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# APPLICATION OF ENERGY-DISPERSION X-RAY ANALYSIS TO DETECT MAGNESIUM STEARATE ON TABLET SURFACES

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**ABSTRACT**

An energy-dispersion X-ray analyzer (EDX) attached to a scanning electron microscope was used to evaluate the distribution of lubricant on the surface of tablets prepared by using an external lubrication system (ELS). Optimal operating conditions for EDX were determined (probe current: 0.40 nA, accelerating voltage: 7.0 kV, and measurement time: 200 sec). Quantitative analysis was found to be possible by using a tablet prepared by the conventional method with magnesium stearate (Mg-St) and determining the amount of Mg detected by EDX. In the application of EDX to ELS, an increase in charged voltage brought about an increase of Mg sensing efficiency on the tablet surface. Further, Mg was not distributed uniformly on the tablet surfaces, with more Mg observed on the punch-side surface than on the die-side surface. These findings indicate that EDX is applicable to investigating the distribution of small quantities of Mg-St and is one of the useful methods for formulation studies based on "Quality by Design".

**Keywords**: Energy-dispersion X-ray analyzer, External lubrication system, Lubricant, Magnesium stearate.

## INTRODUCTION

Traditionally, the quality of pharmaceuticals is assessed by various tests, including measures of dissolution, content uniformity, and so on. However, this quality assurance system, termed "Quality by Testing" (QbT), is changing since the release of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline in 2005 and its revision in 2009 [1]. In the new quality assurance system termed "Quality by Design" (QbD), product quality is built-in through the formulation process. This is a big change from the development based on trial and error and an individual scientist's experience to development based on scientific evidence. To date, various analytical methods such as Raman spectroscopy [2] and near infrared spectroscopy (NIR) [3-5] have been used most frequently for these studies. However, NIR and Raman spectroscopy do not evaluate all the properties of pharmaceutical products. Thus, development of analytical methods applicable to the formulation process is required.

An energy dispersion X-ray analyzer (EDX) attached to a scanning electron microscope (SEM) was found to be very useful to detect the specific element in the sample and is expected to apply to pharmaceutical formulation study. However an application of EDX to pharmaceutical field is quite limited until now [6-11]. In particular, EDX has potential application when material distribution has a significant influence on pharmaceutical properties such as surface coating [12]. EDX is one of the most useful analytical tools for this purpose and performing formulation studies by QbD.

The distribution of magnesium stearate (Mg-St) on the surface of granule and excipientparticle has been evaluated by using EDX [13-16]. However, no studies have reported the distribution of Mg-St on tablet surfaces

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by using EDX. Furthermore, for tablets prepared using an external lubrication system (ELS), there are only two reports that has used NIR [17] and Raman spectroscopy [2]. ELS has the advantages of low lubricant content (1/10) and distribution only on the tablet surface over conventional tableting methods [18-19]. ELS is often applied for the development of orally disintegrating tablets, which dissolve within 30 sec in the mouth [20]. However, problems such as sticking may occur if the lubricant is not dispersed uniformly on the surface of tablet. Therefore, a detailed examination of the distribution of lubricant on the surface of tablets would be useful. EDX is used to measure the distribution of elemental Mg as an index of Mg-St on the surface of tablets prepared by using ELS, and its usefulness as an analytical method for formulation studies is evaluated in the present study.

## MATERIALS AND METHODS

### Materials

Crystalline cellulose, marketed as Ceolus®KG-802, was purchased from Asahi Kasei Chemicals Corp. (Tokyo, Japan) and magnesium stearate (Mg-St) from Taihei Chemical Industrial Co., Ltd. (Osaka, Japan). Direct compression lactose powder (Dilactose®S) was obtained from Freund Corporation (Tokyo, Japan). Other chemicals were reagent grade.

### Methods

#### Preparation of tablets

#### The conventional method

Dilactose®S was uniformly mixed with Mg-St of 1 (w/w)%, 3 (w/w)% and 5 (w/w)% in a stainless vessel and then sieved thrice by using a 710 μm aperture sieve. This mixed power was tableted by using a tableting machine (MINIPRESS MII, RIVA Sociedad Anonma, Buenos Aires, Argentina) equipped with φ7.5 flat face punch at a tableting rate of 20 tablets/min and a compression force of 9.8 kN. This tablet (average weight: 200 mg) was used for the quantitative analysis of Mg-St by using EDX.

#### Preparation of tablets by using ELS

A tableting machine (AQU3 0512SW1AI, Kikusui Seisakusho Ltd., Kyoto Japan) was used to prepare tablets (φ8 R12 punch) consisting of Ceolus®KG-802 by using ELS (ELS-P2, Kikusui Seisakusho Ltd., Kyoto Japan). Tablet weight, tableting force, and tablet hardness were about 200 mg, 10 kN, and 0.5 kN, respectively. These tablets were used for evaluation of the applicability of EDX in determining the distribution of Mg-St on tablet surfaces. In this system, the charged voltage of ELS, which influences the amount of Mg-St adhesion to the tablet, was varied from 0 to 40 kV (0 kV, 10 kV, 20 kV, 30 kV, and 40 kV) to obtain different samples for the study. The spray rate of Mg-St and tableting rate were kept constant at 38 ± 2 g/h and 30 rpm, respectively. In this method, the lubricant is expected to exist only on the tablet surface. In order to investigate whether Mg-St is present inside the tablets prepared by using ELS, the tablet was cut by the cutter, and the cutting surface was observed by using EDX. Further details of ELS have been presented in a previous report [19].

### Measurement of Mg by EDX

#### Preparation of samples for measurement

A sample tablet was fixed on an aluminum stage by using carbon paste and double-sided tape, and carbon deposition was performed by using a vacuum deposition device (VE-2020, Vacuum Device Ltd., Mito, Japan) to obtain a carbon thickness of around 20 nm. A SEM (SEMEDX type N, Hitachi High-Technologies Corporation, Tokyo¸ Japan) with EDX (Super Xerophy detector, EMAX-500, Horiba, Ltd., Tokyo, Japan) was used in this study.

#### Operational conditions of EDX

There are three operation conditions (probe current, accelerating voltage, and measurement time) that have a significant influence on the results of the measurement by using EDX. Therefore, probe current (0.1 nA, 0.2 nA, 0.3 nA, 0.4 nA, and 0.5 nA), accelerating voltage (5.0 kV, 7.0 kV and 10.0 kV), and measurement time (100 sec and 200 sec) were varied to evaluate their effects on the results and to obtain optimal operational conditions. Measurement of Mg was carried out with a magnification of 500 × (about 0.045 $mm^2$ area) to investigate its distribution state followed by area and line analyses.

Analytical software installed in the EDX was used for data analysis. Quantitative correction by using the standard-less Φ(ρZ) method, peak resolution by using the overlap factor method, and background subtraction processing based on two automatic set BG points (4.80 keV and 8.50 keV) were adopted for this data treatment, but low-energy BG correction was not employed in this study. Measurements were repeated five times for each sample and three tablets (total points = 15/ sample). Specific X-ray energies (Kα) of Mg (1.253 keV), carbon (0.277 keV) and oxygen (0.525 keV) were used for analysis in this study. Mg concentration was calculated as weight percentage ((w/w)%) according to standard-less Φ(ρZ) method.

#### Quantitative analysis of Mg-St

Tablets containing three different concentrations of Mg-St were prepared by using the conventional method and the relationship between concentration and Mg

detected by using EDX was examined. On the spectrum of EDX as shown in Figure 1, three main peaks due to Mg, carbon, and oxygen were observed in this procedure.

## RESULTS AND DISCUSSION

### Optimal conditions for EDX measurements

The influences of probe current, accelerating voltage, and measurement time were investigated to determine the optimal operating conditions for the EDX analysis. For this investigation, tablets prepared by using ELS under a charged voltage of 40 kV were used because these tablets are more practical for study.

### Influence of probe current

The Mg concentrations obtained are summarized in Table 1 for probe currents from 0.10 nA to 0.50 nA with an accelerating voltage of 10.0 kV and a measurement time of 200 sec. With an increase of probe current, Mg concentration and dead time (DT) increased from 0.30 (w/w)% to 0.52 (w/w)% and 3.1 % to 13.2 %, respectively. The standard deviation of the data tended to decrease with an increase of probe current. Electrostatic charge of the sample increased at a probe current of 0.5 nA making it impossible to detect Mg stably. Based on these results, 0.4 nA of probe current was chosen as the optimal condition for the measurement.

### Influence of accelerating voltage

Mg concentration, 2 σ, and DT under acceleration voltages of 5.0 kV, 7.0 kV, and 10.0 kV are summarized in Table 2, carried out at a probe current of 0.40 nA and measurement time of 200 sec. In general, accelerating voltage, which is two to five times higher than that required to excite an element, is considered effective for detection [21]. Therefore, 3.0 kV to 7.0 kV should be sufficient for the detection of Mg, whose specific X-ray energy is 1.253 kV. As a result, an accelerating voltage of 7.0 kV was employed in this study due to the relatively high Mg concentration, low 2 σ, and short DT.

### Influence of measurement time

Mg concentrations detected at measurement times of 100 sec and 200 sec under a probe current of 0.40 nA and an accelerating voltage of 10.0 kV are shown in Table 3. Mg concentration increased from 0.46 ± 0.07 (w/w)% to 0.57 ± 0.05 (w/w)% (mean ± 2 σ) with an increase of measurement time from 100 sec to 200 sec, indicating that the increase of measurement time led to higher concentration of Mg due to a decrease of background noise. Therefore, a time of 200 sec was employed for further experiments.

Probe current, accelerating voltage, and measurement time have a significant influence on analytical results. Therefore, it is necessary to evaluate the impact of these parameters in advance to establish the optimal conditions for sample measurements.

### Quantitative analysis of Mg

A typical EDX spectrum obtained from a tablet surface prepared with a Mg-St concentration of 1 (w/w)% by using the internal addition method is shown in Figure 1. A large peak of carbon and oxygen and a small peak of Mg were observed. The small peak observed near oxygen is considered a false peak because of the simultaneous entries of carbon and oxygen in the detector. The Mg concentration from this spectrum as calculated by the standard-less Φ(ρZ) method was 0.32 (w/w)%; concentrations of carbon and oxygen were 55.18 (w/w)% and 44.50 (w/w)%, respectively.

The same measurement and calculation were made for tablets containing 3 (w/w)% and 5 (w/w)% Mg-St by using the internal addition method. As shown in Figure 2, a linear relationship between weight % of Mg-St and Mg concentration was obtained, showing that this method is useful for quantitative analysis, and the linear relationship can be used as a calibration curve. However, the composition of tablets prepared by using the internal addition method must be the same as that of the tablets prepared by using ELS. Differences in the composition will lead to an inaccurate calculation of weight % of lubricant.

### Mg concentration on tablet surfaces by area analysis

A spectrum similar to that in Figure 1 was obtained with tablets prepared by using ELS. However, the same calibration curve could not be used to determine Mg-St concentration because the composition of tablets prepared by using ELS was different from those prepared by using the internal addition method. Therefore, the quantity of Mg-St on the tablet surface was expressed as Mg weight % from the spectrum. An area analysis of SEM images was then performed with the digital beam control (DBC) function (Figure 3). In this analysis, the image was 256 × 256 pixels with 256 gradations. As shown in Figure 3, Mg was uniformly distributed over the tablet surface, but small clumps were observed in many places, and no Mg was detected in the hollows among cellulose fibers. Yamamura also reported that distribution of Mg-St was not uniform on the tablet surface based on the results from NIR analysis [22]. These data confirm that neither the macro state nor the micro state is dispersed uniformly.

The Mg concentrations for tablets prepared by using ELS under different charged voltages are summarized in Figure 4 & Figure 5 and show that Mg on the side face (die side) was less than that on the top surface (punch side). Mg concentration on both tablet sides was found to increase as the charged voltage increased from 0 kV to 20 kV and plateaued at charged

voltages over 20 kV. In addition, Mg concentration on the side face was slightly lower than that of the punch face. On the other hand, the variation of the die side was smaller than that of the punch side. This is probably because the side face of the tablet rubs the wall of the die when the tablet is ejected from the die. The concentration of Mg on the cutting face of the tablet was almost negligible (data not shown).

**Line analysis**

The results of a line analysis of the tablet surface and the cutting face are shown in Figure 6 and indicate that there is very little Mg on the cutting surface. This observation suggests that there is very little Mg-St inside of tablet. On the other hand, a high peak of Mg was observed on the surface. This result is consistent with Figure 3.

This result indicates that most of the Mg-St is on the surface of tablets prepared by using ELS and is in agreement with its expected mechanism. This type of analysis will be useful for formulation studies based on scientific evidence by using EDX.

**Fig 1. Energy-dispersion X-ray (EDX) spectrum of a tablet prepared by using external lubrication system (ELS) under charged voltage of 40 kV. The solid line indicates the baseline**

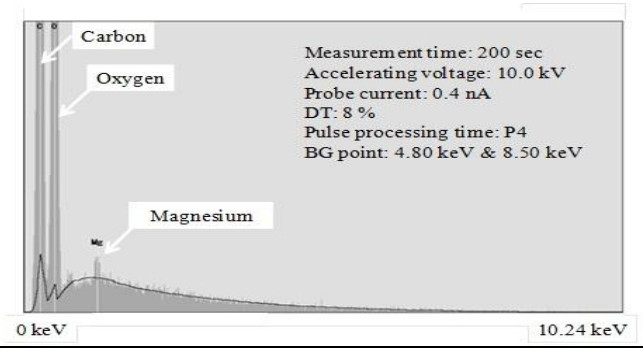



**Fig 2. Relationship between magnesium stearate (Mg-St) concentration ((w/w)%) in tablet and Mg ((w/w)%) detected by using energy-dispersion X-ray (EDX)**

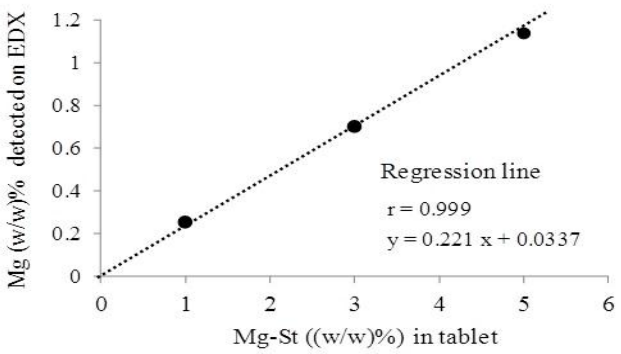



**Fig 3. Scanning electron microscope (SEM) and energy-dispersion X-ray (EDX) images of carbon (blue), oxygen (green), and Mg (red) (magnification: 500 ×)**

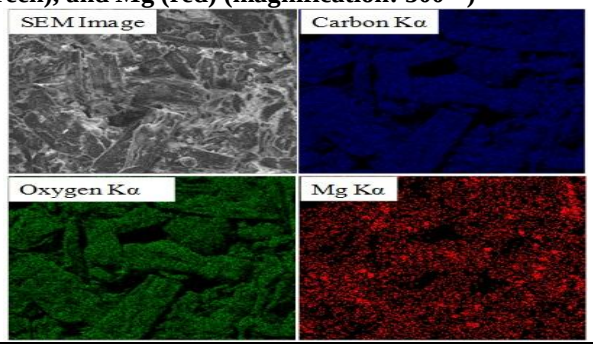



**Fig 4. Changes of the amount of magnesium (Mg) on tablet surface (punch side) upon varying the charged voltage of external lubrication system (ELS)**

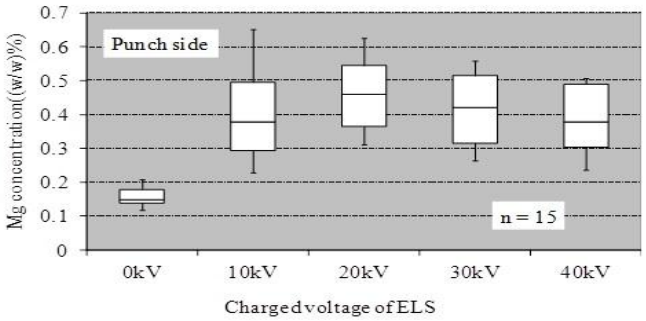



**Fig 5. Changes of the amount of magnesium (Mg) on tablet surface (die side) as the charged voltage of external lubrication system (ELS) is varied**

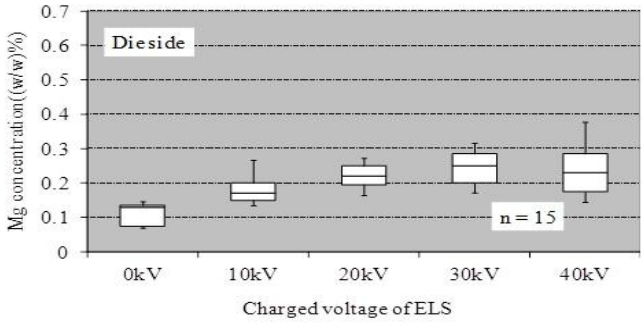
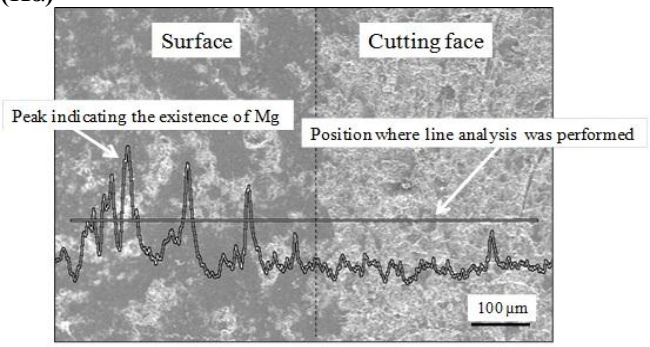



**Fig 6. Line analysis of magnesium (Mg) element on tablet and cutting surfaces. Peak obtained was of Mg (K*α*)**



## CONCLUSION

EDX was confirmed to be a useful method to detect small amounts of Mg and its distribution on the surface of tablets. It was found that the distribution of Mg was not uniform. For example, the Mg concentration on the punch and the die sides was different. In addition, concentration of Mg inside the tablet was negligible. This finding is believed to be specific for tablets prepared by using ELS; however, further examination under altered spray conditions in ELS will be necessary. When the material distribution is uniform from a macro perspective, the material seems to be localized from a micro perspective. In many cases, this kind of material localization does not have a serious influence on pharmaceutical quality. However, for current pharmaceutical development based on QbD, EDX will be extremely useful to investigate the micro-distribution of the material in pharmaceuticals.

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