The physico-chemical properties of the anti-tuberculosis drug ethionamide

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Abstract

Methods of recrystallisation from solution using various solvents as well as physical vapour deposition (PVD) methods were employed in an attempt to create different polymorphic forms of the anti-tuberculosis drug ethionamide.

Through recrystallisations a variety of products were obtained, though not a single form proved to be a different polymorphic form. A single form obtained from *N,N*-dimethylformamide (DMF) was proven to be a non-stoichiometric solvate through thermogravimetric (TGA) and infrared (IR) analyses. This clathrate showed improved water solubility in comparison with the raw material (RM), though the toxicological attributes of the solvent makes the product pharmaceutically non-applicable.

The physical vapour deposition methods used led to the formation of at least one novel polymorphic form, though the methods employed to isolate this form demonstrated some less than ideal results. The influence of variation in temperature and pressure proved to produce some varying patterns in the attributes of the products formed and the methods used were shown to deliver reproducible results. Thermal and diffraction analyses were utilised for the characterisation of the physico-chemical properties of the various forms obtained.

Tendencies of phase transitions occurring during the heating of the raw material, observed through differential scanning calorimetry (DSC), were explored and this method was used to identify possible phase transitions and the conditions needed to manipulate the sample into going through these transitions. Thermal microscopy (TM) in combination with polarised light microscopy was used to visualise the occurrences observed in the DSC traces. Sublimation of the RM and subsequent recrystallisation was observed and various methods were employed to manipulate this process.

The DSC traces of the various forms were investigated and compared to results obtained from the TM and crossed polarisers combination. The influences of the variable conditions used to create the various vapour deposition products were studied and patterns in properties altered by these variations, such as melting point, were identified. Variable temperature X-ray diffractometry (VTXRD) was used to verify whether the conclusions made were consequential of the alteration of the

molecular coordination found within the crystals. These results were not decisive, as the variation in heating rates used made comparison of the events seen in the DSC traces impossible. This is because the heating rates used proved to have an effect on the kinetics of the phase transitions occurring with these crystal structures. Another aspect thought to affect the results obtained through powder X-ray diffractometry (XRPD) and VTXRD was that the samples were milled in preparation for this method. The effect of milling on a specific form obtained was shown to alter the properties of this form in a way that indicated possible phase transitions induced by this method. Comprehensive characterisation of the molecular coordinations of the various forms obtained through the PVD methods was not achievable since these methods and the small crystal sizes rendered single crystal X-ray diffractometry (SCXRD) impossible.

The hypothesis was made that the various forms obtained were either different ratios of two polymorphic forms; each having a unique internal molecular packing arrangement or a mixture of various ratios of more than two separate polymorphic forms.

A presumed more stable form (i.e. a form having a higher melting point) was obtained on separate occasions. Isolation of this form was not accomplished, though not proven to be unattainable. Through optimisation of experimental conditions, it should be possible to prepare and isolate this solid-state form.

Uittreksel

Metodes van rekristallisasie vanuit verskeie oplosmiddels asook fisiese damp neerslag metodes was aangewend in die poging om verskillende polimorfiese vorms van die anti-tuberkulose middel, etionamied te berei.

Deur rekristallisasie is ŉ verskeidenheid produkte verkry, alhoewel nie ŉ enkele vorm ŉ nuwe polimorfiese vorm was nie. Termogravimetriese (TGA) en infrarooi (IR) analises het getoon dat ŉ enkele vorm verkry deur rekristallisasie vanuit *N,N*-dimetielformamied (DMF) ŉ nie-stoigiometriese solvaat is. Hierdie klatraat (gasheer-gas kompleks) het verbeterde water oplosbaarheid in vergelyking met die grondstof getoon, maar weens die toksisiteit van die oplosmiddel het hierdie produk geen moontlikheid vir farmaseutiese toepassing nie.

Die fisiese damp neerslag metodes wat gebruik was, het gelei tot die vorming van minstens een nuwe polimorfiese vorm, alhoewel die metodes gebruik om die vorm te isoleer, minder as ideale resultate getoon het. Die invloed van veranderinge in temperatuur en druk, het verskille in die eienskappe van die gevormde produkte veroorsaak. Die metodes het ook herhaalbare resultate gelewer. Termiese en diffraksie analises was aangewend vir die karakterisering van die fisies-chemiese eienskappe van die verskeie vorms.

Die geneigdheid van fase veranderings om plaas te vind gedurende die verhitting van die grondstof, was ondersoek d.m.v. differensiële skanderingskalorimetrie (DSC). Die metode en kondisies wat die monster sodanig sal manipuleer om deur die fase oorgange te gaan, is ook ondersoek. Termiese mikroskopie (TM) in kombinasie met gepolariseerde lig mikroskopie was gebruik om die fase oorgange te visualiseer. Sublimasie van die grondstof en daaropvolgende rekristallisasie was waargeneem en verskeie metodes was aangewend om die proses te manipuleer.

DSC termogramme van die verskillende vorms was ondersoek en vergelyk met TM resultate. Gekruisde polarifilters is aangewend tydens die TM eksperimente. Die invloed van verskillende kondisies tydens fisiese damp neerslag eksperimente was bestudeer en patrone in die verandering van eienskappe soos smeltpunte, was geïdentifiseer. Variërende temperatuur X-straal diffraktometrie (VTXRD) was gebruik om te verklaar of die gevolgtrekkings gemaak die gevolg is van veranderinge in die

molekulêre koördinasie binne die kristalle. Die resultate was nie deurslaggewend nie weens die verskil in verhittingstempo tussen die DSC en VTXRD resultate, wat die resultate onvergelykbaar gemaak het. Die rede hiervoor is dat die verhittingstempo ŉ invloed het op die kinetika van fase oorgange wat plaasvind met hierdie kristalstrukture. Verder meer word monsters gemaal vir XRPD en VTXRD analises, wat sodoende ook die eienskappe van die monster gaan beïnvloed. Omvattende karakterisering van die molekulêre koördinasies van die vorms verkry deur die PVD metodes was nie haalbaar nie weens die feit dat die metodes en die klein kristal groottes enkelkristal X-straaldiffraktometrie (SCXRD) onmoontlik gemaak het.

Die hipotese was gemaak dat die verskeie vorms verkry, of verskillende verhoudings van twee polimorfiese vorms was; of elk ŉ unieke interne molekulêre koördinasie het, of ŉ mengsel van verskeie verhoudings van meer as twee afsonderlike polimorfiese vorms was.

ŉ Vermoedelike meer stabiele vorm (vorm met ŉ hoër smeltpunt) was verkry op afsonderlike geleenthede. Isolasie van die vorm was nie behaal nie. Deur optimalisering van die eksperimentele omstandighede behoort dit moontlik te wees om die vaste toestand vorm te berei en te isoleer.