DIDANOSINE AND LOPINAVIR:

NON-CONVENTIONAL SOLID-STATES

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To my parents, Hannes and Esther Lemmer, and my wife, Helanie.

Thank you for all your love and support.

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ABSTRACT

The physicochemical properties of several novel polymorphs and amorphous forms of the antiretroviral (ARV) agents, didanosine and lopinavir, are reported. The polymorphs were prepared from recrystallisation and the glasses from cooling of the melt. These products were then characterised by means of thermal, absorption and diffraction analyses and compared to the raw material for polymorphic differences.

Didanosine yielded recrystallisation products from methanol, ethanol, 1- and 2-propanol, 1-butanol and acetonitrile. Of all these, only the product obtained from methanol exhibited a powder x-ray diffraction (PXRD) pattern different from that of didanosine raw material. To investigate methanol's capacity to produce new polymorphs of didanosine, supersaturated solutions of didanosine in water were prepared and different amounts of methanol were added as antisolvent. The crystals hereby obtained, displayed macro- and microscopic morphologies similar to that of the crystals obtained from pure methanol, however, their infrared (IR) absorption spectra and PXRD diffractograms differed slightly from those of the raw material and the crystals obtained from methanol alone. All of didanosine's recrystallisation products from alcohols exhibited non-stoichiometric weight loss from the start of a thermogravimetric analysis (TGA), long desolvation times on hot stage micrographs and broad desolvation endothermic peaks on differential scanning calorimeter (DSC) thermograms. This lead to the conclusion that the solvent was not incorporated into channels, as is usually the case with solvates, but rather that it formed a thin film around the crystals and was present in the capillary network between the fine, elongated crystals. Upon drying the didanosine crystals from alcohols lost their morphologies and reverted back to the same polymorphic form as the raw material. The presence of solvent around the crystals was necessary for them to maintain their morphologies. This same metastability was observed upon storing of the recrystallisation products, where they started to revert back to the raw material even while under the recrystallisation medium. At around two weeks small bundles of powder formed on top of the mesh network of crystals and after one month only powder remained, analysis of this powder proved it to be the same polymorphic form as the raw material, indicating that the raw material is the most stable form of didanosine. Comparison between the results from the solubility study and scanning electron microscope (SEM) micrographs, showed an increase in solubility corresponding to a decrease in crystal size. The different crystal morphologies had no influence on the wettability or the acid lability of didanosine, a direct result of the film of solvent coating the crystals. Any liquid that came into contact with the crystals was automatically dispersed across its surface.

Lopinavir formed several recrystallisation products including large hexagonal plates from acetone, long hexagonal staffs from ethyl acetate, needles from diethyl ether and resins from chloroform and dichloromethane. Initial thermal analysis showed all the recrystallisation products, even the more crystalline ones, to be at least partially amorphous. For comparative purposes, two additional glasses were prepared from cooling of the melt. One was cooled at ambient temperature and the other was quench cooled using liquid nitrogen. Activation energies for β-relaxations (ΔE_β) and glass transitions were calculated from non-isothermal kinetics data obtained by DSC and from the activation energies for glass transition of each sample, the fragility (m) and strength (D) parameters of each sample were calculated. Comparisons between the ΔE_β and m were in excellent coherence to the macro- and microscopic characteristics of each sample and offered valuable insight into certain physical behaviour. The amorphous content of each sample was determined by means of DSC and Fourier transform infrared (FTIR) spectroscopy. Results from the solubility study exhibited little coherence with the crystalline/amorphous content of the samples analysed as well as with the m and D values. There was however, an inverse correlation between the solubility and the ΔE_β of each sample, suggesting that the increased local molecular motilities of the samples with low ΔE_β values (and the subsequent decrease of the contact angle), facilitated dissolution from these regions, leading to surface roughening and an increasing in effective surface area. The progression of this process, resulting from the ongoing coupling of the β-relaxations, eventually increased the solubility of the samples exhibiting the lowest ΔE_β values.

UITTREKSEL

Die fisies-chemiese eienskappe van verskeie nuwe polimorfe en amorfe vorme van die antiretrovirale (ARV) middels, didanosien en lopinavir, word gerapporteer. Die polimorfe is berei deur middel van rekristallisasie en die glase deur verkoeling van gesmelte grondstof. Die produkte hierdeur verkry was gekarakteriseer deur middel van termiese-, absorpsie- en diffraksie analises en vergelyk met die grondstof vir polimorfiese verskille.

Didanosien het rekristallisasie produkte gelewer uit metanol, etanol, 1- en 2-propanol, 1-butanol en asetonitriel. Van hierdie produkte het net dié verky uit metanol ‘n poeier x-straal diffraksie (PXSD) patroon getoon wat verskil van die van die grondstof. Om metanol se vermoë om nuwe polimorfe van didanosien te vorm verder te ondersoek is oorversadigde oplossings van didanosien in water voorberei en metanol is bygevoeg, in vergestelde hoeveelhede, as teenoplosmiddel. Die kristalle wat hierdeur verkry was het makro- en mikroskopies dieselfde vertoon as die kristalle verkry uit skoon metanol, maar met klein verskille in hul infrarooi (IR) absorpsie spektra en PXSD diffraktogramme relatief tot die grondstof en die kristalle verkry uit skoon metanol. Al didanosien se rekristallisasie produkte het nie-stoichiometriese gewigsverlies getoon vanaf die aanvang van verhitting tydens termogravimetriese analise (TGA), asook lang desolverings tye op termomikroskoop mikrograwe en breë desolverings endoterme op differensiaalskandeerkalorimeter (DSK) termogramme. Hierdie bevindinge het gelei tot die gevolgtrekking dat die oplosmiddel nie vasgevang of geïnkorporeer is in die kristalstruktuur van die polimorfe (soos wat gewoonlik die geval is met solvate) nie, maar eerder dat dit in die kapillêre netwerk tussen die lang, fyn kristalle en ook as ‘n dun film rondom die kristalle voorkom. Tydens droging het die didanosien kristalle, verkry uit alkohole, hul kristalvorm verloor en geheel en al teruggekeer na die grondstof. Die teenwoordigheid van oplosmiddel om en tussen die kristalle is nodig vir hierdie kristalle om hul kristalvorm te behou. Hierdie selfde metastabiele gedrag word ook geopenbaar as die kristalle toegelaat word om lank te staan in die rekristallisasie media. Na omtrent twee weke begin klein bondels poeier bo-op die kristalnetwerk vorm en na omtrent een maand is geen teken van kristalle meer oor nie. Analises van hierdie poeier het getoon dat dit dieselfde polimorf is as die grondstof. Vergelyking tussen die data verkry van die oplosbaarheidstudie en skandeer elektronmikroskoop (SEM) mikrograwe toon ‘n verhoging in oplosbaarheid met ‘n afname in kristalgrootte. Die verskillende kristalmorfologieë het geen invloed gehad op die benatting van die kristalle, en dus ook nie op die suurlabiliteit daarvan nie, as ‘n direkte gevolg van die oplosmiddel film rondom die kristalle. Enige vloeistof wat in kontak gekom het met die kristal was outomatiese gedispergeer oor die oppervlak.

Lopinavir het verskeie uiteenlopende rekristallisasie produkte gevorm, insluitend heksagonale plate uit asetoon, lang heksagonale stawe uit etielasetaat, naalde uit diëtieleter en harse uit chloroform en dichloormetaan. Aanvanklike termiese analiese het getoon dat al die rekristallisasie produkte, selfs die meer ooglopend kristallyne produkte, gedeeltelik amorf was. Vir vergelykende doeleindes was twee addisionele glase berei deur verkoeling van die gesmelte grondstof. Die een glas is toegelaat om geleidelik af te koel by kamertemperatuur terwyl die ander glas geblus was met vloeibare stikstof. Aktiveringsenergieë vir β-verslappings (ΔE_β) en glasoorgange was bereken uit nie-isotermiese DSK data en vanaf die aktiveringsenergie vir glasoorgang van elke monster is die breekbaarheids (m) en sterkte (D) parameters vir elke monster bereken. Vergelykings tussen die ΔE_β en m waardes het goed ooreengestem met makro- en mikroskopiese waarnemings en kon ook gebruik word om sekere fisiese waarnemings te verklaar. Die amorfe inhoud van elke monster is bepaal deur DSK en Fourier transform infrarooi (FTIR) spektroskopie. Die resultate van die oplosbaarheidstudie het weinig ooreenkomste getoon met die kristallyne/amorfe inhoud asook met die m en D waardes. Daar was wel ‘n omgekeerde eweredigheid tussen die oplosbaarheid en die ΔE_β van elke monster, wat tot die gevolgtrekking lei dat die verhoging in lokale molekulêre beweeglikheid in die monsters met lae ΔE_β waardes (en die gepaardgaande verlaging van die kontakhoek) dissolusie van geneesmiddelmolekules vanaf hierdie streke vergemaklik, wat sodoende lei tot ‘n verhoging in oppervlaksgrofheid en effektiewe oppervlaksarea. Die voortsetting van hierdie proses a.g.v. koppeling tussen die β-verslappings lei tot verhoogde oplosbaarhede in die monsters met die laagste ΔE_β waardes.