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RESEARCH ARTICLE

Non-invasive and rapid analysis for observation of internal structure of press-coated tablet using X-ray computed tomography

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Abstract

Background: Since the internal structure of a tablet can be measured without destruction of the sample by X-ray computed tomography (CT), it could be applied to quality control of tablets during the manufacturing process. *Aim*: A novel, fast, noninvasive tablet observation method was developed to evaluate the internal structure of commercial press-coated tablets by using X-ray CT. *Method*: Thirty-two CT image slices of four kinds of commercial press-coated tablets (tablets A, B, C, and D) were measured 300 m interval between edges of the tablet by using an X-ray CT. The thinnest layer thickness of the tablets and distance between centers of gravity (DCG) of tables were calculated. *Results*: The order of the TLT of the tablets was tablet B > tablet C > tablet D > tablet A. The result indicated that the order of DCG was tablet A > tablet D > tablet C > tablet B. Noninvasive observation of the internal structure of commercial, press-coated tablets by X-ray CT has been demonstrated to be useful in quality control of production. *Conclusion*: The internal structure of press-coated tablets could be observed without pretreatment, without destruction, and very rapidly by X-ray CT.

Key words: *Noninvasive observation; press-coated tablets; quality control of production; X-ray computed tomography*

Introduction

In recent years, high-resolution computed tomography (CT) is being used in hospitals to diagnose many diseases, such as cerebral abscess and/or cerebral intracerebral hemorrhage, in human patients without any surgical invasion. The advantage of using X-ray CT is that it can take cross-sectional images, and the accumulated cross-sectional images can be used to produce three-dimensional images and are analyzed noninvasively. In particular, X-ray absorption rates are different for each internal structure. Each slice of data can be processed with the help of a computer and can be reconstructed as a three-dimensional picture or data. Therefore, X-ray CT has been used to observe the CT images of animals and the internal structures of small objects.

Micro CT and CT for animals have also been developed to observe small objects and have already been used in various research and development activities for ceramics, semiconductors, and electric devices. Micro CT can obtain a higher-resolution CT image compared with the conventional CT, but micro CT requires more time to obtain those images. In contrast, X-ray CT for animals can observe the internal structure of the objects in short time. X-ray CT for animals has been used in the development of drugs for osteoporosis and in the evaluation of their curative effects[1,2,3,4,5]. In the pharmaceutical industry, X-ray CT is being used to evaluate the geometrical structures of the tablets. It reported about the differences in density distribution within a tablet[6,7]. Recently, a research investigated the density analysis of intact solid oral dosage forms using terahertz pulsed spectroscopy[8].

As the press-coated tablet[9,10,11] is a multicomponent tablet, consisting of two or three layers with a central part or core, it can offer long-term drug release and help in reducing the number of dosage forms; hence, the

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press-coated tablet can be considered a useful dosage form for patients. However, the thickness of the outer layer of the press-coated tablet influences the drug-release profile, which affects the quality of the press-coated tablets. The gap of the core in the press-coated tablet directly influences its medicinal effect through variability in drug release.

Recently, process analytical technology (PAT) has become very important in drug manufacturing. PAT guidelines by the US Food and Drug Administration[12] and online real-time analysis as a tool to monitor and control the manufacturing process have become increasingly accepted in the pharmaceutical industry.

The internal structure of a press-coated tablet can be measured without destructing the sample using X-ray CT, because the X-ray transmittance depends on the density of the tablet, reflecting the geometrical structure. The gap between the inner core and the outer core of the press-coated tablet could be, therefore, observed noninvasively using CT. However, it is necessary to apply fast measurements in order to use PAT in the production of press-coated tablets. If the X-ray CT can qualitatively and quantitatively measure the gap between the outer core and the inner core of a press-coated tablet, then it could be applied for the quality control of the press-coated tablets during the manufacturing process. In the present study, therefore, we investigated the accuracy and the performance of measurement of press-coated tablets using X-ray CT.

Materials and methods

Materials

Three kinds of commercial press-coated tablets were obtained from the market (tablets B, C, and D), as shown in Table 1. Tablet A, a test formulation, was donated by corporation A.

These four different tablets were used for X-ray CT observation.

Table 1. Commercially available press-coated tablets.

Company	Name	Lot no.	Purpose
Tablet A			
Corporation A	Testing formulation	—	Combination cold remedy
Tablet B			
Bayer	Adarat CR	D194	Oral antiarrhythmic agent
Tablet C			
Zenyaku	Katase Tablet	BEU80	Combination vitamins and calcium
Tablet D			
Merck	Alyse Tablet	NR26A	Combination digestive enzyme

Table 2. Specs of commercial CT equipments.

Company	Model	Resolution (μm)	Time[a] (s)	Application
Aloka[b]	LCT100	0.060	5	For animal
Rigaku	System R_mCT	0.020	17	For animal
Shimadzu	SMX-90CT	0.020	40	For object
Yamato	TDM1000, 1300	0.024	120	For object
Tesco	VENLO 320H-ACTIS+3	0.020	67	For object

[a]Time required to take a CT image. [b]This instrument was used in this study.

Methods

X-ray CT

X-ray CT was carried out using LCT-100A (Aloka Co. Ltd., Tokyo, Japan): the tube current was 1 mA; tube voltage was 50 kV; and the slice interval was 300 μm. The performance of commercial CT equipments is shown in Table 2.

Distance between centers of gravity of the outer core and the inner core of the press-coated tablets

Distance between centers of gravity (DCG) of the outer core and the inner core of the press-coated tablets were calculated using the Pythagorean theorem (Aloka Co. Ltd.).

The thinnest layer thickness in the outer layer of the press-coated tablets

The thinnest layer thickness (TLT) of the outer layer was measured on the actual X-ray CT images of the middle slices of the press-coated tablets. Theoretical values of TLT were calculated by assuming that the inner core was exactly in the middle of the press-coated tablet.

Data analysis

All results were expressed as the mean ± standard deviation of 10 tablets. Statistical analysis was conducted using Welch's *t*-test[13].

Results

Qualitative analysis of the press-coated tablets

Observation of the press-coated tablet using X-ray CT

Figure 1 shows the image slices of the internal structure of Tablet A. CT image slices from no. #1 to #32 were

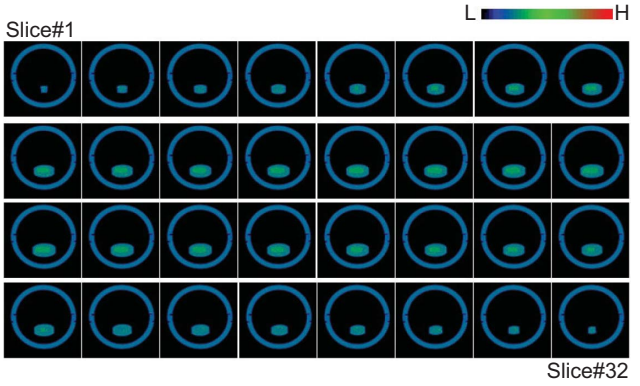

Figure 1. Image of internal structure of the press-coated tablet ["corporation A" (all slices)] using X-ray CT.

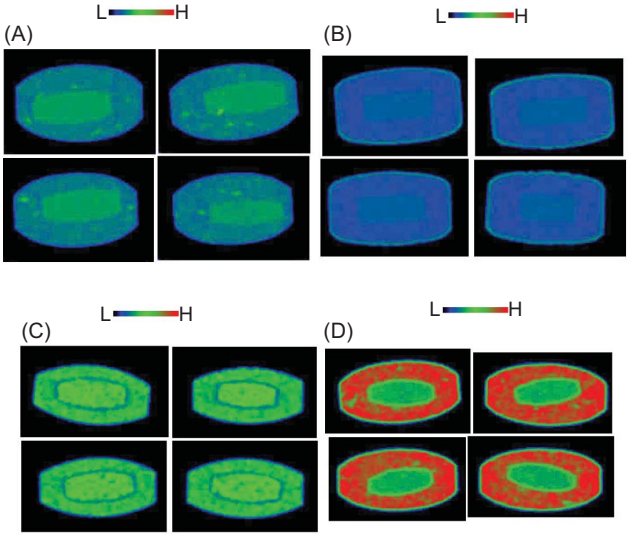

Figure 2. Imaging of commercial press-coated tablets from corporations A(A), B(B), C(C), and D(D) using X-ray CT.

measured at the 300-μm interval between the edges of the tablet. The time required for the X-ray CT measurement was 5 seconds for each slice, and the total time duration was about 160 seconds. The internal structure (inner and outer cores) of the press-coated tablet sample was observed clearly using this method.

Figure 2A–D shows image slices of all commercial press-coated tablets of corporations A, B, C, and D, respectively. Ten samples were measured to evaluate the quality of each sample tablet. The X-ray CT observation indicated that tablet A showed the largest gap of inner core in the tablet, and tablet B showed the inner core almost located in the center. The inner cores of tablets C or D were twisted inside the tablets. The order of degree of core gap in the tablet was tablet A > tablet D > tablet C > tablet B.

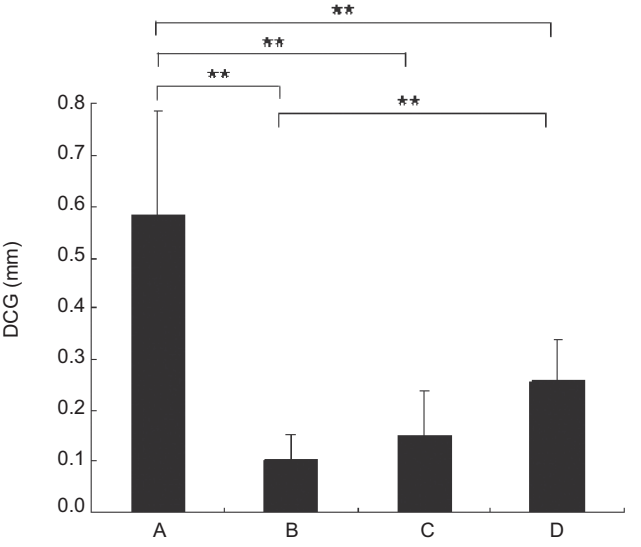

Figure 3. The distance between the centers of outer core and inner core. The data represent the average and standard deviation ($n = 10$).

Quantitative evaluation location of inner core in the press-coated tablet using X-ray CT

DCG of commercial press-coated tablets

Figure 3 showed the DCG of commercial press-coated tablets. The DCG values of tablets A, B, C, and D were 0.58, 0.10, 0.15, and 0.26 mm, respectively. The DCG of tablet A was the longest, but the value had a large standard deviation. In contrast, tablet B has the shortest DCG with small standard deviation. The result indicated that the order of DCG was tablet A > tablet D > tablet C > tablet B. The DCG of tablet A was significantly larger ($P < 0.01$) than those of the others.

The TLT in the outer layer of the press-coated tablets

Because a press-coated tablet with a large gap of inner core might show dissolution variability, it is important to evaluate the TLT in the outer layer of the press-coated tablets.

Figure 4 shows the TLT of the commercial press-coated tablets. The theoretical values of the TLT of tablets A, B, C, and D were 1.54, 1.64, 1.42, and 1.26 mm, respectively. The actual measured TLT values of tablets A, B, C, and D were 0.76, 1.44, 1.11, and 1.04 mm, respectively. The order of TLT of the tablets was tablet B > tablet C > tablet D > tablet A. All tablets showed a statistically significant difference ($P < 0.001$) between the actual and the theoretical TLT.

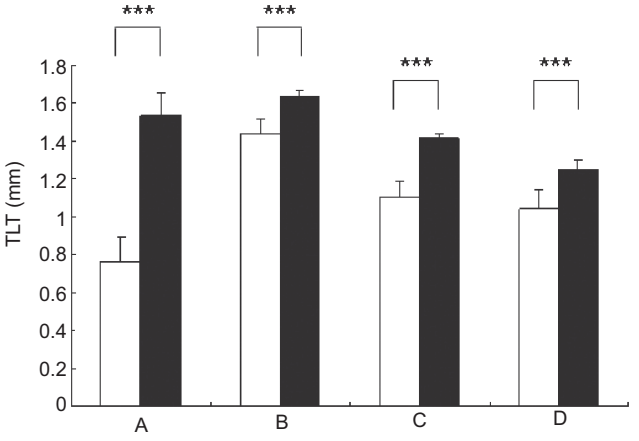

Figure 4. The distance of the edge of inner core to the edge of outer core theoretical value (■) and actual measurement (□). The data represent the average and standard deviation ($n = 10$). ***$P < 0.001$, compared to theoretical value and actual measurement (Welch's t-test).

Discussion

In general, press-coated tablets are manufactured as follows. First, the inner core tablet is prepared. Second, the outer core powder is prepared by weak compression, and then put on the inner core tablet. Third, rest of the outer core powder is applied. Finally, the tablet is compressed to produce the press-coated tablet[9,10,11]. The production of the tablet is carried out using a rotary-type tablet press machine or a single-type tablet press machine. The press-coated tablets are usually prepared using rotary-type press machines, which are very efficient. However, when a machine is used, a centrifugal force is applied to the inner core. This may cause the inner core to incline toward the outside; therefore, the location of the inner core in a press-coated tablet may be distorted. As the internal structure of a press-coated tablet can be observed using X-ray CT imaging, dislocation of the inner core in the tablet could be rapidly monitored nondestructively during the manufacturing process. Ozeki et al.[14,15] proposed a new preparation method for the press-coated tablets. They used the X-ray CT method to evaluate the gap of the inner core in a press-coated tablet. The core of the tablet system was observed, and identically evaluated, but the result was not a quantitative evaluation.

In the present study, locations of the inner core in four kinds of commercially available press-coated tablets were evaluated as shown in Figure 2. On basis of the information from the package leaflet of each pharmaceutical preparation, the density of the inner core was greater than that of the outer core in tablet A, and the inner core was packed in the tablet randomly. The inner core consisted of vitamins (ascorbic acid and hesperidin), but the outer core consisted of acetaminophen, ethenzamide, and so on. The inner core and the outer core of tablet C were almost of the same density; both consisted of additives and enzymatic drugs. However, in tablet D the density of the outer core was much greater than that of the inner core, because the outer core consisted of calcium gluconate and calcium carbonate with high X-ray absorption. In tablets C and D, the inner core was found to be twisted (Figure 2). In contrast, the density of the inner core of tablet B was lower than that of the outer core, because tablet B was a sustained-release tablet, consisting polymeric matrix with low X-ray absorption. The inner core of tablet B was located in the center in an orderly manner. The measurement of the axis angle for twisted tablets relative to the planar cross-sectional axis of the outer core has been examined in the present study, and it will be reported in a future paper.

The DCG result (Figure 3) suggested that tablet A had the highest DCG, and the order was tablet A > tablet D > tablet C > tablet B. The DCG of tablet A was significantly larger ($p > 0.05$) than the DCG of other tablets.

As shown in Figure 4, tablet B and tablet A had the largest and lowest TLT, and the order was tablet B > tablet C > tablet D > tablet A. However, the maximum and minimum differences between the actual and the theoretical TLT were tablet A and tablet B, respectively, and the order was tablet A > tablet C > tablet D > tablet B. The results indicated that tablet B was obtained from a production method with high-quality control, but that of tablet A was poor.

There are two practical purposes for the press-coated tablets. One is sustained drug release dosage form, and the other is the inhibition of solid-state drug interaction in multidrug formulations during storage. Tablet B served the former purpose, but tablets A, C, and D served the latter. As the outer layer thickness of tablet B directly controls the drug release rate, the quality control of TLT was necessarily more stringent to maintain high-quality pharmaceutical properties. In contrast, in tablets A, C, and D various formulation drugs are mixed homogeneously. These may chemically interact and induce side effects, and therefore, must be loaded in different locations in the tablet. For this purpose, it is not so important that the inner core has an accurate location in the tablet.

The noninvasive analysis of the internal structure of the press-coated tablets, for which X-ray CT was used, has the potential to be very fast and useful in PAT manufacturing. The performance of commercial CT equipment is summarized in Table 2. As the CT of corporations 1 and 2 are exclusively used for animal experiments, the time required for measurements using the CT from corporation 1 is shorter than those of others. In contrast, the CT of corporations 3, 4, and 5 are

used exclusively for small, static objects and offer much higher resolution than for animal experiments, but it takes too much time for measurements. In this study, it is very useful that rapid type CT can be observed to monitoring of manufacturing process of tablets similar to PAT.

Conclusion

The internal structure of the press-coated tablets could be observed without pretreatment, without destruction, and very rapidly using X-ray CT. This helps in the quality control process of the press-coated tablets and also identifies any possibility of cracking inside the tablet. This technique will be useful for the quality control of the press-coated tablet production as a tool of PAT.

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