DEVELOPING A STRATEGY TO OPTIMISE ACTIVE PHARMACEUTICAL INGREDIENT FILTRATION AND WASHING

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Crystallization is the principle technology used by the pharmaceutical industry to purify Active Pharmaceutical Ingredients (APIs). Ideally crystallization delivers crystals with the required particle size distribution and associated critical quality attributes required for the formulated drug product. The product crystals are suspended in mother liquors comprising one or more solvents in which some product remains in solution along with a multitude of structurally related impurities, reaction by-products and unconsumed reagents arising from the preceding synthetic steps. The complex nature of the liquid phase presents a number of challenges which must be overcome in order to design a filtration and washing procedure which delivers a wet cake that can be dried without affecting the particle attributes created during the crystallization and which does not compromise the product purity or reduce yield.

A good starting point is to characterize the product crystals and the mother liquors at the end of the crystallization process. The dissolved components in the mother liquor composition can be determined by LC-MS and solvent ratios determined gas chromatography. Another essential piece of information is the solubility of the pure solute in the solvent or solvent mixture at the isolation temperature, typically this is measured by isothermal equilibration and any difference in solubility compared with the solubility of the product in the mother liquors may be attributed to the role of impurities in modifying the API solubility. The product crystal habit may be determined by optical microscopy and the crystal size distribution measured by FBRM or laser diffraction.

The primary filtration task is to separate the mother liquors from the product crystals leaving a filter cake which can be washed effectively. If the cake is de-liquored it is likely to crack or the pull away from the filter walls leaving low resistance pathways through which most of the wash liquid to passes substantially reducing the wash efficiency. Displacement washing a fully saturated cake is much more effective.

A further challenge is selection of the wash solvent(s); multiple criteria may be identified and each can be linked to one or more failure modes. If the product is soluble in the wash solvent product will be lost through dissolution and the product crystal size distribution will be altered. If the product or any of the impurities have very low solubility in the wash solvent then they will be driven out of solution as the mother liquors mix with the wash solvent. This can jeopardize product purity or in the case of product being forced out of solution it may cause particles to become fused together modifying the product particle size distribution.

The role of residual solvent in the filter cake during drying is also critical, if the product or any lingering impurities are soluble then the solvent transports them to the drying surface where they are deposited resulting in crystals becoming fused together leading to a lumpy product which is chemically inhomogeneous.

In the presentation these issues are exemplified and a systematic development strategy is presented.