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放射光粉末回折法による製剤中の微量原薬結晶多形の判別
Identification of Polymorphic Forms of a Drug Substance Present in a Very Small Quantity in a Pharmaceutical Formulation by Synchrotron X-ray Powder Diffraction

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Lactose formulations for inhalation powder containing only about 0.4 % monohydrate or any of major three anhydrate forms of tiotropium bromide were subjected to synchrotron X-ray powder diffraction (XRPD) measurements at SPring-8 beamline BL19B2. Test samples were filled in a Lindemann glass capillary of 1.0 mm diameter without any pretreatment and subjected to the synchrotron XRPD measurements (wavelength: 1.0 Å) using a Debye-Scherrer camera with an imaging plate detector, which was partially masked with lead tapes to cut off intensive diffraction peaks derived from lactose monohydrate. The diffraction patterns of all the crystal forms were clearly recognizable in the diffraction patterns obtained from the lactose formulations. Thus, the analytical method for identification of the all major crystal forms of tiotropium bromide in the lactose formulations was established.

Keywords: X-ray powder diffraction, polymorphic forms, pharmaceutical formulation, tiotropium bromide

Introduction:

For the manufacture and quality control of drug substances having polymorphs and drug products containing such substances, establishing an analytical method capable to identify polymorphic forms is quite important, since differences of polymorphic forms may have an influence on stability of the drug substance and the drug product, function of the drug product and bioavailability. Particularly, synchrotron XRPD is of high interest because an analytical method with high sensitivity and high resolution is needed for identification of a crystal form of a drug substance present in a formulation, i.e. a mixture of multiple components, in a very small quantity [1, 2].

Tiotropium bromide is the active drug substance of Spiriva® inhalation powder used for therapeutic treatment of chronic obstructive pulmonary disease. This compound can be present as monohydrate, which is the crystal form used for the manufacture of the commercial product, and several anhydrate forms as well. It is known that different crystal forms can be generated and a conversion to a different form occurs depending on the manufacturing and storage conditions. However, since tiotropium bromide is present only about 0.4 % in the formulation that consists of lactose monohydrate, identification of its crystal form in the formulation is not possible by the use of a common laboratory XRPD instrument which typically has detection limit at about 5 %.

Therefore, feasibility of detecting the crystal forms of tiotropium bromide by synchrotron XRPD was examined at SPring-8 beamline BL19B2 and experimental conditions for unambiguous identification of its monohydrate and anhydrate (form I) have been elaborated in the previous experiments (Proprietary research, proposal No. 2011B2028, 2012B1838). In the present study, the applicability of the analytical method to identification of all major crystal forms of tiotropium bromide was examined.

Experimental:

Test samples were filled in a Lindemann glass capillary of 1.0 mm diameter without any pretreatment and subjected to synchrotron XRPD measurements (wavelength: 1.0 Å) at beamline BL19B2 using a Debye-Scherrer camera with an imaging plate detector, which was partially masked with lead tapes to cut off intensive diffraction peaks derived from lactose monohydrate. By exposing tiotropium bromide for 2 h, diffraction patterns of monohydrate and anhydrate form I in the lactose formulation were successfully detected and unambiguously distinguished in the previous experiments. In the present study, lactose formulations containing 0.4 % monohydrate or any of major three anhydrate forms of tiotropium bromide were subjected to measurements under the identical conditions in order to confirm the applicability of the method to all major crystal forms of tiotropium bromide.

Result and discussion:

The diffraction patterns of all the crystal forms shown in Figure 1 were clearly recognizable in the diffraction patterns obtained from the lactose formulations shown in Figure 2. Thus, the applicability of the method to the all major crystal forms was confirmed.

The established analytical method offers benefits for identifying the drug substance crystal form in a mixture of multiple components (pharmaceutical formulation) without major sample preparation steps, and the assessment of changes in manufacturing process, formulation etc. during the product lifecycle. The principle of the method is considered potentially applicable to any other drug substances and formulations with very low drug content.

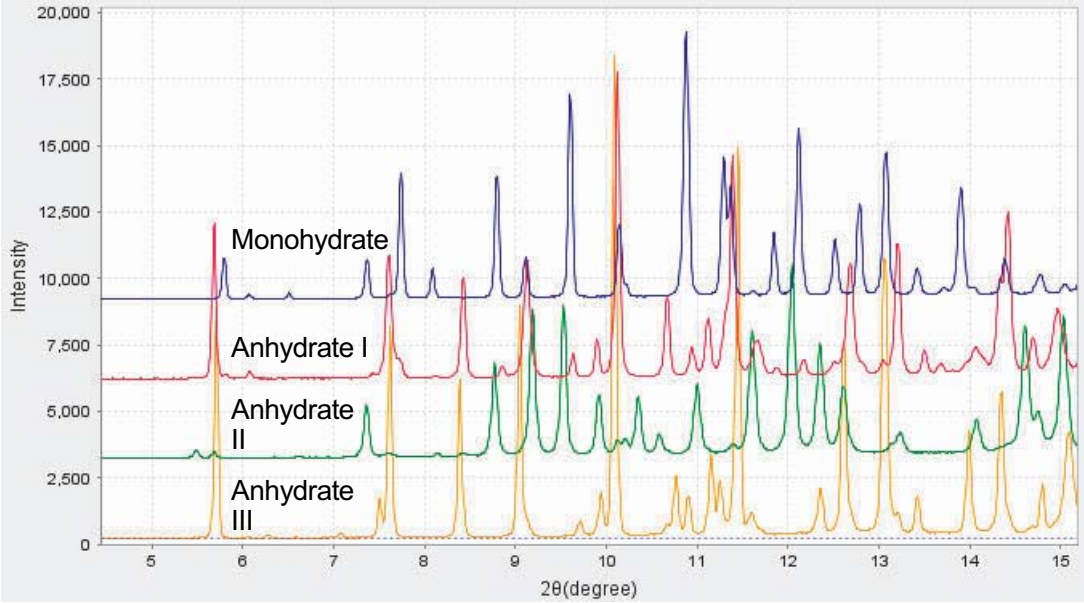

Figure 1. Diffraction patterns of pure crystal forms of tiotropium bromide (5-min beam exposure without masking)

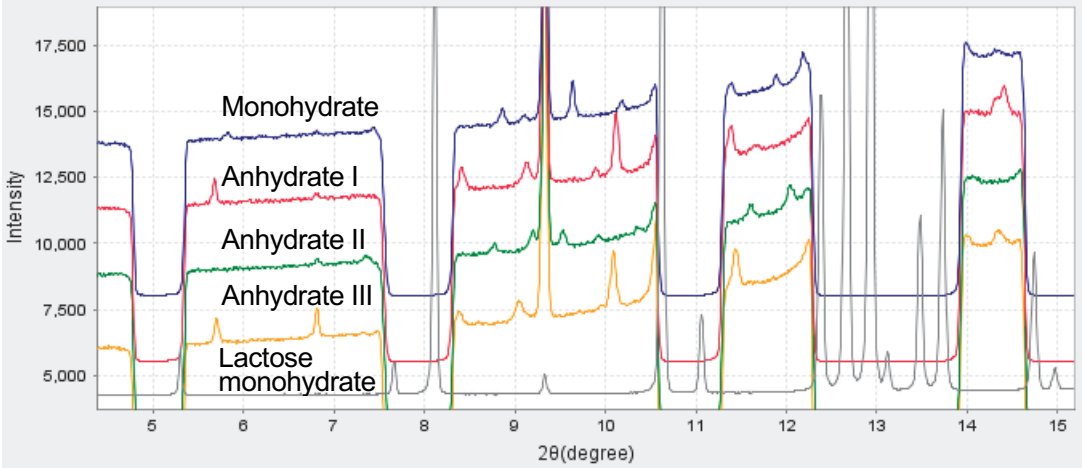

Figure 2. Diffraction patterns of crystal forms of tiotropium bromide in the lactose formulations (2-h beam exposure with lead tape masking)
Regions of 4.7°-5.4°, 7.5°-8.4°, 10.6°-11.3°, 12.3°-14.0° and 14.6°- 2θ were masked with lead tapes. Diffraction pattern of lactose monohydrate (5-min beam exposure without masking) is also shown for a comparison.

Reference:

[1] K. Masuda et al., *Chemical and Pharmaceutical Bulletin*, **59**, 57-62, (2011).

[2] H. Yamada et al., *Journal of Pharmaceutical and Biomedical Analysis*, **56**, 448-453, (2011).