Effect on Additive Structure on Crystal Nucleation: Sulfathiazole

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Crystal nucleation events are notoriously susceptible to influence by extraneous molecular specie. Researchers Blagden, Davey *et al* have shown that in the presence of small quantities of the *N*-acetyl precursor to sulfathiazole selective nucleation of the metastable polymorph sulfathiazole can be achieved [1]. It was proposed that the difference in the hydrogen bonding at the sulfathiazole aniline moiety which particularly distinguishes form I from the other three polymorphs. In form I, only one of the aniline hydrogens is utilised while in forms II, III and IV both are used. It was proposed that the *N*-acetyl derivative is capable of entering the interwoven hydrogen bonded chain network without disrupting the structure, while incorporation into crystal nuclei of forms II, III and IV prevents further development of the hydrogen bonding network of these forms.

A feature of the above hypothesis worth further examination is the toleration of the replacement of an amine proton with the considerably more sterically demanding acetyl group. We have investigated the effect of various sulfathiazole *N*-substituents, in particular the effect of groups which are less (e.g. *N*-formyl,) or more (e.g. *N*-pivaloyl,) sterically demanding than N-acetyl. Additives of 'polymeric' design with the potential for increased efficacy have also been investigated, where design of the additives is based on consideration of the crystal structures of the polymorphs under study.

[1] Blagden N., Davey. J., Rowe R., Roberts R., *Int. J. Pharm.*, 1998 **172**, 169-177.

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