A Novel Rapid Quantitative Analysis of Drug Migration on Tablets Using Laser Induced Breakdown Spectroscopy

Makoto Yokoyama,*[,a] Martine Tourigny,[b] Kenji Moroshima,[a] Junsuke Suzuki,[a] Miyako Sakai,[a] Kiyoshi Iwamoto,[a] and Hirofumi Takeuchi[c]

[a] *Formulation Research Laboratory, Eisai Co., Ltd., 1 Kawashimatakehaya-machi, Kakamigahara, Gifu 501–6195, Japan:* [b] *Pharm Laser; Boucherville, Quebec J4B6Y4, Canada: and* [c] *Laboratory of Pharmaceutical Engineering, Gifu Pharmaceutical University; 5–6–1 Mitahora-higashi, Gifu 502–8585, Japan.*
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There have been few reports wherein drug migration from the interior to the surface of a tablet has been analyzed quantitatively until now. In this paper, we propose a novel, rapid, quantitative analysis of drug migration in tablets using laser induced breakdown spectroscopy (LIBS). To evaluate drug migration, model tablets containing nicardipine hydrochloride as active pharmaceutical ingredient (API) were prepared by a conventional wet granulation method. Since the color of this API is pale yellow and all excipients are white, we can observe the degree of drug migration by visual inspection in these model tablets. In order to prepare tablets with different degrees of drug migration, the temperature of the drying process after tableting was varied between 50 to 80 °C. Using these manifold tablets, visual inspection, Fourier transform (FT)-IR mapping and LIBS analysis were carried out to evaluate the drug migration in the tablets. While drug migration could be observed using all methods, only LIBS analysis could provide quantitative analysis wherein the average LIBS intensity was correlated with the degree of drug migration obtained from the drying temperature. Moreover, in this work, we compared the sample preparation, data analysis process and measurement time for visual inspection, FT-IR mapping and LIBS analysis. The results of the comparison between these methods demonstrated that LIBS analysis is the simplest and the fastest method for migration monitoring. From the results obtained, we conclude that LIBS analysis is one of most useful process analytical technology (PAT) tools to solve the universal migration problem.

Key words laser induced breakdown spectroscopy; drug migration; process analytical technology; tablet skin analysis; nicardipine hydrochloride

The uniform distribution of pharmaceutical materials such as active pharmaceutical ingredient (API), lubricants and other components is critical in order to achieve optimal product performance. A poor distribution of pharmaceutical materials may lead to many manufacturing problems (*e.g.* sticking, capping, binding and migration) during formulation development. Our current study is focused on the evaluation of one of these problems, drug migration, in fast-disintegrating tablets (FD).

FD are becoming popular as novel delivery systems for drug administration. They are more convenient for children and elderly patients with swallowing difficulties. Many companies have developed FD that disintegrates easily in the mouth. The three techniques most commonly applied to formulate FD are freeze-drying, moulding and compaction. Although freeze-drying and moulding often result in a lack of tablet hardness due to a highly porous tablet structure, compaction is a convenient and cheap way to produce tablets with sufficient structural integrity.[1)]

In the development of FD, a wet granulation method is popular. This method is applied in modified technology for moulding and compaction as a direct compression of wet granulation method. In the case of the wet granulation method, a drying process is usually required after tableting of wet granules that contains API and sugar or sugar alcohol as main excipients. During this drying progress, manufacturing problems such as migration are often encountered. In the case of a migration occurring in FD, there are some problems such as the change of the disintegration time and the taste in a mouth, and then the sticking on manufacturing process. Researchers often must develop strategies of overcome the migration of API of the tablet surface during the drying process. Although the concept of migration is well-known, there are few reports regarding drug migration during using wet granulation method. Only studies investigating the influence of drying temperature and granulation liquid viscosity on the drug migration have been reported.[2—4)] Beyond these wet granulation studies, there are only a few additional reports about migration in coated tablets and hard capsules.[5—8)]

Notably, all the studies described above evaluated migration in only qualitative manner. In other words, there have been no reports investigating drug migration by quantitative analysis until now. In the present study, we extend drug migration from a qualitative concept to a quantifiable phenomenon.

In this study, we used laser-induced breakdown spectroscopy (LIBS) to quantitatively investigate drug migration in tablets. LIBS is a type of plasma spectrochemistry used for elemental composition analysis. Two major plasma spectrochemistry techniques, inductively coupled plasma (ICP) and LIBS, are described in the U.S. pharmacopeia. Compared with ICP, LIBS has an advantage that it is not necessary to dissolve the pharmaceutical materials in a sample before analysis. In LIBS, a solid, liquid, or gaseous sample is heated directly by a pulsed laser and the volatilized constituents in the sample are analyzed quantitatively. LIBS is still an emerging analytical technology for pharmaceuticals,[9)] thus there are only some reports using LIBS for investigation of pharmaceutical materials.[10—17)]

To evaluate drug migration, model tablets containing nicardipine hydrochloride as API were prepared using a direct compression of wet granulation method with different

* To whom correspondence should be addressed. e-mail: m2-yokoyama@hhc.eisai.co.jp

drying temperatures. Since the color of API is pale yellow and those of excipients are all white, we can observe the degree of drug migration by visual inspection using this model tablets. Visual inspection, Fourier transform (FT)-IR mapping and LIBS analysis were used to evaluate the drug migration in the tablets. We also evaluated the advantages of LIBS for sample preparation, data analysis process and measurement time *versus* visual inspection and FT-IR mapping. Our findings conclude that LIBS analysis is a very useful process analytical technology (PAT) tool for solving the problem of drug migration.

Experimental

Materials Povidone (Plasdone K-29/30, ISP Japan Ltd., Japan), D-mannitol (Merck Ltd., Japan) and ethanol (Anhydrous ethanol, Japan Alcohol Trading Co., Ltd., Japan) were used in this study. Nicardipine hydrochloride (Industria Ricerche Chimiche D'albano, Italy) was used as the model drug.

Preparation of Model Tablets Povidone, D-mannitol and nicardipine hydrochloride were mixed in a mixer (R-8, Nippon Rikagaku Kikai Co., Ltd.) for 5 min. After mixing the powders, 55% ethanol aq. solution was gradually added to the mixture in quantity sufficient to achieve the state of wet granules. Approximately 280 mg of wet granules were compressed at 0.5 kN force with flat-faced round type punches, in a die of 8.0 mm internal diameter using a universal testing machine (Autograph AG-5000A, Shimadzu Corp., Kyoto, Japan). In this manner, tablets with a thickness of about 5 mm were prepared. The tablets were then dried at different temperatures ranging from 50 to 80 °C for 4 min.

Visual Inspection of Tablets Surface analysis was carried out by visually inspecting the surface of tablets. Core analysis was carried out by visually inspecting the core of the tablets after cutting the tablets with a knife. The analysis scheme is shown in Fig. 1A.

Fourier Transform (FT)-IR Mapping 2D analysis was conducted using FT-IR (Spectrum spotlight 300, Perkin Elmer Japan, Co., Ltd., Japan) in the range of 7800 to 680 cm^{-1}. Surface analysis and core analysis were performed by scanning and mapping the surface and core of tablets using principle component analysis (Hyper View, Perkin Elmer). The measurement area for the mapping was 3.6×3.9 mm at 25 μm per pixel and the measurement time was about 2.5 h. The analysis scheme is shown in Fig. 1B.

LIBS Analysis Depth profiles of the near surface of the tablets were directly assessed using LIBS (PharmaLIBS250, Pharma Laser, Canada) in the range between 508.6 and 517.2 nm to detect the carbon double bond (C_2) on the aromatic ring of the API. The pulse lasers of 150 mJ were shot at 7 spots on the surface of each tablet. Ten shots were repeated at each spot on each tablet to enable breakdown of the near surface of tablet. The measurement time was about 1 min. The analysis scheme is shown in Fig. 1C.

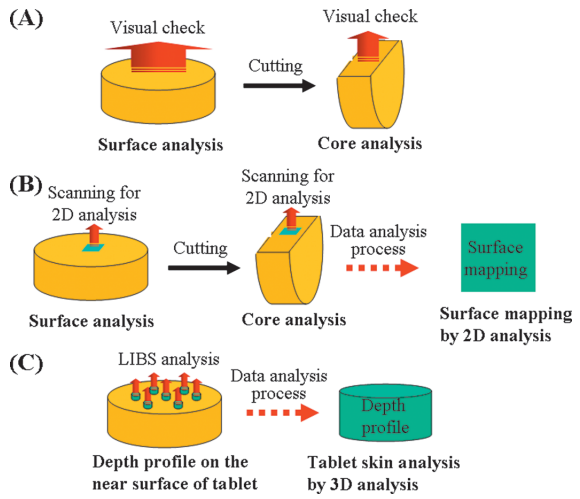

Fig. 1. Analysis Scheme of Visual Inspection, FT-IR Mapping and LIBS Analysis

(A) Surface and core analysis by visual inspection. (B) Surface and core analysis by FT-IR mapping. (C) Tablet skin analysis by LIBS.

Results and Discussion

Drug Migration in Tablets Figure 2 shows a photo-

Fig. 2. Extreme Case of Drug Migration Caused by Excess Ethanol (Actual Photograph)

Table 1. The Average C_2 Intensity during LIBS Tablet Skin Analysis of Tablets Dried at Different Temperatures

Drying temperature (°C)	Average of C_2 intensity (counts)	RSD (%) between inter-tablets (n=4)
50	520822	2.0
60	527954	6.2
70	536808	5.0
80	549397	0.5

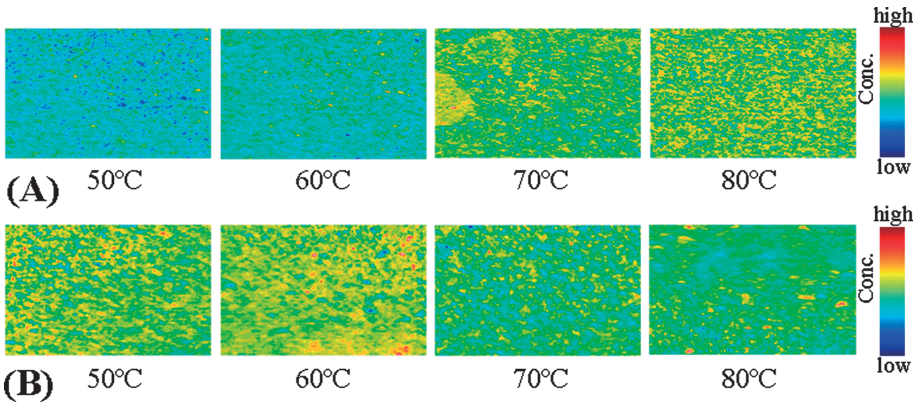

Fig. 3. Results of FT-IR Mapping for 2D Analysis

(A) Analysis of the surface of tablets prepared with different drying temperatures. (B) Analysis of the core of tablets prepared with different drying temperatures.

Table 2. Comparison of the Capability of Visual Inspection, FT-IR Mapping and LIBS Analysis

Analytical technology	Comparison of ability to confirm the migration problem			
	Confirmation of drug migration	Sample preparation (cutting of the tablets)	Data analysis process	Measurement time without sample preparation
Visual inspection	Impossible	Needed	Not needed	At the moment
FT-IR mapping	Possible (qualitative)	Needed	Needed (special process by chemometrics)	2.5 h
LIBS analysis	Possible (quantitative)	Not needed	Needed (only target peak detection)	1 min

graph of extreme drug migration in a tablet after drying with excessive ethanol. Although the surface color of the tablets was almost white before drying, the surface after drying became pale yellow. This result indicated that the pale yellow API moved to the surface with ethanol during ethanol evaporation because of its high solubility in ethanol.

Although we could observe this drug migration visually due to the color difference between the API and excipients in the above extreme condition, we could not clearly recognize coloration differences in drug migration in the model tablets used in this study. Yellow was weak and scattered on the surface and core of the model tablets prepared using drying temperatures between 50 °C and 80 °C.

In general, visual inspection also could not be used as a universal method to evaluate the drug migration because the color of many API is the same white as that of many excipients.

Two Dimension (2D) Analysis Using FT-IR Mapping Figure 3 shows the results of FT-IR mapping for 2D analysis. In the surface analysis results, localized regions of high API concentration increased as drying temperature increased. On the other hand, localized regions of high API concentration in the tablet core decreased as drying temperature increased. From these results, it was concluded that the degree of drug migration was scaled with drying temperature.

In this model, we could observe the drug migration qualitatively using FT-IR mapping. However, some issues may prevent validation of 2D FT-IR mapping as a method for monitoring drug migration. The calculation process requires complicated statistical methods including chemometrics, and uneven surface can affect 2D mapping results. The tablet cutting process required to examine the tablet core is inconvenient and may lead to these irregular surfaces. Therefore, 2D FT-IR mapping may not become a universal method for migration monitoring.

Tablet Skin Analysis Using LIBS Analysis Table 1 shows a summary of the average C_2 intensity of LIBS analysis using 4 tablets with the different drying temperatures. The results per tablet contain the average of 10 laser shots in 7 spots on the near surface of tablet. In general, the depth of penetration per a laser pulse is several tens of μm in the coating and several hundreds of μm in the tablet core. The exact depth is dependent on the pharmaceutical materials and the hardness of tablets. In this study, the near surface of tablet using LIBS analysis is called "Tablet skin analysis."

As seen in Table 1, the average C_2 intensity increased as drying temperature increased. These results indicate that tablet skin analysis using LIBS can assess drug migration quantitatively. The calculated RSD% for 4 tablets at each drying temperature indicate variability was higher at 60 °C and 70 °C temperatures than at 50 °C and 80 °C. As migration was found to scale with temperature, this may indicate that migration from the tablet core to the surface is nearing completion at the 80 °C conditions. Greater variability may thus be observed at intermediate temperatures relative to the low and high temperature conditions where a small or large amount of drug migration of the surface may be expected.

Generally, API contains one or more specific element such as metal, halogen and aromatic ring *etc.* Therefore, drug migration would be able to be evaluated using LIBS analysis targeting these specific elements in the API. Moreover, the tablet skin analysis using LIBS does not require sample preparation such as tablet cutting, and the simple, quantitative value provided by LIBS lends itself readily to method validation and PAT analysis. Consequently, the tablet skin analysis using LIBS would become a universal method to assess drug migration.

Conclusion

In this work, visual inspection, FT-IR mapping and LIBS analysis were compared to evaluate drug migration using model FD tablets. The sample preparation, data analysis process and measurement time of each analytical technology are summarized in Table 2.

Since drug migration occurs in three dimensions as API moves from the core to the tablet surface, it was necessary to evaluate the surface API concentration and core API concentration after cutting the tablet while using visual inspection and FT-IR 2D mapping. Compared with these techniques, LIBS Tablet skin analysis could evaluate drug migration directly without sample preparation owing to its ability to survey the near surface region of the tablet. Furthermore, we have shown that Tablet skin analysis could assess the drug migration quantitatively.

We believe that Tablet skin analysis using LIBS should be used as a PAT tool to solve the problem of drug migration and can contribute to formulation development of new FD.

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