 14-lid, ring-makrolied antibiotikum, en 'n derivaat van eritromisien. Klaritromisien word algemeen vir die behandeling van bakteriële infeksies, soos kroniese boonste - en onderste - respiratoriese -, vel - en sagte weefsel -, sowel as vir gastroïntestinale (duodenale ulkusse, veroorsaak deur *H. pylori*) infeksies gebruik.

Tydens hierdie studie is polimorfiese en pseudopolimorfiese vorme geëvalueer en gekarakteriseer, deur van tegnieke, soos x-straal poeierdiffraktometrie, infrarooi-spektrofotometrie, differensiële skanderingskalorimetrie, termogravimetriese analise en termiese mikroskoskopie gebruik te maak.

Beskikbare literatuur het Vorm 0, 'n solvaat; Vorm I, 'n metastabiele polimorf; Vorm II, 'n termodinamies meer stabiele polimorf; Vorm III, 'n solvaat (uit asetonitriel) en 'n amorfe Vorm IV beskryf.

Klaritromisien is deur middel van 'n stadige rekristallisasie-metode uit verskeie oplosmiddels gerekristalliseer. Die termodinamies meer stabiele Vorm II is uit asetoon, metanol, benseen, dimetielformamied en tetrahidrofuraan gerekristalliseer. Rekristallisasies vanuit asetonitriel het, in teenstelling met die literatuur, nie Vorm III opgelewer nie, maar wel Vorm II. Twee nuwe vorme, naamlik Vorm V vanuit etielasetaat, en 'n chloroform-solvaat, Vorm VI, is ook tydens hierdie studie berei.

Rekristallisasies vanuit beide etanol en isopropanol het elk Vorm II, sowel as die gedesolveerde solvaat, Vorm 0, opgelewer. Alhoewel Vorm 0 alreeds voor analise gedesolveer het, dus die rekristallisasie oplosmiddel verloor het, het hierdie kristalle die struktuur van die gesolveerde Vorm 0 behou.

Vorm 0 is vanuit n-propanol, n-butanol, dioksaan en dichloormetaan gerekristalliseer.

Vorms 0, I, III, V en VI het na blootstelling van die kristalle aan standaardtemperatuur en standaarddruk (STD) toestande, na die termodinamies meer stabiele Vorm II omgeskakel.

Die dissolusie-resultate rakende chloroform rekristallisasie het getoon dat desolvering die dissolusie-tempo kan verbeter, aangesien die chloroform-solvaat swak gedissoleer het (61% na 30 minute), terwyl die gedesolveerde vorm byna volledig binne 30 minute opgelos het (96%), in die 0.1 M natrium-asetaatbuffer.

Die dissolusie-resultate het goeie dissolusie-profiele vir meeste van die vorme getoon.

Aims and Objectives

Identification and Evaluation of Different Clarithromycin Polymorphic Forms

Clarithromycin, the semi-synthetic derivative of erythromycin, is used in the treatment of certain infections (caused by bacteria), such as ear -, lung -, gastric -, skin - and throat infections. Since clarithromycin has been introduced as a measure of prevention and treatment of *Mycobacterium avium* infections in patients with AIDS, the need for cost effective generics has become essential.

A literature search revealed five patents that had been registered on clarithromycin, which included the solvated Forms 0 and III, a metastable Form I, a thermodynamically more stable Form II and an amorphous Form IV. Since these patents were not very informative with regards to the physico-chemical properties of these polymorphic forms, it was decided to investigate the different polymorphic forms of clarithromycin.

The following study objectives were set and pursued:

- A literature search to investigate and identify the physico-chemical properties of the different polymorphic forms described in the patents;
- The preparation of different clarithromycin crystal forms through recrystallisation from various solvents;
- The characterisation of the different crystal forms as either polymorphs, or pseudopolymorphs, according to their physico-chemical properties, using a representative set of analytical techniques; and
- The determination of the dissolution profiles of some selected crystal forms.

It was hoped that the characterisation and evaluation of the various clarithromycin polymorphic forms would aid in providing a better understanding of the solid-state properties of this macrolide antibiotic.

An attempt was also made during this study to establish a more comprehensive set of guidelines to the pharmaceutical industry that would aid in selecting the best form of clarithromycin to be used in manufacturing.

The outcomes of this study also aimed at identifying and describing those analytical methods that could be used for the identification of the selected raw materials.

These objectives were chosen, since only an understanding of the behaviour and the solid-state properties of drugs would lead to the implementation of acceptable methods that would ensure safe and effective dosage forms.

5.4 Conclusion

The results relating to chloroform recrystallisation showed that desolvation can improve the dissolution rate, since the chloroform solvate had a poor dissolution performance (61% after 30 minutes), whilst the desolvated form was almost completely dissolved within 30 minutes (96%), in the 0.1 M sodium acetate buffer. Hence, the dissolution profiles differed significantly, as illustrated by the similarity factor of 20.45 for the chloroform solvated and desolvated forms.

The dissolution results showed good dissolution profiles for most of the samples. All of the Form II samples showed good dissolution values without significant differences.

The dissolution profiles of the clarithromycin crystals that were recrystallised from acetone, dichloromethane (desolvated) and chloroform (desolvated), showed similar dissolution profiles ($100 < f_2 > 50$), when compared to that of the raw material, Form II.

A comparison of the chloroform solvate and dichloromethane solvate with the raw material, Form II, showed significant differences in their dissolution profiles, as illustrated by the similarity factors of 17.17 and 37.48, respectively.

The dissolution profiles of the dichloromethane solvated and desolvated forms also showed similarities ($f_2 = 53.97$).

Chapter 6

Summary and Conclusion

The solid-state properties of pharmaceutical compounds, including polymorphic forms, solvates and salt formations, may have a profound impact on their solubility and stability (Huang & Tong, 2004:332). It is important to keep these influences of polymorphism on solid-state properties, as well as the influences of such properties on pharmaceutical dosage forms in mind, when manufacturing generic products. The application of these basic physico-chemical principles, combined with appropriate analytical methodology, may provide a strategy for scientific and regulatory decisions relating to solid-state behaviour (Byrn *et al.*, 1995:945).

The flow chart on page 148 (figure 6.1) summarises the objectives and outcomes of this study.

In the first chapter of this study, the influences of polymorphism and pseudopolymorphism on the solid-state properties of drugs were discussed. Continuous evaluation of a pharmaceutical formulation, during both the manufacturing process and the storage thereof, thus monitoring the quality and stability of the polymorphic form in the formulation, is extremely important in assuring safe and effective drugs.

Chapter 2 described the physical properties of clarithromycin, a 14-membered-ring, macrolide antibiotic, and a derivative of erythromycin. It was said that its spectrum of activity and its clinical uses are very similar to those of erythromycin, but that its absorption is more consistent, whilst it also has a longer half-life.

Since different polymorphs have different physical properties, which may influence the stability and bioavailability of active pharmaceutical compounds, it was necessary in this study to evaluate the recrystallised clarithromycin crystal forms, for the possible occurrence of polymorphism. The purpose of chapter 3 thus was to describe a set of representative analytical techniques that may be used to evaluate the physico-chemical properties of different crystals forms.

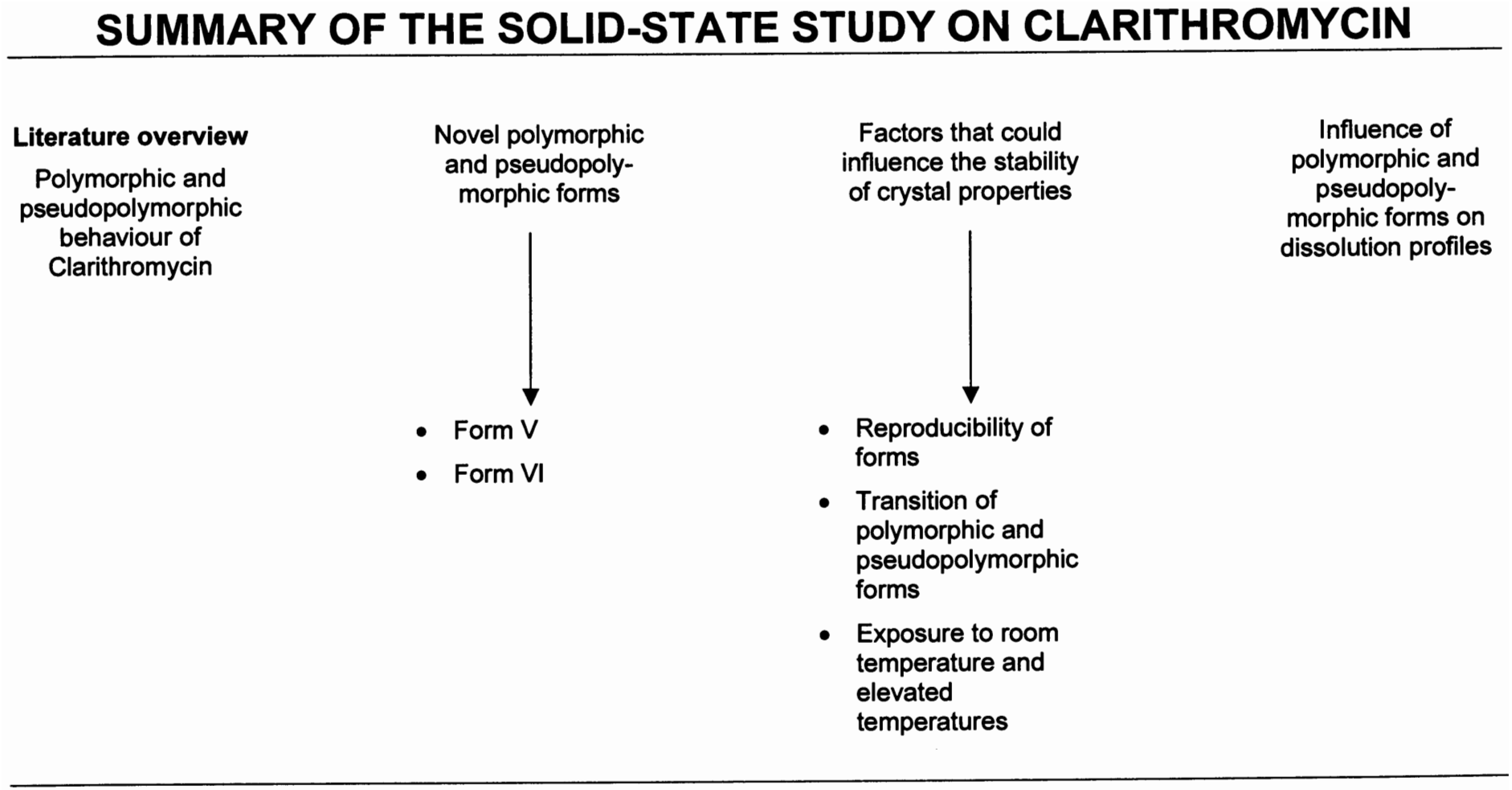

Figure 6.1 Summary of the solid-state study on clarithromycin.

The clarithromycin polymorphic and pseudopolymorphic forms, as described in the literature, were the focus of Chapter 4. Emphasis was thus placed on the basic knowledge available regarding the solid-state properties of clarithromycin, and an integrated characterisation strategy was implemented to broaden the understanding of clarithromycin's properties.

Clarithromycin is reported to have at least 5 polymorphic modifications, i.e. Form 0, a solvate which is converted into Form I, by removing the solvent from the crystal lattice; Form II, which can directly be isolated through recrystallisation from organic solvents, or by heating Form I crystals; Form III, an acetonitrile solvate and Form IV, an amorphous polymorph.

The reproducibility of some clarithromycin polymorphic and pseudopolymorphic forms was found to be inconsistent, for example, Form II was prepared from solvents usually producing Form 0, whereas the recrystallisation of Form III from acetonitrile was unsuccessful.

All the clarithromycin forms that were recrystallised in this study, transformed into the thermodynamically stable Form II, after a period of storage at room conditions.

The recrystallisation of clarithromycin from ethyl acetate produced a new polymorphic Form V.

After approximately six months of storage at room conditions, Form V transformed into the thermodynamically more stable Form II.

The clarithromycin crystals that were recrystallised from chloroform, showed some XRPD peaks correlating with those of the solvated Form 0. However, also peaks distinctive to the new Form VI that was recrystallised in this study, were present. The IR, DSC and TGA results confirmed a chloroform solvate.

The solvated forms that were recrystallised from n-propanol, n-butanol and dioxane, directly transformed into Form II upon desolvation at room conditions. Dichloromethane, however, showed a partial transformation of Form 0 into Form I, with only a fraction of Form I transforming into Form II, thus resulting in a mixture of Forms 0, I and II upon desolvation at room conditions.

Clarithromycin crystals that were recrystallised from ethanol and iso-propanol, upon desolvation at room conditions, retained the structure of the solvated Form 0, hence producing desolvated solvates.

In order to evaluate the effect of polymorphic orientation on the dissolution profile (extent and rate) of clarithromycin, six powder samples were chosen for dissolution testing, and the outcome of this study was described in Chapter 5. The crystal forms chosen, included the commercially available clarithromycin raw material (Form II), Form II crystals recrystallised from acetone, the dichloromethane solvated Form 0, the desolvated Form II, the chloroform solvated Form VI and the desolvated Form II.

The results relating to chloroform recrystallisation, showed that desolvation can improve the dissolution rate, since the chloroform solvate had a poor dissolution performance (61% after 30 minutes), whilst the desolvated form was almost completely dissolved within 30 minutes (96%), in the 0.1 M sodium acetate buffer. Hence, the dissolution profiles of the chloroform solvated and desolvated forms differed significantly, as illustrated by their similarity factor of 20.45.

The dissolution results showed good dissolution profiles for most of the samples. All of the Form II samples showed good dissolution values, without significant differences.

The dissolution profiles of the clarithromycin crystals that were recrystallised from acetone, dichloromethane (desolvated) and chloroform (desolvated), showed similar dissolution profiles ($100 < f_2 > 50$), when compared to that of the raw material, Form II.

A comparison of the chloroform solvate and dichloromethane solvate with the raw material, Form II, showed significant differences in their dissolution rates, as illustrated by the similarity factors of 17.17 and 37.48, respectively.

The dissolution profiles of the dichloromethane solvated and desolvated forms also showed similarities ($f_2 = 53.97$).

To conclude, important parameters for characterisation of polymorphic forms were investigated during this study, in order to determine and clarify the solid-state stability and transformation of clarithromycin polymorphic and pseudopolymorphic crystal forms.

Although literature described five polymorphic forms of clarithromycin, few of the patents presented an adequate classification strategy, such as XRPD -, IR -, DSC – and / or TGA analyses . Hence, an opportunity for the development of a well-balanced set of analytical techniques, that would aid in investigating the solid-state properties of clarithromycin crystal forms, and that would provide a comprehensive frame of reference for the pharmaceutical industry, existed.

The outcomes of this study emphasised the need for a set of uniform classification standards. There is a growing need to employ minimum characterisation strategies and standard requirements regarding the sensitivity of apparatus, hence the validity of information, such as XRPD peak positions that are used during the characterisation process. These standards would assist pharmaceutical engineers in identifying and classifying the most suitable crystal form for use in pharmaceutical manufacturing.

The importance of reproducibility also needs to be emphasised, since it frequently happens that a certain polymorphic form occurs once and may not necessarily be easily reproduced. Since the use of a metastable form may lead to changes in the stability of a dosage, the thermodynamically more stable Form II, would be preferred for use during the manufacturing of clarithromycin dosage forms.

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Annexure 1

Poster presented

Characterisation of Different Clarithromycin Polymorphic and Pseudoploymorphic Crystal Forms.

25th Academy of Pharmaceutical Sciences Annual Meeting : Grahamstown, South Africa.

September 2004.

The Characterisation of Different Clarithromycin Polymorphic and Pseudopolymorphic Crystal Forms

M. de Jager[1], W. Liebenberg[1], M. Brits[1]

[1] Research Institute for Industrial Pharmacy, School for Pharmacy, North-West University, Potchefstroom Campus, Potchefstroom, 2520, South Africa.

Purpose

To prepare different crystal forms of clarithromycin from organic solvents by recrystallisation, and to determine the physico-chemical properties of these different crystal forms.

Background

Clarithromycin is a 14-membered ring macrolide antibiotic - a derivative of erythromycin, with a similar spectrum of activity and clinical uses, but with a more consistent absorption and a longer half-life. [1]

Methods

Clarithromycin raw material was recrystallised from acetone, methanol, ethanol, n-propanol, iso-propanol, n-butanol, DMSO, THF, DMF, ethyl acetate, chloroform, ACN, benzene, dioxane, ethanol-water mixture (50:50). Various analytical techniques used to characterise the different polymorphic forms of clarithromycin included: DSC (Shimadzu DSC-50), TGA (Shimadzu TGA-50), IR (Nicolet Nexus 470-FT-IR spectrometer), XRPD (Bruker D8 Advanced diffractometer) and TM (Nikon thermomicroscope).

Results

The literature[2-4] describes Forms 0, I, II, III and IV as follows: Form 0 a solvate, Form I a metastable form, Form II the stable form, Form III an acetonitrile solvate and Form IV as amorphous. Drugs currently on the market are formulated from the thermodynamically more stable Form II. Therefore, preparation of the current commercial entity requires converting the Form I crystals into Form II.

Crystals recrystallised from dioxane showed definite similarities to those of the Form 0 as described in the literature. Acetone, ethanol, ethanol-water mixture (50:50), ethyl acetate and THF produced crystals similar to those of the described Form II.

According to TGA and DSC results it seemed that recrystallisation from chloroform produced crystal forms representative of a chloroform solvate. The XRPD patterns of the chloroform solvate confirmed that it differed from the published solvates, Forms 0 and III.

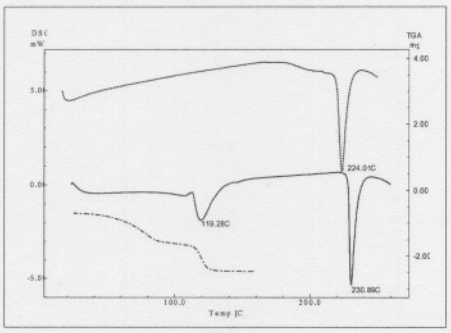

Figure 1: Overlay of DSC thermograms: Form II (red) and $CHCl_3$ solvate (blue). TGA thermogram (blue dotted line) of the chloroform solvate indicating a weight loss of 20.274%.

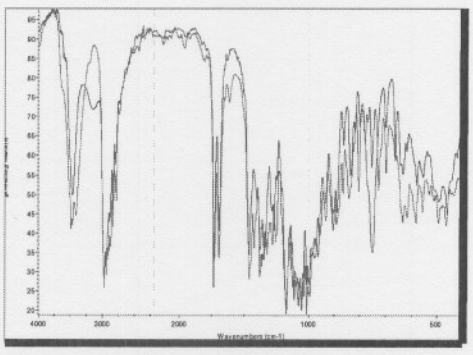

Figure 2: Overlay of IR-spectra: Form II (red) and $CHCl_3$ solvate (blue).

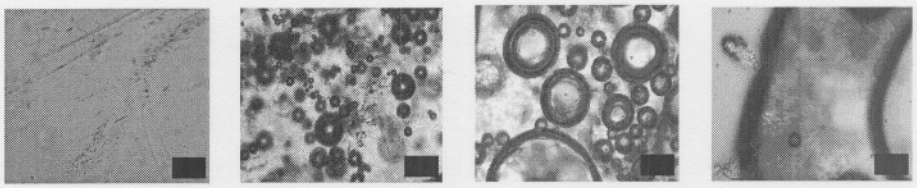

Figure 3: TM images of the chloroform solvate submerged in silicon oil, indicating the desolvation process at various temperatures: (A) 30°C, (B) 119°C, (C) 145°C, (D) Melting process.

Table 1: XRPD peak-list for Form 0[2], $CHCl_3$ solvate & Form III[4] for the range: 3 – 25 °2θ.

Form 0	$CHCl_3$ solvate	Form III
4.60	4.56	
6.50	6.49	
7.60		
	9.09	9.05
9.20	9.83	9.14
10.20	10.09	
11.00	10.92	
11.60	11.59	
	11.80	11.80
12.50	12.44	12.17
	13.02	
13.80	13.65	
14.80	14.75	
	15.07	15.28
	15.86	
		16.04
	16.25	16.55
17.00	16.88	
	17.09	17.70
	17.93	
18.20	18.24	18.17
	18.77	18.79
19.50	19.73	
	20.28	
	20.81	
	21.81	
	22.43	
	22.83	
23.10	23.35	
	23.71	
24.00	24.25	24.94

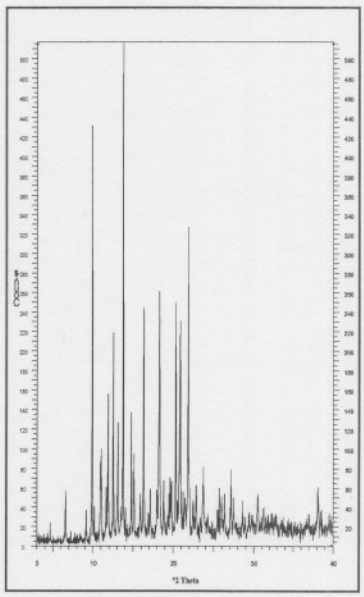

Figure 4: XRPD pattern of the chloroform solvate.

Conclusion

Apart from the published solvates, i.e. Forms 0 and III (from acetonitrile) as described in literature, a chloroform solvate with different physico-chemical properties were prepared and characterised according to differences shown in the DSC, TGA, IR and XRPD results.

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3. Liu, J.; Riley, D.A., Preperation of crystal form II of clarithromycin. US 5,844,105, December 1, 1998.
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5. Structural formula of clarithromycin obtained from: www.dragonpharm.com, 19 August 2004.

YUNIBESITI YA BOKONE-BOPHIRIMA
NORTH-WEST UNIVERSITY
NOORDWES-UNIVERSITEIT

Potchefstroom Campus

Annexure 2

Concept article

to be submitted for publication

Characterisation of two new crystal forms

of clarithromycin

CHARACTERISATION OF TWO NEW CRYSTAL FORMS OF CLARITHROMYCIN

M de Jager, M Brits & W Liebenberg

Research Institute for Industrial Pharmacy, North-West University, Potchefstroom Campus, Potchefstroom, 2520, South Africa.

INTRODUCTION

Clarithromycin, a 14-membered-ring, macrolide antibiotic, is a derivative of erythromycin. Its spectrum of activity and its clinical uses are very similar to those of erythromycin, but its absorption is more consistent, whilst it also has a longer half-life (Dollery, 1999:C248).

Clarithromycin is reported to have at least 5 polymorphic modifications, U.S. Patent Numbers 5,945,405 (Form 0); 5,858,986 (Form I); 5,844,105 (Form II); 6,627,743 B1 (Form III) and 6,599,884 (Form IV).

These forms can be summarised as: Form 0, a solvate, which is converted into Form I by removing the solvent from the crystal lattice; Form II which can be isolated directly through recrystallisation with organic solvents or by heating the crystals of Form I; Form III, an acetonitrile solvate; and Form IV, an amorphous polymorph.

The Merck Index (2001:408) reports a melting point of 222-225°C for clarithromycin (crystals from ethanol) and a melting point of 217-220°C for needles recrystallised from a chloroform and diisopropyl ether mixture.

The aim of this study was to prepare and characterise novel polymorphic forms.

EXPERIMENTAL

Methods of preparation

In this study, clarithromycin raw material was recrystallised from a number of solvents. The raw material that was used in this study was obtained from Teva (Tech *Ltd.* control no. 376100102). Saturated solutions of clarithromycin powder were prepared in various solvents. These saturated solutions were prepared in

glass polytops, by heating each solvent close to its boiling point, whilst stirring continuously with a magnetic stirrer and slowly adding the clarithromycin powder.

The polytops were then sealed with perforated plastic caps, allowing the solvent to slowly evaporate at room temperature. The results that were obtained will be described in the following section, according to the different solvents used.

X-Ray Powder Diffractometry (XRPD)

The X-ray powder diffraction (XRPD) profiles were obtained at room temperature with a Bruker D8 advance diffractometer (Bruker, Germany). The measurement conditions were: target, Cu: K_β -filter, Ni; voltage, 40 kV; current, 30 mA; divergence slit, 2 mm; anti scatter slit, 0.6 mm; detector slit, 0.2 mm; scanning speed, 2°/min (step size 0.025°; step time, 1.0 sec). Approximately 200 mg of sample was loaded into an aluminium sample holder, taking care not to introduce a preferential orientation of the crystals.

Thermal Analysis

Differential scanning calorimetry (DSC) thermograms were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan). Samples weighing approximately 3-5 mg were heated in closed aluminium crimp cells, at a rate of 10°C/minute, under nitrogen gas flow of 35 mL/minute.

Thermogravimetric (TGA) thermograms were recorded with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan). The sample weight was approximately 5-8 mg and a heating rate of 10°C/minute, under nitrogen gas flow of 35 mL/minute, was used.

Infrared Spectrophotometry (IR)

IR spectra were recorded on a Nicolet Nexus 470-FT-IR spectrometer, over a range of 600 - 4000 cm^{-1}. The diffuse reflectance method was used.

Scanning electron microscopy (SEM)

Photomicrographs of the possible clarithromycin polymorph crystal forms were obtained with a Philips XL 30 Scanning electron microscope (Philips, Netherlands). The samples were adhered to a small piece of carbon tape, mounted on a metal stud and coated with a gold-palladium film (Eiko Engineering ion Coater IB-2).

RESULTS AND DISCUSSION

The crystals that were recrystallised from ethyl acetate were characterised and identified. These crystals recrystallised from ethyl acetate showed a unique XRPD pattern, compared to the forms reported in literature, and was hence identified as the following form in the existing nomenclature, i.e. Form V. Although the XRPD pattern of these crystals showed significant differences, the IR spectrum did not show any differences when compared with that of Form II. The melting point as determined from DSC analysis, was recorded as 223°C. After approximately six months at room conditions, Form V transformed into the thermodynamically more stable Form II. The diffraction XRPD pattern of Form V is shown in figure 1.

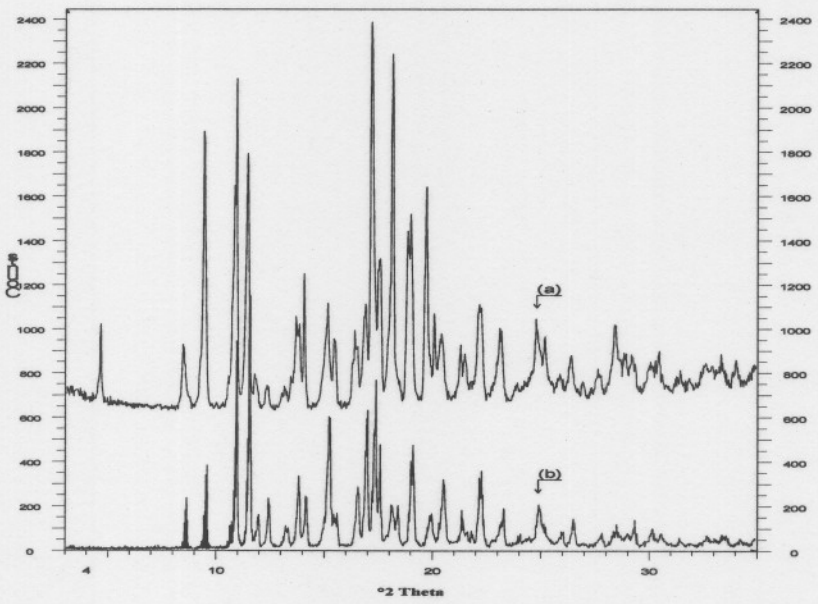

Figure 1 An overlay of the XRPD patterns of clarithromycin crystals recrystallised from ethylacetate: (a) Form V and (b) Form V after 6 months.

The powdered sample (Form V) was dispersed in KBr and its DRIFTS was recorded (Figure 2).

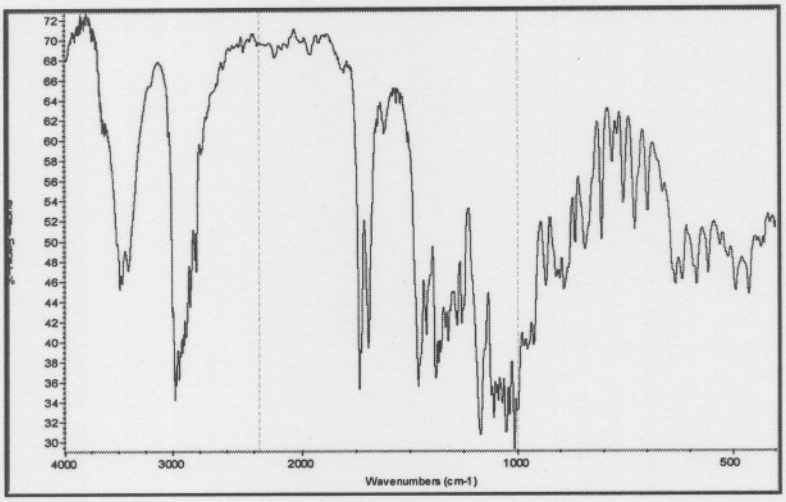

Figure 2 The IR spectrum of clarithromycin crystals recrystallised from ethyl acetate (Form V).

Approximately 2-5 mg of the crystals were weighed into an aluminium crimp cell and sealed. The DSC thermogram was recorded, which showed a melting endotherm at a temperature of 223.66°C (figure 3).

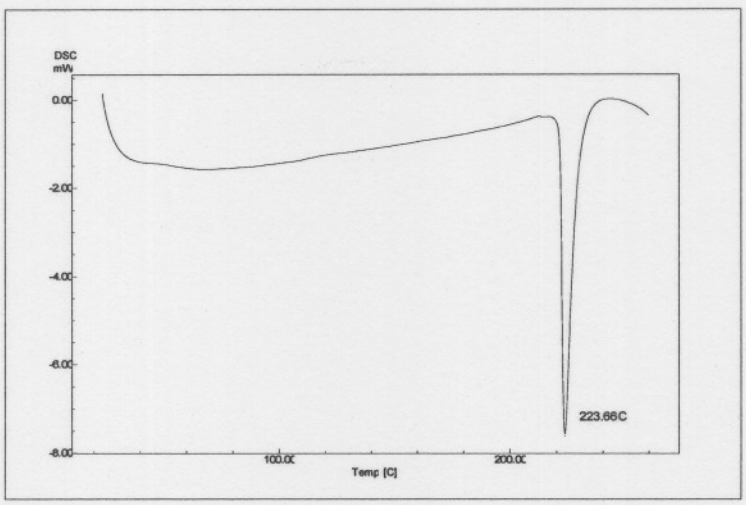

Figure 3 The DSC thermogram of clarithromycin crystals recrystallised from ethyl acetate (Form V).

The SEM photomicrograph of Form V (figure 4) showed shapeless crystals of varying shapes and sizes.

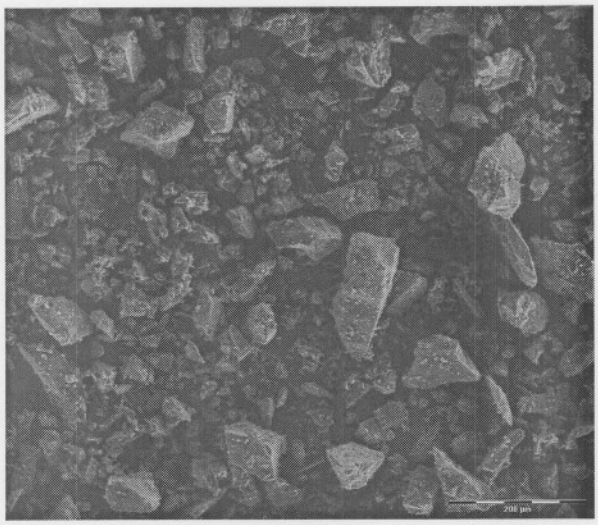

Figure 4 SEM photomicrograph of clarithromycin Form V recrystallised from ethyl acetate.

The crystals obtained from chloroform through slow recrystallisation showed some XRPD peaks that correlated with those of the solvated Form 0. Some of the XRPD peaks, however, also showed peaks distinctive of a new form that was classified during this study as Form VI. The IR, DSC and TGA results confirmed a chloroform solvate. This characterisation and identification of these crystals were done according to the characterisation methods.

The XRPD patterns were recorded on the powdered samples of the crystals that were recrystallised from chloroform. The majority of XRPD peaks showed resemblances to both the solvated Forms 0 and III, as described in literature. However, there were also peaks present that suggested a new crystal form not yet reported in the literature, i.e. Form VI (figure 5).

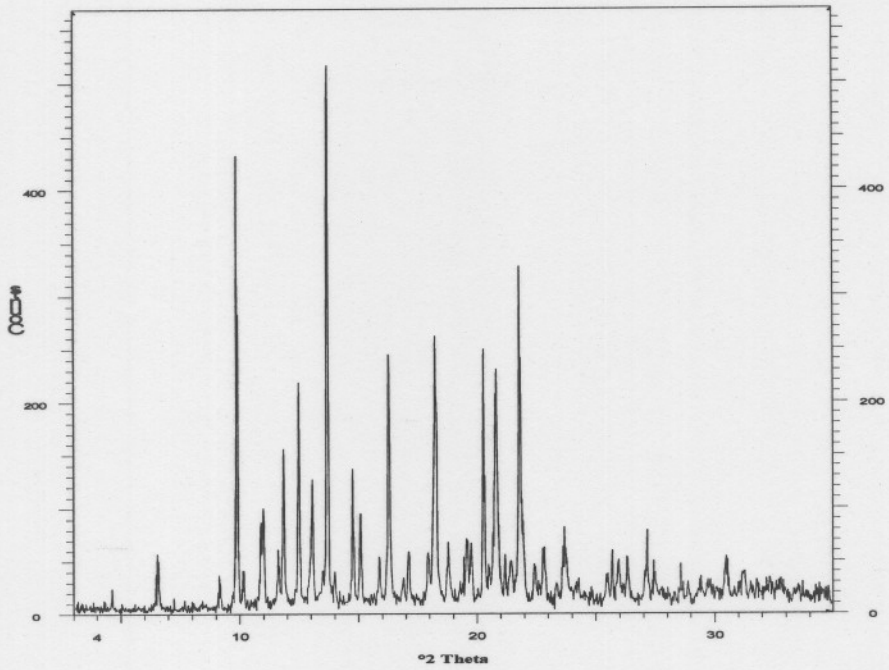

Figure 5 The XRPD pattern of clarithromycin crystals recrystallised from chloroform.

Crystals that were recrystallised from chloroform were powdered, dispersed in KBr and the DRIFTS recorded. The IR spectrum showed similarities to that of Form I (figure 6).

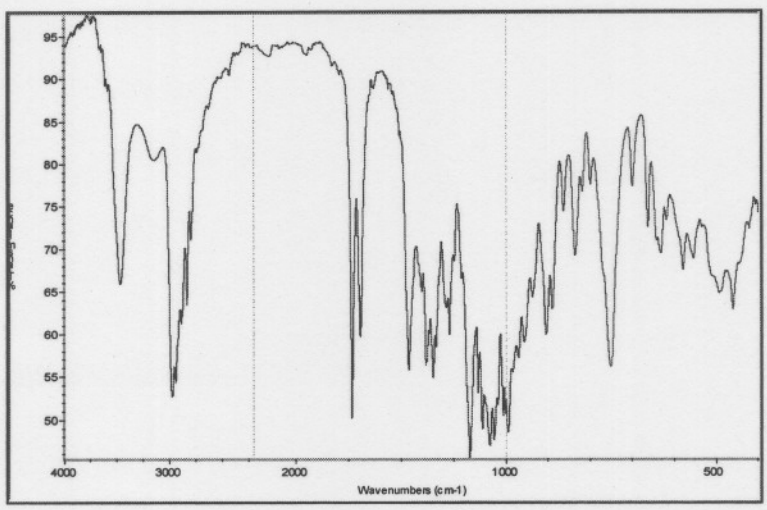

Figure 6 The IR spectrum of clarithromycin crystals recrystallised from chloroform.

Approximately 2-5 mg of the crystals that were recrystallised from chloroform were weighed into an aluminium crimp cell and sealed. The sample was heated at a rate of 10°C/min, under a nitrogen purge of 35 ml/min. These crystals showed an exotherm at 112.50°C, a desolvation endotherm at 119.28°C, a small endotherm at 146.09°C and a melting endotherm at a temperature of 230.89°C, as illustrated in figure 7. The TGA thermogram showed a weight loss of 13%, indicating a chloroform solvate, thus correlating well with the theoretical weight loss of a chloroform solvate of 13.75%.

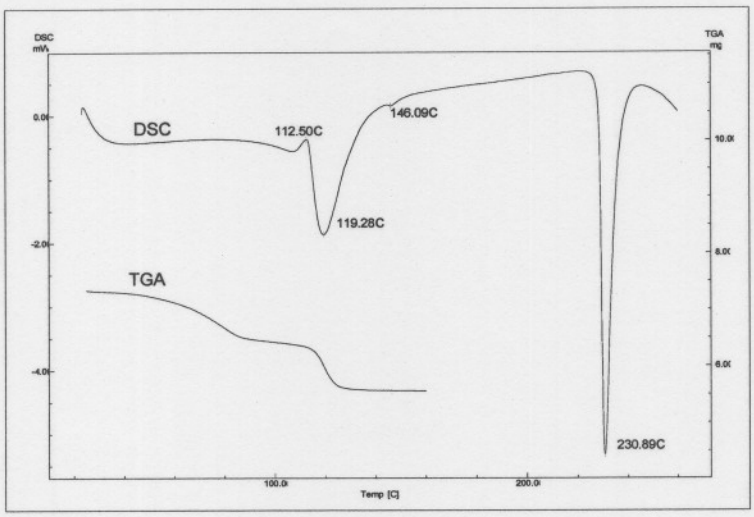

Figure 7 DSC and TGA thermograms of clarithromycin crystals recrystallised from chloroform.

The SEM photomicrograph (figure 8) of crystals obtained through recrystallisation from chloroform (chloroform solvated Form VI) showed shapeless crystals, varying in shapes and sizes.

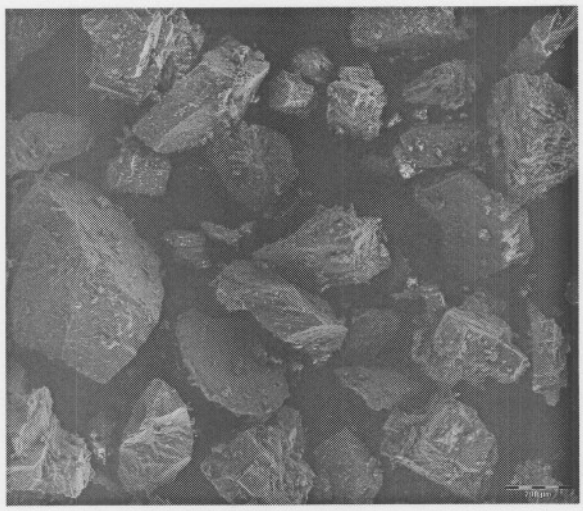

Figure 8 SEM photomicrograph of the clarithromycin chloroform solvate.

The recrystallisation from chloroform produced a new solvated form, Form VI. This form had a melting point of 230°C, somewhat higher than that of the other forms. The DSC and TGA results confirmed the presence of a solvate, and the IR spectrum was comparable to that of Form I, except for the broad "shoulder" in the region of 3060-3270 cm^{-1}.

CONCLUSION

Different solvents were used for the recrystallisation study of clarithromycin. Two new forms were prepared, i.e. a new polymorphic form from ethyl acetate, Form V, and a chloroform solvate, Form VI.

These new forms were characterised, using spectral and thermal methods. The existence of solvates was also confirmed with thermal microscopy.

Although IR may be used as a method for the identification of clarithromycin, it was not an effective method of characterisation for distinguishing between the various polymorphic and pseudopolymorphic crystal forms of clarithromycin. Contrary, XRPD proved to be an effective method of differentiation.

AVRUTOV, I., LIFSHITZ, I., BOROCHOVITZ, R., MASARWA, B. & SCWARTZ, E. 2003. Process for preparing clarithromycin polymorphs and novel polymorph IV. United States Patent. Patent Number : 6,599,884.

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