The physico-chemical properties of spiramycin and clarithromycin

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B. Pharm

Dissertation submitted in partial fulfilment of the requirements for the degree *Magister Scientiae* in Pharmaceutics at the Potchefstroom Campus of the North-West University

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November 2012

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Abstract

The physico-chemical properties of spiramycin and clarithromycin

In most cases, organic materials exist in the solid phase as polymorphs, solvatomorphs or amorphous forms. Physico-chemical properties in the solid-state are all affected primarily in terms of dissolution, solubility, bioavailability, stability and processability. Therefore investigation into the polymorphic behaviour of APIs has become a mandatory part of drug characterisation studies by pharmaceutical companies (Giron, 2001).

The influence polymorphism has on bioavailability and the need for the development of drugs in the amorphous form have instigated regulatory bodies such as the FDA to require solid-state characterisation of pharmaceuticals (Strachan *et al*., 2005). Subsequently a study was conducted to determine the physico-chemical properties of two poorly water-soluble macrolides; clarithromycin and spiramycin. Characterisation methods included: XRPD, IR, TGA, DSC, SEM, Karl Fischer titration, solubility and stability studies.

Recrystallisations of spiramycin from various solvents indicated that this API mainly exists in the amorphous form. The DSC proved to be of little value in the characterisation of this particular macromolecular antibiotic, since wide inter-sample variations were mostly obtained. TGA results showed higher solvent uptake than expected. This was ascribed to the amorphous, sponge-like character of this drug.

For the sake of reproducibility and quality of the results, characterisation of spiramycin was more reliant on spectroscopic and crystallographic methods. Samples generated from 2-butanol, chloroform, ethyl acetate, 1.4-dioxane, methanol, *n*-propanol, iso-propanol and tetrahydrofuran showed characteristic peaks in the range of 2000-2400 cm^{-1} that were not present in the IR spectrum of the raw material. Conversely, the XRPD patterns were all

identical, exhibiting a characteristic “halo” pattern with no detectable Bragg diffraction peaks. A solubility assessment showed no significant differences between the raw material and the recrystallisation products. In fact the raw material seemed to be the form with the highest solubility, albeit it only by a small margin.

According to the literature, clarithromycin exists in five forms. Form 0 exists as a solvate, form I is a metastable form, form II is the stable form (Liu & Riley 1998; Deshpande *et al.,* 2006), form III is a solvate of acetonitrile (Liu *et al.,* 2003; Liang & Yao, 2008) and form IV is a hydrate (Avrutov *et al.,* 2003). The stable form II is used in formulations currently on the market.

A follow-up study was done relating to a study performed by De Jager (2005). The raw material (form II) was recrystallised from acetonitrile, chloroform and ethyl acetate.

Two new crystal forms were prepared from chloroform and acetonitrile. With the necessary driving force, both of these crystals forms are able to convert to the thermodynamically stable form II. In addition, a solvate recrystallised from chloroform together with its corresponding desolvate, showed a 4 and 1.5 fold respective increase in solubility when compared to the raw material.

The recrystallisations from ethyl acetate delivered crystals with an XRPD pattern similar to form II. This proved that clarithromycin can be recrystallised directly from this solvent without the need of an additional conversion step, as was the case in the study done by De Jager (2005).

Key words: polymorphism, macrolides, solvatomorphs, amorphous, solubility.

Uittreksel

Die fisies-chemiese eienskappe van spiramisien en klaritromisien

Organiese stowwe bestaan in die algemeen in die soliede vorm as polimorfe, solvate of amorfe. Die fisies-chemiese eienskappe word primêr beïnvloed in terme van dissolusie, oplosbaarheid, biobeskikbaarheid, stabiliteit en vervaardigbaarheid. Die bestudering van die polimorfe gedrag van aktiewe bestanddele maak daarom deeluit van die roetine-ondersoek deur farmaseutiese maatskappye gedurende karakteriseringstudies (Giron, 2001).

Die invloed wat polimorfisme het op biobeskikbaarheid en die toenemende aanvraag na amorfe geneesmiddels, het regulatoriese instansies soos die FDA genoodsaak om karakterisering van die soliede vorm van farmaseutiese middels te vereis (Strachan *et al*., 2005). Gevolglik is ŉ studie uitgevoer om die fisies-chemiese eienskappe van twee swak wateroplosbare makroliede te bepaal. Die karakteriseringsmetodes het ingesluit: XRPD (x-straalpoeierdiffraksie), IR (infrarooispektroskopie), TGA (termogravimetriese analises), DSC (differensiële skanderingskalorimetrie), SEM (skanderingelektronmikroskopie), Karl Fischer-titrasie, oplosbaarheid- en stabiliteitstudies.

Rekristallisasies van spiramisien vanuit verskeie oplosmiddels het aangedui dat hierdie middel hoofsaaklik in die amorfe vorm bestaan. Die feit dat groot variasies verkry is tussen monsters, het bewys dat die DSC nie ŉ geskikte karakeriseringsmetodeis vir hierdie spesifieke makro-molekulêre antibiotika nie. Die TGA-resultate het gedui op ŉ boverwagte hoeveelheid vasgevangde oplosmiddel. Dit kan toegeskryf word aan die amorfe, sponsagtige karakter van hierdie geneesmiddel.

Ter wille van herhaalbaarheid en die kwaliteit van die resultate het karakteriseringstudies meer staat gemaak op spektroskopiese en kristallografiese metodes. Monsters verkry vanuit 2-butanol, chloroform, etielasetaat, 1.4-di-oksaan, metanol, *n*-propanol, isopropanol

en tetrahidrofuraan het beduidende verskille getoon met die grondstof in die area tussen 2000-2400 cm^{-1} tydens die IR-bepalings. In teenstelling hiermee was daar geen verskille wat die XRPD-patrone betref nie en ŉ karakteristieke “halo” patroon met geen Bragg-diffraksiepieke is verkry. ŉ Oplosbaarheidsbepaling het op geen noemenswaardige verskille gedui tussen die rekristallisasieprodukte en die grondstof nie. Inteendeel, uit die resultate lyk dit of die laasgenoemde effens meer oplosbaar is as die ander vorms.

Volgens die literatuur bestaan klaritromisien uit vyf vorms. Vorm 0 is ŉ solvaat, vorm I is ŉ metastabiele vorm, vorm II is die stabiele vorm (Liu & Riley*,* 1998; Deshpande *et al.,* 2006), vorm III is ŉ solvaat van asetonitriel (Liu *et al.,* 2003; Liang & Yao, 2008) en vorm IV is ŉ hidraat (Avrutov *et al.,* 2003). Die stabiele vorm, vorm II, is die vorm wat tans in formulerings op die mark verskyn.

ŉ Opvolgstudie is gedoen na aanleiding van ŉ studie gedoen deur De Jager (2005). Die grondstof (vorm II) was gerekristalliseer vanuit asetonitriel, chloroform en etielasetaat.

Twee nuwe kristalvorms is berei vanaf chloroform en asetonitriel. Met die nodige dryfkrag, kan beide hierdie kristalvorms oorskakel na die termodinamiese stabiele vorm. Voorts het die solvaat gerekristalliseer vanuit chloroform tesame met die ooreenstemmende desolvaat ŉ 4- en 1.5-maal dienooreenkomstige verhoogde oplosbaarheid getoon in vergelyking met die grondstof. Herkristallisasie vanuit etielasetaat het kristalle gelewer met XRPD-patrone soortgelyk aan vorm II. Dus kan die stabiele vorm direk vanaf etielasetaat gerekristalliseer word sonder die addisionele tussenstap wat benodig was in die studie deur De Jager (2005).

Sleutelwoorde: polimorfisme, makroliede, solvate, amorfe, oplosbaarheid.

Aims and Objectives

The physico-chemical properties of spiramycin and clarithromycin

Most pharmaceuticals in the solid phase are able to crystallise into more than one crystal form. While many others exist in either a partially or entirely disordered or amorphous state. It is therefore crucial to have knowledge of the physico-chemical concepts underpinning the behaviour of these systems (Craig *et al*., 1999).

Clarithromycin is a semi-synthetic 6-*O*-methyl derivative of erythromycin with a better pharmacokinetic profile, fewer gastro-intestinal side-effects, increased acid stability and bioavailability (Rodvold, 1999; Amini & Ahmadiani, 2005). Its approval in the treatment of *Mycobacterium avium* infection in patients with acquired immunodeficiency syndrome (AIDS) is another major advantage over the parent compound (Salem, 1996). Spiramycin, a 16-membered macrolide, has been effectively implemented in the treatment of toxoplasmosis in pregnant women (Rubinstein & Keller, 1998).

A drawback for both these macrolides however, is their poor water solubility profiles. The solubility of the API has a direct influence on its bioavailability and can often be the rate limiting factor in dissolution and oral absorption. An investigation into the physico-chemical properties of the macrolide group would offer insight into the most appropriate form to be incorporated into the solid dosage form.

Subsequently the following objectives were set:

- Through the recrystallisation of the raw materials in various organic solvents, prepare different crystal forms and possibly find a novel crystal form with improved solubility characteristics.
- Preparing an amorphous form, with improved solubility and stability characteristics.

- Solid-state characterisation of all the obtained forms of each API in terms of its physico-chemical properties with special emphasis on the solubility and thermodynamic stability.
- Implementation of different analytical techniques to identify the obtained forms as being either polymorphs, solvates or amorphous.