Characterization of the solid phase of pipemidic acid at equilibrium with saturated solutions in solvent mixtures

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The use of solvent mixtures is often exploited as a method to increase solubility of poorly soluble drugs. The importance of ensuring saturation conditions during solubility experiments in order to obtain reliable solubility values is well known. However, it should be taken into account that the time required to attain equilibrium solubility may be very long and the solvents may induce solid phase modifications, that could modify the solubility with respect to that of the original powder, thus leading to errors in the experimentally determined solubilities.

In the present work, we studied the dissolution and solubility properties in different solvent mixtures of pipemidic acid, a quinolonic anti-bacterial agents commonly used in the treatment of urinary infections. The characteristics of the drug solid phase, during solubility experiments, was carefully investigated with the aim of detecting possible crystalline modifications, such as polymorphic transitions or solvate formations, that might modify drug chemicophysical properties. Aqueous and non-aqueous binary mixtures were prepared by using Lewis base (dioxane and ethyl acetate) and amphiprotic cosolvents (ethanol and water), so as to test the influence of both the nature and polarity of the cosolvents. Differential Scanning Calorimetry (DSC) and X-ray powder diffraction were used to characterize and investigate the solid state properties of the original powders and of the corresponding solid phases at equilibrium with the different solvents and solvent mixtures examined. The solid phases of pipemidic acid did not show any change after equilibration with pure solvents ethyl acetate and ethanol, as well as with their non aqueous mixtures. In contrast, the formation of a solvate in pure dioxane and a trihydrated form in aqueous mixtures of water with both ethanol or dioxane in a concentration range from 10 to 100% water was demonstrated.