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Evaluation of the crystalline and amorphous states of drug products by nanothermal analysis and Raman imaging

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ABSTRACT

In recent years, amorphous formulations and other special dosage forms of drug products have been investigated to achieve adequate solubility and disintegration. We have evaluated the distribution of crystalline and amorphous states of a drug product using Nanothermal analysis (Nano-TA) and Raman imaging methods. Compared to conventional differential scanning calorimetry, Nano-TA can be used to more rapidly characterize the crystalline and amorphous states of model formulations, including their ingredient distributions, without any sample preparation. In the current study, imaging maps obtained for specific model formulations were evaluated on the basis of their visual appearance and the physicochemical properties of the active pharmaceutical ingredient (API). In addition, the crystalline and amorphous states of the model formulations were distinguished by Raman mapping. Nano-TA was found to be useful for the characterization of crystalline and amorphous states of APIs and the distribution of other ingredients. This technology could be used to monitor the changes in crystalline forms of drug substances and dosage forms during processing. In addition, Nano-TA can be used to characterize amorphous states.

1. Introduction

Recently, in pharmaceutical development, the use of amorphous formulations has attracted attention as a possible approach to increase the disintegration of tablets, thereby enhancing the effects of drugs. The higher solubility of the amorphous state compared to that of the crystalline state is very important in cases where limited water-solubility leads to low absorption [1–8]. In general, amorphous formulations have higher solubility and permeability than crystalline forms. However, the amorphous state is more hygroscopic, less physically and chemically stable, and often more difficult to recrystallize. Therefore, it is difficult to predict the stability of amorphous drugs [9].

The International Conference on Harmonization (ICH) [10] states that crystalline form and particle size must be defined during the development of drug substances. Similarly, the ICH [11] states that in all cases, the product should be designed to meet patients' needs and the intended product performance. The physicochemical properties (e.g., solubility, water content, particle size, and crystal properties) that can influence the performance of the drug product and its manufacturability, or that are specifically designed into the drug substance, should be identified and examined. This understanding can be gained by the application of process analytical technology (PAT) and prior knowledge. For instance, near infrared (NIR) imaging, which rapidly detects chemical composition without destroying the sample, is expected to be applied to PAT and in-line monitoring systems in the pharmaceutical manufacturing process [12]. In addition, the ICH [13] states that an effective quality risk management approach can further ensure the high quality of drug products for patients by providing a proactive means for identifying and controlling potential quality issues during development and manufacturing. In this way, not only the quality assurance of the final drug product but also that of the entire manufacturing process has been improved through a greater understanding of the process.

Conventional drug manufacturing processes include grinding, mixing, granulation, drying, compression, and coating. Compression absorption by porous additives can cause changes in the crystal form of products during grinding. To ensure quality, it is necessary to understand the effects of these processes on drug properties and to prevent such changes from occurring under optimized manufacturing conditions. It is important to establish a method for

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Table 1
Composition of model formulations.

Formula	Degree of crystallinity	Composition and ratio					
		ESM	Sylysia 350	Lactose	MCC	L-HPC	Mg-St
Placebo	–	–	–	74	20	5	1
A	100	10	–	64	20	5	1
B	29.9	10	4	60	20	5	1
C	5.4	10	6	58	20	5	1
D	2.5	10	8	56	20	5	1

evaluating changes from crystalline to amorphous states during manufacturing because in some cases crystalline and amorphous states are mixed in the final drug product.

Differential scanning calorimetry (DSC) [14], thermogravimetric/differential thermal analysis (TG–DTA), X-ray powder diffraction [15], and Raman spectroscopy are all used to detect the amorphous and crystalline content of compounds. However, when applying these methods to dosage forms such as tablets, preparation and destruction of the sample is required. Following this sample preparation, the homogeneity of distribution of the active pharmaceutical ingredient (API) and other ingredients in the tablet cannot be evaluated.

The surface state of drug products can be analyzed by measuring surface free energy, and the distribution of the ingredients in the drug product can be visualized without destructive preparation of the sample, using two-dimensional mapping techniques such as Raman imaging [16,17], NIR imaging [18], and laser-induced breakdown spectroscopy (LIBS) [19]. In these methods, it is possible to evaluate the homogeneous distribution of the API and other ingredients in the tablet. In some cases, crystalline and amorphous states are mixed in the tablet; therefore, chemical imaging is used to analyze the distribution and degree of crystallinity. However, this conventional imaging method takes a long time to determine these characteristics. A local thermal analysis method has been developed to rapidly determine the degree of crystallinity. This method uses a transition temperature distribution imaging device to measure components and the thickness of multilayer film materials [20]. NIR is widely used to detect the concentration and distribution of drug substances and ingredients, but the determination of crystalline and amorphous components using this method is affected by other formulation ingredients. The amorphous state is neither molten nor solid and has no melting temperature (T_m); therefore, evaluation using Nano-TA is not possible.

The purpose of the present study was to describe the use of Nano-TA and Raman Imaging for the detection of crystalline and amorphous states in pharmaceutical materials. Ethosuximide (ESM) was selected as the API for model formulations. ESM (product name Epilim petit mal) has been used since 1967, and has a reportedly stable amorphous state. The solid state of ESM changes from crystalline to amorphous by melting and adsorption onto hydrated silicon dioxide. Using this process as a model, the distribution of crystalline and amorphous states in sample formulated drug products was evaluated using Nano-TA and Raman imaging methods.

2. Material and methods

2.1. Materials

ESM was purchased from Katwijk Chemie bv, Katwijk, Netherlands. Additional reagents used include lactose monohydrate (Super Tab 11SD, DMV, Germany) as a filler, hydrated silicon dioxide (Sylysia 350, Fuji Silysia Chemical Ltd., Aichi, Japan) as the porous additive, microcrystalline cellulose (MCC, Avicel PH102, Asahi Chemical, Japan) as a binder, low substituted hydroxylpropyl-cellulose (L-HPC, Shin-Etsu Chemical Co. Ltd., Tokyo, Japan) as a disintegrant, and magnesium stearate (Mg-st, Taihei Chemical Industrial Co. Ltd., Tokyo, Japan) as a lubricant.

2.2. Preparation of absorbed ESM granules

Samples of ESM were melted and adsorbed onto hydrated silicon dioxide to change the crystalline form to the amorphous form. Absorbed ESM granules were prepared with varying degrees of crystallinity by changing the amount of hydrated silicon dioxide used.

2.3. Composition of model formulations

The composition and mass fractions of model formulations can be seen in Table 1. Five different model formulation tablets including a placebo formulation (P) as a control, a crystalline model formulation that was free of amorphous ESM (A), and mixed formulations (B, C, and D) containing both crystalline and amorphous forms were prepared by varying the ratio of hydrated silica dioxide.

2.4. Tablet preparation

Samples of ESM were melted for 24 h at 60 °C. Hydrated silicon dioxide was then adsorbed onto ESM using a stirring granulator (NMG3L, Nara Machinery, Tokyo, Japan). The adsorbed substance was then cooled to room temperature and milled in a speed-mill (Power Mill Type P-3S, Syowa Giken Industrial Co. Ltd., Saitama, Japan). Next the adsorbed granules were mixed with the other ingredients to produce the final solid form material. The same mixing and blending times were used in all batches. Tablets with flat surfaces, a diameter of 8 mm, and a weight of 200 mg were compressed with a compaction force of 10 kN using a rotary tablet machine (AP15, Hata Iron Works, Kyoto, Japan).

2.5. X-ray powder diffraction (XPRD)

XPRD measurements were performed on a Rigaku XPRD analyzer (model Mini Flex 600) with CuKα radiation. The voltage and current of the X-ray tube were 40 kV and 15 mA. The 2θ scanning range was 2–36°. The step size was 0.02° and the scanning speed was 10°/min.

2.6. Differential scanning calorimetry (DSC)

The composition of absorbed granules (ESM and hydrated silicon dioxide) and model tablets was analyzed using a Rigaku DSC analyzer (model DSC8230). The temperature axis of the equipment was calibrated using zinc and indium. Runs were performed under an air atmosphere in open aluminum pans, with sample weights of 3–5 mg. The heating rate was 2–5 °C min^{-1} over a temperature range of 30–150 °C.