New Perspectives of ^{19}F MAS NMR in the Characterization of Pseudopolyamorphism of Pharmaceutical Solids: Comparative Factor Analysis

Jiri Brus[†*], Martina Urbanova[†], Ivana Sedenkova[†] and Hana Brusova[‡]

[†] *Department of Structure Analysis, Institute of Macromolecular Chemistry, Heyrovsky sq. 2, 162 06 Prague 6, Czech Republic*
[‡] *Department of Development, Zentiva k.s., U kabelovny 130, 102 37 Prague 10, Czech Republic.*

Abstract

A new time-saving method for identification of various pseudopolyamorphs of pharmaceutical solids in dosage forms is introduced. The method is demonstrated on a moderately-sized active pharmaceutical ingredient ($C_{33}H_{35}FN_2O_5$) exhibiting extensive polymorphism. In the proposed strategy ^{19}F MAS NMR spectra of various forms of the API are processed by factor analysis. From the resulting set of subspectra $S_j(^{19}F)$ the sample-specific factors $V_{i4}(^{19}F)$ unambiguously identifying every modification of the API were derived. Regardless the API was in the pure form or in the tablet formulation, every modification of the API was always characterized by the same set of V_{ij} coefficients. In this way the ability of the proposed procedure to unambiguously characterize semicrystalline forms of fluorine-containing API in dosage forms was confirmed. The total experimental time required to the identification of an unknown sample is less than one hour. Furthermore, new perspectives of "comparative" factor analysis to describe initial motifs of molecular arrangement arising in the amorphous/partially-ordered phase are demonstrated. The proposed procedure is based on the cross-correlation of V_{ij} factors independently derived by factor analysis of ^{19}F MAS NMR, ^{13}C CP/MASNMR and XRPD data. It was found out that certain factors exhibit highly linear correlation. In the particular case of the investigated API the linearly correlating factors are $V_{i4}(^{19}F)$, $V_{i4}(^{13}C)$ and $V_{i7}(XRPD)$. Consequently ^{19}F NMR, ^{13}C NMR and XRPD signals reflecting primary structural motifs that cause differences between the semicrystalline forms of the API could be identified in the corresponding subspectra $S_4(^{13}C)$, $S_4(^{19}F)$ and $S_7(XRPD)$. As these signals can be assigned to the specific molecular sites or to the characteristic interatomic distances the proposed comparative factor analysis provides a deeper insight into the systems exhibiting extensive variability and can be used to better describe initial structural motifs the formation of which induce crystallization.

$$Y_i = \sum_{j=1}^{n} w_j V_{ij} S_j$$