Regular Article

An Application of X-Ray Fluorescence as Process Analytical Technology (PAT) to Monitor Particle Coating Processes

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Received November 9, 2017; accepted March 19, 2018; advance publication released online March 30, 2018

An attempt to apply X-Ray Fluorescence (XRF) analysis to evaluate small particle coating process as a Process Analytical Technologies (PAT) was made. The XRF analysis was used to monitor coating level in small particle coating process with at-line manner. The small particle coating process usually consists of multiple coating processes. This study was conducted by a simple coating particles prepared by first coating of a model compound (DL-methionine) and second coating by talc on spherical microcrystalline cellulose cores. The particles with two layered coating are enough to demonstrate the small particle coating process. From the result by the small particle coating process, it was found that the XRF signal played different roles, resulting that XRF signals by first coating (layering) and second coating (mask coating) could demonstrate the extent with different mechanisms for the coating process. Furthermore, the particle coating of the different particle size has also been investigated to evaluate size effect of these coating processes. From these results, it was concluded that the XRF could be used as a PAT in monitoring particle coating processes and become powerful tool in pharmaceutical manufacturing.

Key words X-ray fluorescence; Process Analytical Technology; small particle coating; layering; masking

Around in the year 2000, U.S. Food and Drug Administration (FDA) had notified to pharmaceutical companies that pharmaceuticals must be manufactured with careful control to maintain the quality of the resulting products so as to be acceptable in the market.¹⁾ Furthermore, to comply with the requirements of International Conference on Harmonisation (ICH) Q8, Q9 and Q10,²⁾ FDA urged to adopt Process Analytical Technology (PAT)³⁾ to assure quality of products during manufacturing at-line, in-line and on-line manner.

Many pharmaceutical companies and academia have employed various technologies for PAT. Near-(N)IR and Raman spectroscopy are commonly used as PAT tools for the purpose.⁴⁾ Regarding the NIR, there are many applications such as identification of raw materials to monitoring in blending and coating processes *etc.*⁵⁾ Raman spectroscopy has also been used for identification of materials, monitoring of blending processes *etc.* as well as imaging of tablet.^{6,7)} Apart from them, Laser induced phenomena and Terahertz have been applied for PAT recently.⁸⁾ Although these spectroscopic methods have their advantages, other technologies has been used for monitoring processes.⁹⁾ An X-ray fluorescence (XRF) has been used as an in-process control for estimating the thickness of laminating and coating in electronics fields for long time.^{10,11)} The XRF enables simple and effective measurement with non-destructive manner. Although the XRF is widely used for other fields such as material science, painting *etc.* besides electronics, there has been very limited applications in the pharmaceutical field.^{12–14)}

Recently, small particle coating technologies have been applied to make orally disintegrating (OD) tablets which readily disintegrate in the oral cavity. For the particle coating, the size of particles used for OD tablet is between 100 and 500 μm to achieve good texture. With the technology needs

are increasing, some specific machines and equipment such as a tumbling fluid bed granulator and a centrifugal granulator have been developed in Japan.¹⁵⁾ The main purpose of the particle coating is to give some functions such as sustained release, enteric nature and taste masking to the small particles. In the case of multi-coating particles, the number of coating increases to achieve the particle quality such as dissolution, particle strength, hardness and disintegration of the resulting tablet, *etc.*¹⁶⁾

In this paper, we prepared some particles including DL-methionine as a model compound and investigated whether the XRF technology can be applied to estimate the coating amount and masking efficiency in the small particle coating processes or not. Two coating processes (first coating by the model compound and second coating by talc based formulation) were used to obtain samples for the XRF measurement. Since the simple double coated particles (the first coating demonstrates layering and the second coating shows both of masking and layering) can simulate multi-coated particles, this double coated particles were adopted. Furthermore, the effect of core particle size for double coating processes (layering and mask coating) was also investigated by the XRF technology.

Experimental

Materials As a core material, Celphere® (Asahi Kasei Chemicals Co., Japan) was adopted. The shape of the material is spherical and then it is very easy to perform homogeneous and efficient particle coating. The Celphere® has four different sizes and grades (CP-102, CP-203, CP-305 and CP-507) with the parameters listed in Table 1.¹⁷⁾ Grade of the Celphere® is named after the particle size. Therefore, D_{50} of CP-102, CP-203, CP-305 and CP-507 is 160, 235, 385 and 585 μm ,

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Table 1. Characteristics of Celphere[®] with Different Sizes¹⁷⁾

CP number	CP-102	CP-203	CP-305	CP-507
Particle range	106–212	150–300	300–500	500–710
D_{50} (μm)	160	235	385	585
Apparent density (g/cm^3)	0.83	0.87	0.97	0.97
Degree of sphericity	1.2	1.1	1.1	1.2
Particle size by LA-950, D_{50} (μm)	172.5	269.9	415.6	628.1
Surface area (cm^2/cm^3)	354	223	145	95.2

Table 2. Formulation of Celphere[®]-DL-Methionine Particles (1.7% DL-Methionine for First Coating and 1.4% DL-Methionine for Second Coating)

Raw material	Maker	Formulation (g)
Core material		
Celphere [®]	Asahi Kasei	1000
Layering solution (solid content <i>ca.</i> 13%)		
DL-Methionine	Wako Pure Chemical Industries, Ltd.	20
Filler & Binder	—	112
Water	—	868
Masking coating solution (solid content is <i>ca.</i> 19%)		
Talc	Matsumura Sangyo	125
Lactose+Corn starch+HPC+Macrogol	—	155
Water	—	1220

respectively. Prior to coating to these core materials, particle size of these cores was measured with a Laser Scattering Particle Analyzer (Horiba LA-950: Horiba Machinery Co., Ltd., Japan) and the data and surface area were also listed in the table.

In this study, DL-methionine was used as a model compound as it contains sulfur atom that XRF signal emits. DL-methionine was purchased of special grade from Wako Pure Chemical Industries, Ltd. (Japan) Other raw materials used for coatings were obtained from the following companies: Lactose monohydrate (DFE Pharma, Germany), Hydroxypropyl Cellulose (HPC) (Nippon Soda Co., Japan), Talc (Matsumura Sangyo, Japan), Macrogol (NOF Corporation, Japan) and Corn Starch (Nichii-den Chemical Co., Japan). Formulations and quantities for manufacturing with small scale are shown in Table 2.

Method The preparation of the samples was carried out with a LAB-1 fluid bed granulator or an MP-01 tumbling fluid bed granulator equipped with fluid bed granulator mode (both are machines by Powrex Co., Japan). The manufacturing conditions for the sample preparation are shown in Table 3.

The XRF technology enables identification and composition of elements contained in specimen by irradiating X-ray. Figure 1-A shows outcomes by irradiating X-ray to the specimen. There are many signals generated by the X-ray irradiation, resulting that a lot of information are included in the output signals. In this study, an energy dispersive XRF instrument as shown in Fig. 1-B was used for at-line or in-line measurement. In this method, high purity silicone detection is used to take the XRF emitted from the matter (specimen).^{10,11)}

A schematic of the particle coating process is shown in Fig. 2. As explained in Introduction, model particles with two different coating layers, one with model compound and a second with talc suspension, were measured. Figure 2 shows the processes applied for this study. The manufacturing conditions are shown in Table 3. In both coating processes, a similar con-

Table 3. Manufacturing Conditions for Small Particle Coating Processes

Condition item	First coating	Second coating
Equipment	MP-01 or LAB-1	MP-01 or LAB-1
Scale (kg) (at the end of process)	1132 g	1412 g
Air volume (m^3/h)	85	75
Inlet air temp. ($^{\circ}\text{C}$)	80	75
Spray speed (g/min)	10–20	10–20
Spray amount (kg) (solution base)	1	1.5
Spraying time (min)	50–100	75–150

dition was applied to obtain similarly coated particles of both the model compound and talc.

In the first coating process, DL-methionine is coated on the surface of core materials (microcrystalline cellulose sphere). After the first coating, the second (mask) coating was made to cover the DL-methionine.

A solution containing a binder and DL-methionine was sprayed onto 1000 g of core material followed by talc. The amount of spray for first and second coatings was approximately 1000 and 1500 g, respectively. As a consequence, the spray coating time will fluctuate with the different core particles (see Table 3).

The measurement was made with a MESA-500 (Horiba Machinery Co., Ltd.). The equipment is an Energy Dispersive Type X-ray Fluorescence Analyzer. Since the instrument is a desk-top type XRF analyzer, measurements were performed at-line analysis. The X-ray tube voltage was set at 15 kV for sulfur and silicone detection in all experiments. Samples were set to the measuring chamber and XRF was measured under vacuum condition. The calibration was carried out using two different alloys as standard materials and using a standard method and program. The XRF intensities were measured by counting the detection signal for 100 s except for measuring time study.

Fig. 1. Schematic Draw of X-Ray Related Signals and Energy Dispersive XRF Apparatus

(A) Response from X-ray irradiation. (B) Energy dispersive XRF apparatus.

Fig. 2. Schematic of Small Particle Coating Processes

Fig. 3. Sulfur XRF Signals and Variation of DL-Methionine First Coated Particles (CP-507) against Measurement Time (Variation Is S.D.)

Results and Discussion

Effect of Measurement Time Prior to evaluation of the coated particles, effect of measuring time of XRF by using CP-507 first coated particles was investigated. Data are shown in Fig. 3.

As seen from the Fig. 3, it was shown that measured value did not fluctuate at all with the measurement time, meaning that constant signals were obtained by the XRF measurement even shorter measurement time. Furthermore, the variation such as relative standard deviation (R.S.D.) was very small (3.3% of R.S.D. for 50s), indicating that the measurement of 50s was sufficient to estimate the coating process. Though longer measurement time gave values with less variation (e.g. 0.9% of R.S.D. for 200s), 100s were adopted to acquire the data for this study.

First Coating Process of CP-102 In the first coating

Fig. 4. Sulfur XRF Signal Change in First Coating Process to CP-102 Cores

process, a model compound (DL-methionine) was coated to core material, Celphere® CP-102. Figure 4 shows sulfur XRF profile of the first coated particles emitting sulfur signal of DL-methionine. As coating amount to the cores increases, XRF intensity of sulfur increases. The coating amount to the core can be estimated by measuring the XRF signals from the element contained in the particles.

As seen in the figure, the XRF intensity was proportional to the coating amount (horizontal axis means spraying amount). Since the coating amount is related with the formulation shown in Table 2, the value simply indicates actual spray amount loaded to the core. From the XRF signal, coating (coated) amount can be estimated, and evaluation of the coating process could be made by monitoring the signal.

Second Coating Process to the First Coated Particles of CP-102 To the first layer of coated particles, a second coating of a suspension containing talc was applied to mask the DL-methionine coated layer. The formulation and coating conditions are shown in Tables 2, 3, respectively. Figure 5 showed the profile of sulfur signal which was attenuated by shielding the DL-methionine.

The phenomena obey Lambert-Beer's law as same mechanism with absorption of visible light. Therefore, the sulfur signal decreases exponentially, as the second coating layer of talc increases according to Lambert-Beer's law. The decay parameters relate to the density *etc.* of the coated material.

Fig. 5. Sulfur XRF Signal Change in Second Coating Process to CP-102 First Coated Particles

For these two different coating processes, the XRF can give some important characteristics such as coating amount and efficiency.

Effect of Core Particle Size Similar approach was made to evaluate coating processes to four different sizes of core materials listed in Table 1. The study was conducted to clarify how much particle size of core materials affects the coating efficiency *etc.* in the processes and to know whether such data can be obtained by the XRF or not.

First Coating For the first coating process, coating of materials such as active pharmaceutical ingredients (drug), raw materials *etc.* are used to form part of the core coat. To these different sizes of cores, DL-methionine was coated and sulfur XRF signal monitored. Figure 6 shows the XRF intensity profiles for the first coating process.

From these profiles, it was found that the core particle size becomes larger, as the XRF signals of sulfur became larger. In the case of smaller core (CP-102), the XRF signal became smaller than that of larger cores, indicating that the XRF signals might reflect the coating amount to the core. Since the surface area of larger core particles is smaller, the coating amount per particle tends to be larger. It was inferred that the XRF reflected both of the coating amount on the core and inside bulk particles. Therefore, the slope did not reflect the surface area of different sizes of cores.

The initial slope of the plot is proportional to the coating amount to the core particles. In the case of smaller particles, linearity of the plot is relatively good. However, in the case of larger core, the slope deviates from the linear line, indicating that the coating amount increases, the XRF signal becomes plateau. This is seen in the case of simple coating processes in material science.¹⁸⁾ In the case of thickness in flat material, once the thickness exceeds limiting thickness, XRF signal becomes lower than expected. This phenomenon is observed and considered to be due to the limitation of X-ray penetration to the samples.^{18,19)} In light of the fact, the lowering of the XRF intensity for larger particles might reflect the same coating status of this particle with that of flat coating result, though detail survey of the thickness has not yet been made.

Second Coating To the first coated particles, second coating was applied and the sulfur signal of XRF was counted. As is the same with Fig. 7, the sulfur signal decreased with

Fig. 6. Sulfur XRF Signal Changes in First Coating Process of Different Core Sizes

Fig. 7. Sulfur XRF Signal Changes in Second Coating Process of Different Core Sizes

an increase in the coating amount. In all core materials, XRF sulfur signals decreased exponentially. This reflected the attenuating phenomena according to shielding effect of sulfur signal by the second coating materials such as talc.

From the curve fitting equations derived from the plots, the shielding efficiency can be estimated. These parameters also reflect the shielding effect mainly by talc coating against sulfur signal of XRF.

In this XRF measurement, some additional signals derived from the elements contained in the coating materials (talc) having silicone (Si) and magnesium (Mg) were also counted at the same time. This second coating also means talc coating to the first coated particles. Instead of DL-methionine, it is like talc coating to the first coated particles. Figure 8 shows the Si signal increase by the second coating. As seen in the figure, it was also estimated that the second coating of the first coated particles by talc was relatively strong. In the case of Mg, though the signal was very small, the same tendency that Mg XRF signal increased with increasing coating amount of the second coating materials as well as that of Si. From both signals (Si and S), we could see the coating level of small particles.

By assuming a flat coating with two layers, initial substrate coating and subsequent mask coating can be simulated by a fundamental parameter method. Based on the concept,

Fig. 8. Sulfur (S) and Silicone (Si) XRF Signal Changes of Different Core Sizes

Fig. 9. Simulation for XRF Signals in First and Second Coating Processes

Table 4. Relationship between Coating Parameters and Surface Area

	Celphere®	CP-102	CP-203	CP-305	CP-507
1/(Ratio of surface area)	1.00	1.59	2.44	3.73	
Ratio of layering slope	1.00	1.30	1.66	2.47	
Ratio of decay parameter	1.00	1.60	2.66	3.25	

XRF signal from the substrate coating (first coating) is expressed as an equation of $1 - \exp(-f(k_2, D))$. On the other hand, mask coating (second coating) effect by talc suspension can be expressed by Lambert–Beer's law as an equation of $A \exp(-f(k_1, D))$. Where, A is a coefficient including incident X-ray intensity, yield *etc.* and $f(k_1, D)$ and $f(k_2, D)$ are functions of total mass absorption coefficients, density, thickness *etc.* By using these equations, simulated curves were drawn as Fig. 9. As seen in the figure, XRF increases by substrate (the first coating) and XRF decrease by the second coating has also been well demonstrated in flat coating system.²⁰⁾

The result of the sulfur signal change showed that XRF measurement might give some important features in the small particle coating processes. The strength of the signal is increased with increasing DL-methionine content. The signal decreased as the second coating amount increased. The extent of the signal is dependent on the coating amount and matrix effect. The detailed properties of the coating layer depend on

Fig. 10. Relationship between First and Second Coating, and Particle Size

the formulation, the coating processes and the method. The profiles in Fig. 9 were similar in the profiles of Fig. 8, indicating that these phenomena (emission and absorption *etc.*) in flat coating also reflected in this particle coating process.

From the particle size of the spherical microcrystalline cellulose (Celphere®) measured with the Horiba LA-950 Laser Scattering Particle Analyzer, surface area of core particles was calculated as shown in Table 1. Based on the surface area, relationship between first coating and second coating were estimated. The results were shown in Table 4 and Fig. 10. There was a good relationship between first coating, second coating and surface area. However, in the case of first coating, the slope does not reflect the surface area exactly. It was inferred that the XRF intensities might reflect not only coating effect but also bulk sulfur signals and bulkiness.

As shown in these results, it was found that the coating amount in particle coating process can be estimated by an XRF technology. The method can also be utilized to estimate the coating efficiency in the small particle coating process.

Since the coating efficiency can be estimated, once the control data (to make calibration curve *etc.*) can be obtained for the formulation and the process, the coating amount to the particles can be easily elucidated. As far as the manufacturing of coated particles is made well and the XRF of the resulting particles can be measured well, particle coating status in the process can be easily estimated by the XRF technology.

Conclusion

It was explored that an XRF technology can be used for PAT to monitor the interim particle coating level during the particle coating process. For the processes, such as first coating (layering), the XRF can be used for estimating the coating amount. For subsequent second (mask) coating to the first coated particles, the coating efficiency was also estimated by the XRF from both of first and second coated materials at the same time. This measurement was made non-invasively and at-line manner within very short time. There are rooms to extend the manner from at-line to on-line and in-line, because many portable XRF instruments have been developed. It was found that the particle size effect in particle coating process could be measured by the XRF. The data showed that XRF can give parameters related with coating amount and efficiency which depends on the coating formulation and

the process conditions, from which we can observe how well the manufacturing process has worked or not by monitoring the data produced by the XRF. The application of the XRF to the small particle coating process as part of PAT would be valuable for process monitoring. Although NIR and Raman technologies have been widely used for the purpose, the XRF might give another option as one of PAT technologies. It is therefore concluded that the application of the XRF techniques as part of PAT for particle coating processes could give benefit to future production and processes in terms of quality. The XRF method would be a valuable tool as PAT.

Acknowledgments The authors thank Dr. T. Yashiki (former head of Pharmaceutical Development Laboratories of Eli Lilly Japan K. K.) on supporting this study and also thank Mr. N. Thakore for contributing to the preparation of this manuscript.

Conflict of Interest The authors declare no conflict of interest.

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