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Development of a method for the determination of caffeine anhydrate in various designed intact tables by near-infrared spectroscopy: A comparison between reflectance and transmittance technique

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ABSTRACT

Using near-infrared (NIR) spectroscopy, an assay method which is not affected by such elements of tablet design as thickness, shape, embossing and scored line was developed. Tablets containing caffeine anhydrate were prepared by direct compression at various compression force levels using different shaped punches. NIR spectra were obtained from these intact tablets using the reflectance and transmittance techniques. A reference assay was performed by high-performance liquid chromatography (HPLC). Calibration models were generated by the partial least-squares (PLS) regression. Changes in the tablet thickness, shape, embossing and scored line caused NIR spectral changes in different ways, depending on the technique used. As a result, noticeable errors in drug content prediction occurred using calibration models generated according to the conventional method. On the other hand, when the various tablet design elements which caused the NIR spectral changes were included in the model, the prediction of the drug content in the tablets was scarcely affected by those elements when using either of the techniques. A comparison of these techniques resulted in higher predictability under the tablet design variations using the transmittance technique with preferable linearity and accuracy. This is probably attributed to the transmittance spectra which sensitively reflect the differences in tablet thickness or shape as a result of obtaining information inside the tablets.

1. Introduction

Recently, the concept of process analytical technology (PAT) was introduced in the FDA's Guidance for Industry [1]. PAT enables quality assurance of a whole batch by monitoring the critical-to-quality attributes (CQAs) during the manufacturing processes. As a PAT tool, near-infrared (NIR) spectroscopy is extensively used to monitor such CQAs as moisture content in the granules and crystal form of a drug during the granulating—drying process [2–7], compact hardness during the roller compaction process [8,9], blend uniformity during the powder blending process [10–18], lubricant uniformity during lubricating [19–21], tablet hardness during the tableting process [22] and film quantitation during the film coating process [23,24] because of its rapid and non-destructive process. NIR spectroscopy is also used for tablet content uniformity testing [25–29] and can be applied derivatively to monitor the drug content in each tablet during the tableting process.

In order to introduce PAT tools to production in a factory, it is necessary to identify the CQAs and to establish a monitoring method for the CQAs during the production process by the use of PAT tools during pharmaceutical development which includes formulation optimization. Since the NIR spectra are affected by the components and compositions of drug products, separate calibration models for uniquely different formulations are usually needed, and the development of separate calibration models is time-consuming. In order to overcome this problem, the establishment of formulation-independent calibration models is desired. Weiβner et al. reported the development of excipient-independent calibration models [30] and Li et al. reported the development of a calibration-free semi-quantitative method [31]. Optimization of the tablet design, including embossing and scored line, are also made during pharmaceutical development in order to reduce the risk of such troubles as tableting deficiency including capping in the tableting process, and abrasion in the coating process [32,33] and

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furthermore to allow discrimination between tablets of different strengths or rival products. As well, a scored line is applied to some tablets so that the dose can be easily divided in clinical practice. However, very few studies have been reported on the NIR spectral changes by different tablet designs and their effects on the results from NIR analysis.

NIR spectroscopic analysis of tablets is non-destructive and measures the absorption of irradiated light onto the tablet. Some of irradiated NIR light penetrates through the tablet following a straight path or a scattering path. After partially penetrating into the tablet, the irradiated NIR light may also reflect off the surface of the tablet by scattering. The NIR transmittance technique detects the light penetrated through the tablet, and the NIR reflectance technique detects the light reflected from the tablet. It is known that the packing conditions of a sample affect the propagation of the irradiated light in the sample, hence affecting the absorption of irradiated light due to Beer's law accounting for the proportional relationship of the path length to the absorption of irradiated light. The effect of the sample density on the light path was proposed by Tsuchikawa et al. using time-of-flight near-infrared spectroscopy by means of a relationship between the pore structure of the sample and the light transmittance of NIR [34,35]. The theory is as follows. Since a high porosity sample has a larger air/solid boundary surface area, the intensity of the scattered light is greater than that of the straight light in the sample. Conversely, since a tightly packed sample has a larger solid/solid boundary surface area, the intensity of the scattered light is less than that of the straight light. In fact, spectral shift resulting from changes in the tablet density has been reported [27,28]. As well, changes in the tablet shape probably affect its packing conditions and hence its light propagation, as well as changes in tablet surface shape, such as embossing and scored line, which may affect its reflected light.

From the point of view of measurement techniques, many studies on the comparison of the transmittance with the reflectance techniques in terms of accuracy have been made and the transmittance technique has shown higher accuracy [36,37]. These results may be derived from differences in the detecting volume of the tablets, that is, the detecting volume using the transmittance technique is larger than that using the reflectance technique, which analyzes only the tablet's surface layer [38]. These previous studies were conducted with fixed tablet designs. However, taking various tablet designs into account, it is not necessarily appropriate to suggest that the accuracy using the transmittance technique is higher.

The purpose of the present work is to develop an assay method which is readily applicable to various designed tablets using only one calibration model. In this paper, the effect of such elements of tablet design as thickness, shape (round), embossing and scored line on the NIR spectra and drug content measurement by NIR spectroscopy using the reflectance or transmittance technique was investigated. In addition, the prediction accuracy of the transmittance technique was compared with that of the reflectance technique and the reason for their difference in accuracy was discussed. Tablets containing caffeine anhydrate as an active pharmaceutical ingredient (API) at various concentrations were prepared by direct compression. To obtain various designed tablets, the tablets were compressed at various compression force levels with different shaped punches. Their NIR spectra were measured by the reflectance or transmittance technique. High-performance liquid chromatography (HPLC) was used as a reference method. Cal-

Table 1
Formulation, compaction pressure, and shape of tablets for the calibration set and prediction set

Batch no.	CAF (mg per tablet)	MCC (mg per tablet)	C-Na (mg per tablet)	Mg-St (mg per tablet)	Pressure (kN)	Tablet shape
For calibration set						
1	90	201	6	3	9.0	Flat faced
2	96	195	6	3	9.0	Flat faced
3	102	189	6	3	9.0	Flat faced
4	108	183	6	3	9.0	Flat faced
5	114	177	6	3	9.0	Flat faced
6	120	171	6	3	9.0	Flat faced
7	126	165	6	3	9.0	Flat faced
8	132	159	6	3	9.0	Flat faced
9	138	153	6	3	9.0	Flat faced
10	96	195	6	3	6.5	Flat faced
11	96	195	6	3	11.5	Flat faced
12	96	195	6	3	14.0	Flat faced
13	96	195	6	3	16.5	Flat faced
14	114	177	6	3	6.5	Flat faced
15	114	177	6	3	11.5	Flat faced
16	114	177	6	3	14.0	Flat faced
17	114	177	6	3	16.5	Flat faced
18	132	159	6	3	6.5	Flat faced
19	132	159	6	3	11.5	Flat faced
20	132	159	6	3	14.0	Flat faced
21	132	159	6	3	16.5	Flat faced
22	96	195	6	3	9.0	Flat beveled edge
23	114	177	6	3	9.0	Flat beveled edge
24	132	159	6	3	9.0	Flat beveled edge
25	96	195	6	3	9.0	Convex
26	114	177	6	3	9.0	Convex
27	132	159	6	3	9.0	Convex
For prediction set						
28	120	171	6	3	6.5	Flat faced
29	120	171	6	3	11.5	Flat faced
30	120	171	6	3	9	Flat beveled edge
31	120	171	6	3	9	Convex
32	120	171	6	3	9	Flat faced

CAF: caffeine anhydrate, MCC: microcrystalline cellulose, C-Na: croscarmellose sodium, Mg-St: magnesium stearate.