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Influence of ethanol water-content on gatifloxacin recrystallisations

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Gatifloxacin is a flouroquinolone anti-bacterial agent. This study proved that even the presence of small amounts of water in the recrystallisation medium influenced the product obtained. Different crystal forms were produced from various binary mixtures of ethanol and water. Where mixtures had a water content greater than (or equal to) 50% v/v, only hydrated crystal forms were produced and no ethanol was incorporated into the lattice.

Gatifloxacin, a flouroquinolone antibiotic, is a synthetically derived analogue of nalidixic acid. Because it is active against various gram-positive and gram-negative bacteria, it is used for the treatment of acute sinusitis, lower respiratory tract-, urinary tract- and various soft tissues infections (Chambers 2001).

It is common practice to use mixtures of solvents in the crystallisation process of API's (Byrn et al. 1999). The addition of an *anti-solvent* is often employed to speed-up the crystallisation process as the anti-solvent decreases the solubility of the solute in the solvent. By adding various ratios of an anti-solvent to the solvent, it often happens that crystals with different solvate composition and stoichiometry are formed (Byrn et al. 1999).

Preliminary studies revealed great inconsistency in the experimental data of gatifloxacin recrystallisation products obtained from different batches of ethanol. The products obtained were analysed by means of X-ray powder diffractometry, thermal gravimetric analysis, Karl Fischer, thermal microscopy (TM), differential scanning calorimetry and DRIFT-IR spectrometry.

Recrystallisation of gatifloxacin from 99–100% ethanol produced a mono-ethanol solvated crystal form, which gave an isomorphic desolvate upon drying. Recrystallisation of gatifloxacin using 95% ethanol produced an unstable crystal form. The XRPD pattern of this form differed from that of the recrystallised product obtained when using absolute ethanol (99–100%). This crystal form was classified as a mono-ethanol-hemihydrate (i.e. solvated-hydrate). The recrystallisation product from 75% ethanol and 25% water was found to differ from the forms

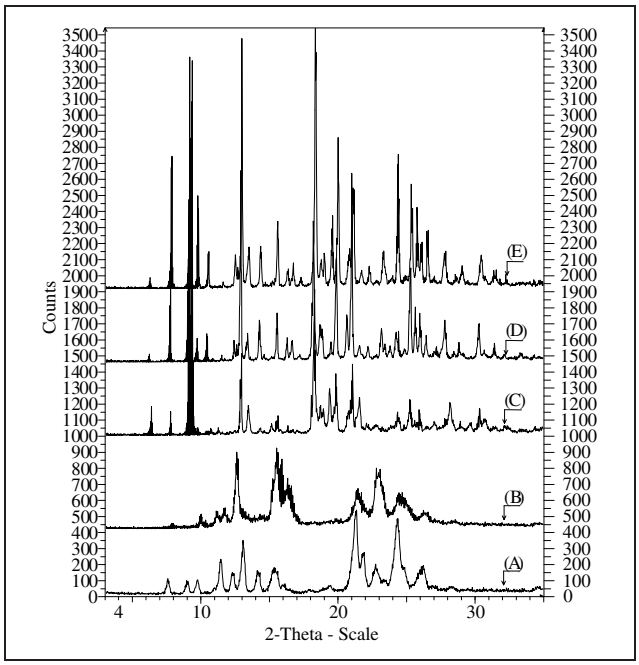

Fig. 1: XRPD patterns of the samples obtained from recrystallisation solvents A–E, whereas (A) is absolute ethanol (99–100%), (B) is ethanol (95%), (C) is ethanol : water (75 : 25), (D) is ethanol : water (50 : 50) and (E) is ethanol : water (25 : 75)

described above. These crystals showed a total weight loss (TGA) of 15.5% and a total water content of 8.6% (KF). Theoretical ethanol content for a hemi-ethanol solvate is 5.5%, whilst the theoretical water content for a sesquihydrate is 6.9%. Thus, the recrystallisation product from this medium was classified as a hemi-ethanol-sesquihydrated form of gatifloxacin. The recrystallisation product from 50% ethanol and 50% water showed a total weight loss (TGA) of 7.2% and a total water content of 8.1% (KF). These results suggest that this crystal form contained mainly water and may therefore be classified as a sesquihydrate. The XRPD pattern of this sample resembled that of the commercially favoured sesquihydrate (Reddy et al. 2004). The XRPD pattern for the product obtained from 25% ethanol and 75% water was the same as that of the sample obtained from the 50 : 50 mixture.

Fig. 1 illustrates the different XRPD patterns of the recrystallisation products. The peak intensity at ($I/I_{max} = 100\%$) was 528 and 505 for the products from solvents A and B respectively and 2085, 2197 and 1596 for the products from solvents C, D and E. The higher peak intensity observed for the products obtained from solvents C, D and E is characteristic of crystalline powders with a high degree of crystallinity. A previously described crystal form (form E), an ethanol solvate (Raghavan et al. 2002), was obtained by a recrystallisation process using 90–95% ethanol. Form E has been described as a six-sided platelet ethanol solvate with large solvent channels, causing it to be unstable in the absence of the mother liquor (Raghavan et al. 2002). These large solvent channels could cause instability of the crystal structure of the ethanol solvate and the mono-ethanol-hemihydrate leading to the lower peak intensity of the products, indicating a less crystalline product. It seems that ethanol as recrystallisation medium could cause instability of the crystal lattice, resulting in lower intensity counts. The superimposed DSC thermo-

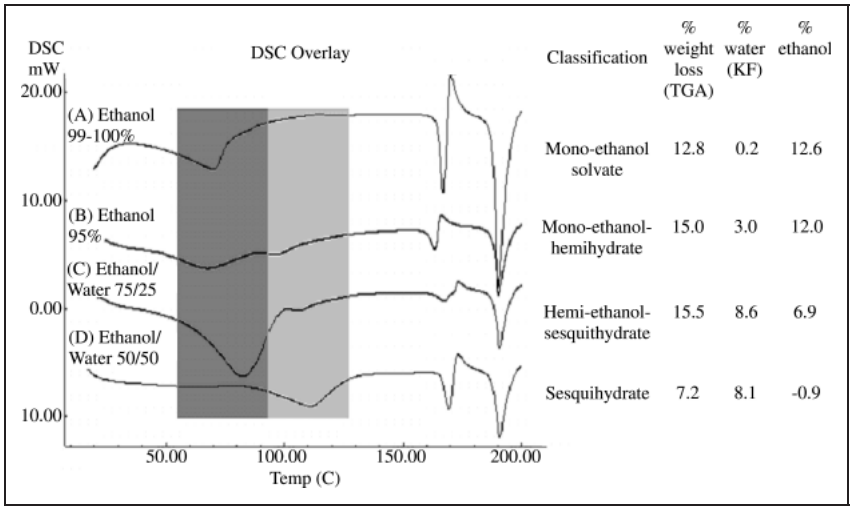

Fig. 2:
Superimposed DSC thermograms of samples obtained from solvents A–D. The lighter shade of gray indicates temperature regions associated with dehydration and the darker shade indicates temperature regions associated with desolvation

grams of the samples from the recrystallisation media (A–D) are illustrated in Fig. 2. The DSC thermograms of the sample from solvent E were not included, as they were identical to those of the sample from solvents D. The desolvation step and dehydration step correlated well with the boiling points of ethanol and water respectively. TGA results and KF titrations indicated that the % ethanol incorporated into the crystal forms related to the % ethanol in the recrystallisation medium. The same holds true for water content.

Whilst XRPD, DSC and TGA results showed definite differences between the products obtained from the various recrystallisation media, DRIFT-IR spectrometry was used to further investigate/clarify the different forms obtained. The most significant differences in the IR spectra of these forms were observed in the range of 4000–2000 cm^{-1}. The mono-ethanol solvate exhibit a broad band around 3400 cm^{-1} that was absent in the DRIFT-IR spectrum of the sesquihydrated form. The sesquihydrate form produced only a band at 3650 cm^{-1}. It can be suggested that the band at 3400 cm^{-1} indicates the presence of ethanol in the lattice, whilst a band present at 3650 cm^{-1} indicates the presence of water in the crystal lattice. The samples containing water and ethanol possessed both the ethanol and water bands, while the pure ethanol solvate and the pure hydrate only revealed the presence of the band at 3400 cm^{-1} and 3650 cm^{-1} respectively. An increase in the water content of the recrystallisation solvent (ethanol) led to an increased incorporation of water into the crystal lattice. The ethanol band was found to diminish (from A to E), while the water band became more prominent as the water content in the recrystallisation solvent used, was increased.

It can thus be concluded that the form obtained from solvent A was undoubtedly an ethanol solvate, whilst solvents D and E produced the sesquihydrate form. Although the products obtained from solvents B and C were classified as a mono-ethanol hemihydrate and a hemi-ethanol sesquihydrate, there is a slight possibility that they may be mixtures of two forms. However, KF result ratios are more indicative of a mono-ethanol hemihydrate and a hemi-ethanol sesquihydrate. Only single X-ray crystallography can prove this beyond doubt, but no suitable crystals could be isolated.

This study revealed that small traces of water in the recrystallisation solvent (ethanol) resulted in different crystal forms. This clearly illustrates the importance of ensuring solvent purity during manufacturing. It was found that gatifloxacin has a tendency to form hydrates. In ethanol : water mixtures, where the water content is greater than (or equal to) 50% v/v, only hydrated crystal forms were produced and no ethanol was incorporated into the lattice. These observations might explain the inconsistent recrystallisation results reported in literature (variation between batches from the same solvent and method). The water content of the solvents used in these studies might have varied, producing new crystal forms or mixtures of forms from the same method. This may also explain why some forms cannot be reproduced using the same method and solvent.

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