Special Feature: Pharmaceutical Analysis (1)

Rigaku's analytical instruments for R&D and production of pharmaceutical materials

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1. Introduction

Solid drugs taken orally are mixtures of active pharmaceutical ingredients (hereinafter referred to as "API"); agents such as excipients added as binders or diluents; and lubricants added to enhance flow properties of particles. In general, active pharmaceutical ingredients are solid organic substances. In many cases, a substance of the same chemical formula can occur in several polymorphic forms with different crystal structures, a phenomenon known as crystal polymorphism. Compounds noted by the same chemical formula but having different crystal structures are known to exhibit different characteristics with regard to stability and bioavailability†. Conventional methods for distinguishing these polymorphs have been based on X-ray diffractometers and thermal analyzers.

Pharmaceutical development in recent years has begun to focus increasingly on stability, ease of administration (swallowing), and the efficacy of the final pharmaceutical production, in addition to the stability and bioavailability of the APIs. In response to the needs of an aging population, for example, development is currently underway in Japan on formulations that allow elderly people to swallow medications more easily. Companies have begun developing unique formulations (e.g., oral disintegrants, films, jellies) with added functionality and need methods to confirm not just the stability of the APIs, but also the stability of these functions. Reports indicate that more than 60% of new pharmaceuticals developed in recent years have low solubility, which has driven efforts to select the ideal additive to improve dissolution and/or to develop highly soluble amorphous formulations.

At the same time, the Japanese government has promoted the use of generic drugs to cut medical costs. In certain Western nations, market shares for generic drugs have reached 60–70%; in Japan, this share remains at 22.8% (see Fig. 1; statistics as of Sept. 2011 by number of products)[(1)]. Several measures including a revised remuneration system for medical care services have been taken to promote the use of generics. With the growing availability of drugs containing the same API from multiple manufacturers and increasing consumer choice, there is growing demand for ways to guarantee safety and quality and to set a product apart from the others.

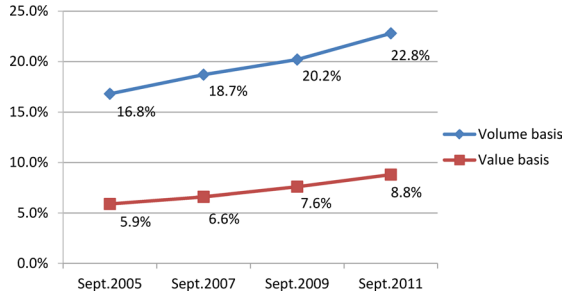

Fig. 1. Changes in the market share of generic drugs (from the Ministry of Health, Labor and Welfare website[(1)]).

In response, instruments used for analysis of these compounds have been modified in various ways and new methods of analysis have been developed. This special issue will focus on solid, orally administered formulations and present an overview of Rigaku's analytical technologies that provide effective solutions to problems encountered from drug R&D to production. This issue also introduces the latest technologies in analysis.

2. Process of Pharmaceutical Drug Research and Development

Figure 2 shows the processes involved in the steps ranging from pharmaceutical drug R&D to production. The development of a single typical drug is said to take more than 10 years and to cost some 100 billion yen. The primary challenge for pharmaceutical companies is to find ways to reduce the time and cost at each step of the process and to get the new drug to market as quickly as possible. Rigaku's analysis technologies have significantly reduced the time required at each step of the analysis and evaluation process.

[Exploration]

This stage involves the exploration and selection of candidate compounds for development as new drugs. The lead compound is determined following a basic investigation and activity screening. At this point, efforts focus on exploring the physical properties of the compound, including those of the different polymorphs,

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† Bioavailability: An indicator representing how much of the administered drug (formulation) reaches the bloodstream and acts on the body.

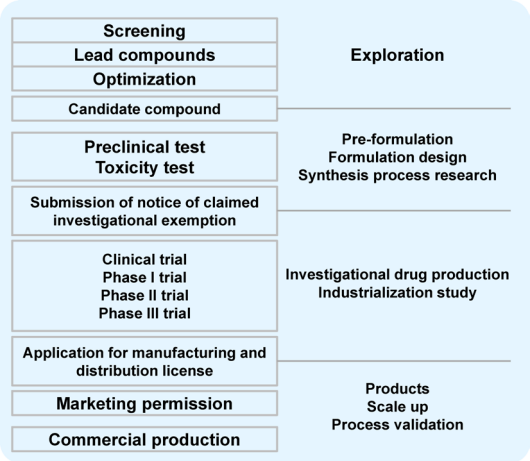

Fig. 2. Process from Pharmaceutical Drug Development to Production.

and optimizing the compound by salt screening to make a final decision regarding the candidate compound. Efforts to hasten the pharmaceutical drug R&D process and improve accuracy have emphasized the importance of the physicochemical approach.

Protein molecules are involved in physiological functions. Invasion by viruses or allergens can disrupt bodily functions, the state known as "being sick." One way in which drugs work is by binding loosely with a specific protein on the surface of the cell membrane and adjusting its function. In order to understand the how the drug molecule specifically interacts with the protein of interest, the atomic resolution structure of the candidate compound and its target protein is determined by single crystal X-ray analysis. The results of such an analysis gives the researchers clues as to how the drug molecules can be modified to bind more tightly to the protein. (For more information, see "Drug discovery by single crystal X-ray structure analysis," starting on page 4.) For single crystal X-ray analysis, the target substance must be crystallized, which is however extremely difficult to accomplish for some proteins. When the protein of interest does not crystallize, the shape of the molecule in solution can be determined by small angle X-ray scattering (SAXS). To meet the needs of this type of analysis, Rigaku has developed the BioSAXS-1000 SAXS system (Fig. 3), an instrument dedicated to the structural determination of proteins in solutions.

As mentioned above, a single API of a single chemical formula may have polymorphic forms with different crystal structures. Depending on the process of formulation or storage conditions, the original crystal forms may undergo polymorphic transformations or dehydration/hydration. Since different polymorphic forms exhibit different properties, it is crucial to select and maintain the optimal crystal forms for the given function of a pharmaceutical product. Before proceeding to the next preformulation stage, it is important to assess a variety of polymorphic forms of the candidate compound; to identify the most stable crystal form; and to determine the conditions under which

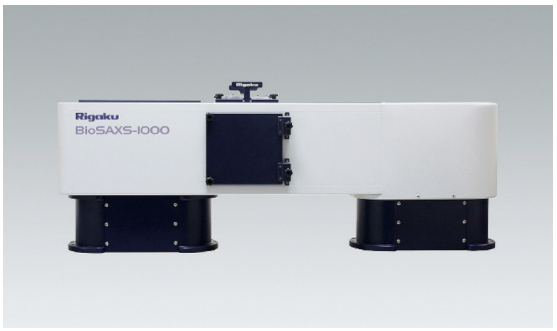

Fig. 3. BioSAXS-1000 small angle X-ray scattering system.

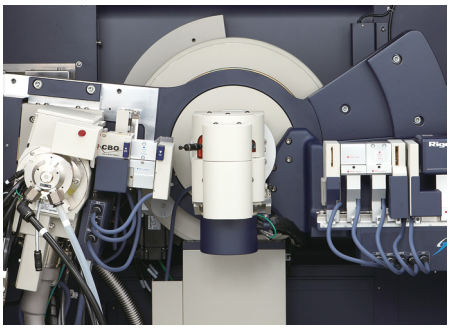

Fig. 4. X-ray DSC for simultaneous X-ray diffraction and differential scanning calorimetry.

a crystal form transforms to the other polymorphic forms and dehydration/hydration occur. Powder X-ray diffractometers and thermal analyzers have conventionally been used to identify the polymorphic form in which a bulk powder occurs following synthesis and various testing and to investigate its phase transformation behavior. Rigaku manufactures and markets an instrument that simultaneously performs X-ray diffraction and differential scanning calorimetry (XRD DSC) to identify different polymorphic forms and pseudopolymorphic forms (hydrates) that appear with rising or falling temperature and humidity (Fig. 4).

[Preformulation and Synthesis Process Research]

The preformulation stage, the first stage of drug product formulation research, evaluates the physical and biological properties of the candidate compound and sets the direction of subsequent formulation research.

In the manufacturing process for orally-administered solid formulations such as pills, inhomogeneous powders are formed into tablets from granular form through grinding, granulation, blending, pressing, and coating processes (6). The powder XRD method is useful in checking whether the target crystal form is retained through each process and in the ultimate product without polymorphic transformations. In recent years, a novel optical system (convergent beam optics using an elliptical multilayer mirror) of powder XRD has entered use that allows non-destructive identification of the crystal form of a drug in tablet form.

See "Evaluation of polymorphic forms by powder X-ray diffraction and thermal analysis methods"

Fig. 5. R_mCT2 3D micro X-ray CT system for laboratory animals.

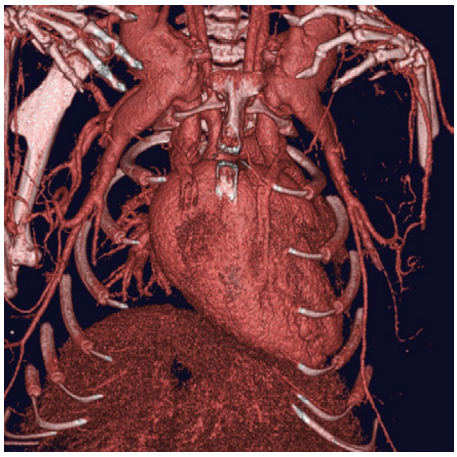

Fig. 6. 3D angiogram of mouse heart and liver.

(starting on page 8) for additional information on instruments that perform simultaneous X-ray diffraction and differential scanning calorimetry and powder XRD instruments.

[Non-Clinical Testing]

The process of drug research and discovery requires evaluations of drug efficacy and safety through non-clinical testing before the clinical testing pharmacological actions and effectiveness. In recent years, micro CT scanners have made it possible to perform non-clinical testing in a manner similar to clinical trials. In contrast to conventional evaluation methods based on dissection techniques, the non-destructive method allows diagnosis of a single test subject over time, significantly improving the reliability of non-clinical testing.

The R_mCT2 3D micro X-ray CT system designed for use with laboratory animals (Fig. 5) is a high-resolution X-ray tomography instrument capable of capturing 3D tomographic images of the internal structures of small animals, pharmacological agents, and diagnostic instruments and analyzing the structures and changes in tumors and organ pathology *in vivo*.

CT diagnostic imaging and fluoroscopic imaging with angiography taken by R_mCT2 (Fig. 6) are used to evaluate heart conditions, vascular stenosis, and various tumors. They are also used for various non-clinical tests, including biochemical examinations of the kidneys and ureters.

In the field of regenerative medicine as represented by iPS cells, morphometrical analysis is performed to assess the status of bone, teeth, or organ regeneration based on 3D images. This approach is also used to evaluate drugs that may be used to treat osteoporosis, drawing on CT values to calculate BMD (bone mineral density).

CT images are also used to confirm the pharmacological action of obesity treatment drugs or nutritional supplements and to separate visceral fat from subcutaneous fat in quantitative measurements of body fat percentage.

At production sites, micro CT and X-ray fluoroscopic imaging systems are used for morphometrical analysis of granular formulations in capsule products and shape inspections of tablets for drug quality control.

3. Production (Scale Up)

Powder X-ray diffractometers and Raman spectrometers are used to confirm the starting and ending APIs. Raman spectrometers can rapidly complete measurements of products in their packaging or containers. Powder X-ray diffractometers allow identification of trace impurities. On the other hand, elemental analysis using X-ray fluorescence spectrometers is highly useful in identifying and analyzing trace metal impurities, such as residual catalysts used in reactions. See "Pharmaceutical raw material inspection with handheld Raman spectrometer" (starting on page 16) for further information on Raman spectrometry and powder XRD instruments. Also see "Analysis of trace impurities in pharmaceutical products using polarized EDXRF spectrometer NEX CG" (starting on page 19) for more information on elemental analysis with the X-ray fluorescence spectrometer.

Reference

(1) http://www.mhlw.go.jp/english/policy_report/2012/09/120921.html