Residual solvents beyond the ICH Q3C guideline

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Solvents are routinely utilized in several stages of pharmaceutical product manufacture, and constitute the most common impurity found in pharmaceuticals, because very often residual amounts remain in the final product. The most common mechanism of incorporation is the entrapment of mother liquor in "pockets" formed in the crystal lattice, known as inclusions. The size of such inclusions may range from molecular dimensions to about 10 μm, the former corresponding to solid solution, the latter to liquid inclusions [1].

Since residual solvents are of no therapeutic value but potentially hazardous to the patient, drug manufacturers are required to completely remove them from the product or keep them below "acceptable limits". However, complete removal is often not possible, and furthermore, each pharmacopoeia sets own limits, resulting in requirements for drug approval different for each region, such as Europe, USA, and Japan. Efforts to equalize the regulations were undertaken by the International Conference on Harmonization (ICH), leading to the ICH guidelines on impurities. Specifically, the ICH Q3C "guideline for residual solvents" [2] attempts a classification of solvents by their toxicity into four groups and sets acceptable limits in pharmaceuticals for human use.

However, the presence of residual solvents at levels well within acceptable limits can entail the risk of inducing phase transformations and jeopardising the physicochemical stability of the active pharmaceutical ingredient (API) and finally the efficiency of the dosage form. An early account of residual solvent occurrence in pharmaceuticals with a discussion of potential effects on the properties of dosage forms was presented by Doelker in 1997 [3], but ever since very few reports of residual solvent effects have appeared in the literature, such as the effect of residual methylene chloride on the crystallinity of ampicillin trihydrate [4], and of residual water on the phase transformation of orthorhombic paracetamol [5,6].

The present study attempts to shed new light on the potential effects of residual solvents, using the moisture-induced transformation of orthorhombic paracetamol (form II) to the stable monoclinic polymorph (form I) as a model-case. Orthorhombic paracetamol was crystallized from seeded ethanol solutions and from the melt, and characterized by powder X-ray diffraction (PXRD), optical microscopy, FT-Raman spectroscopy, thermogravimetric analysis (TGA), thermogravimetry coupled with FTIR spectroscopy (TG-FTIR), and dynamic moisture sorption. It was found that form II grown from ethanol quickly transforms to form I when exposed to moisture, unlike form II grown from the melt, which is stable at high relative humidity (RH) for much longer times. Presence of form I nuclei alone, which seem to be inherent in ethanol-grown form II, could not explain the faster transformation of ethanol-grown form II in comparison with physical mixtures of melt-grown form II and form I. A mass loss of 0.1-0.6% w/w was observed during transformation of solution-grown form II, inversely related to the initial monoclinic content, which proved to be due to residual ethanol, probably incorporated by a solid solution mechanism. The transformation rate was increased by increasing the RH or by grinding, while melt-grown form II was stable during the same time period. Residual ethanol seems to be "forced" out of the crystal lattice by moisture, thus triggering the growth of existing form I nuclei but exerting a weaker effect on nucleation.

Under the light of these experimental findings that come to support earlier observations on the effects of residual solvents [3-6], it becomes obvious that the regulatory framework can be inadequate in certain cases, particularly in formulations containing metastable polymorphs. Drug manufacturers should not be reassured by simply fulfilling compendial requirements on residual solvents. Additional consideration should be given to the possibility of phase transformations induced by residual solvent levels even well within acceptable limits.

References

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