X-RAY POWDER DIFFRACTION IN QUANTIFYING POLYMORPHIC MIXTURES OF PHARMACEUTICAL SOLIDS: A CASE STUDY OF FAMOTIDINE

<u>Zoltán Német</u>[a], Zoltán Varga[a], Ádám Demeter[a], István Sajó[b]

[a] Drug Polymorphism Research Division, Gedeon Richter Plc, H-1475 Budapest, P.O. Box 27, Hungary
[b] Department of X-ray Diffraction, Chemical Research Center of Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary

X-ray powder diffractometric methods were developed for quantitative measurement of the polymorphic forms of famotidine in their binary mixtures. The purpose of the study was to serve a suitable analytical method for the quantification of famotidine polymorphs, and it also aimed to deduce some useful conclusions regarding quantitative polymorph analysis, which could be utilized in industrial practice.

About 10 g of polymorphic mixtures (17 calibration and 6 validation) of form A and form B were prepared by mixing accurately weighed amounts of solids in hexane in which the substance is practically insoluble. Mixtures were measured in triplicate both "as received" and after grinding in a mortar. Both form A and form B of famotidine possess specific X-ray diffraction reflections, which permits simple determination of the phases in their mixtures. Both the plates of form A and needles of form B exhibit preferred orientation; furthermore, the "as received" samples have relatively large particle size (up to 100 micron in the case of form A) causing problems with particle statistics.

The results show that grinding both the calibration mixtures and the analyte is necessary before the measurement. Multivariate data analysis can handle nonlinearities caused by poor reproducibility of the reflection intensities; the obtained limits of detection and quantification are, however, only adequate for samples having similar properties. Significant difference in the performance of seemingly appropriate univariate and much better performing multivariate method can be the indication of this over-fitting; and it can be evidenced by quantifying mixtures of known composition having different particle size and crystal habit than those used for model building. In the case of famotidine polymorphs, though multivariate data analysis can provide better results than univariate one, it seems that if appropriate peak ratios are selected, the difference is negligible.