Relation of Drug Substances to Solvents: Free Solvent, Adsorption, Inclusion and Intercalation

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The detection of solvent content in a pharmaceutical drug substance or drug product is important from a general analytical point of view and also from the safety aspect in the application of a medical product. The solvent may be just physically adsorbed at the solid drug or also trapped in the lattice of the crystalline drug material, which means in both case be present as an impurity, or it can be chemically bound to form a solvate. Thermoanalytical methods are well suited to detect the presence of a solvent and to characterize the kind of solvent and its state of incorporation in a drug substance.

Indication for presence of solvents can be found already when using the DSC for eutectic purity determination with closed and open crucibles. The thermobalance provides direct information on a molecular unspecific level about the content of volatile solvents up to the start of the decomposition of the drug by detection of mass loss steps for evaporation through thermal desorption of the solvents.

The volatility of a pure solvent at a certain test temperature depends on its vapor pressure, within some limits the vapor pressure can be determined by thermogravimetry [1]. The volatility of a solvent incorporated in a drug substance and a drug product is different compared to the free solvent due to the adsorption at the surface or interaction with the lattice. An additional phenomenon is the inclusion of solvents as microscopic droplets caused normally by imperfect crystallization.

Residual solvent can be detected at high temperature up to the melting of drugs, as shown with ethyl acetate included in naftopidil and zaleplon [2]. The pressure of the solvent reaches some bars, due to the intercalation in the crystal lattice, and only during complete melting the solvent is released.

On-line gas analysis methods like Fourier-transform infrared spectrometry and mass spectrometry coupled to a sensitive thermobalance allow detection and identification of traces of solvents in drugs in one experiment. A precise temperature correlation between the different measuring signals enables to describe the relation between the solvent and the drug.

Literature

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