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APPLICATION OF NEAR-INFRARED SPECTROSCOPY FOR EVALUATING GENERIC FORMULATIONS OF THE DRUG AMLODIPINE

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Abstract

Near-infrared spectroscopy enables non-invasive analysis of drug-formulation. This study performed a discrimination test using NIR-MX to profile generic formulations (A – J) of the drug Amlodipine, and compare them to the brand-name, Norvasc[®]. Results from the discrimination test showed that all five of the tablets for generic formulations C and G were detected as heterogeneous tablets.

Next, spectroscopic evaluation using Spectrometer-SPM-002 at the Amlodipine standard peak was performed. Only generic formulation F was found not to be significantly different from Norvasc[®].

Key words: Generic formulations, heterogeneous, manufacturing process, non-invasive.

Introduction

Recently, the cost of medical care in Japan has increased as a result of an aging society. In response to this reality, the Japanese government has initiated a campaign to promote the use of generic formulations. In spite of this initiation, Japanese consumers maintain doubts about the safety and reliability of generic formulations, resulting in lower rates of usage of generic drugs in Japan than in Europe or the United States.[1)] Consequently, reliable evaluation of generic drugs is needed in order to promote their safety to the public.

Amlodipine is a long-acting dihydropyridine calcium channel blocker that does not cause tachycardia which is frequently induced by other dihydropyridine calcium channel blockers such as Nifedipine.[2)3)] This feature makes Amlodipine the most popular antihypertensive drug in Japan. In 2008, Amlodipine's patent expired, leading to the introduction of nearly 30 generic formulations of Amlodipine onto the Japanese market.[4) 5) 6)]

In pharmaceutical industries in Europe and the United States, Near-infrared (NIR) spectroscopy is frequently used to determine the purity and identify pharmaceutical ingredients, because it is non-destructive, and requires no pretreatment.[7]   In this study, we applied NIR spectra to evaluate ten generic formulations of the drug Amlodipine, and then successfully evaluated their similarity versus the brand-name Amlodipine drug, Norvasc[®]. It is not the intention of this part of our test to evaluate whether or not the generic formulations are inferior in quality, unreliable or not safe for use. Instead, the experiment is designed to demonstrate the effectiveness of NIR-MX (Mutual Corp., Japan) as a device, and to show the similarity of generic formulations of a drug to Norvasc[®].

Materials and methods

Materials

Ten oral generic formulations, each containing 5 mg of the drug Amlodipine, and the brand-name product, Norvasc[®], were employed in this study (Table 1). The five milligram tablets of Norvasc[®] were obtained from Pfizer Co., Ltd., and the five milligram tablets of ten generic formulations of Amlodipine, A– J, were purchased from each distribution vendor.

Similarity test of generic formulations versus Norvasc[®] using NIR-MX

The discrimination test for the generic formulations of Amlodipine was performed using a tablet discrimination device equipped with NIR spectoroscopy (NIR-MX, Mutual Corp., Japan) as shown in Fig. 1.

Fig. 1 Tablet discrimination device with near-infrared spectroscopy (NIR-MX, Mutual Corp., Japan)
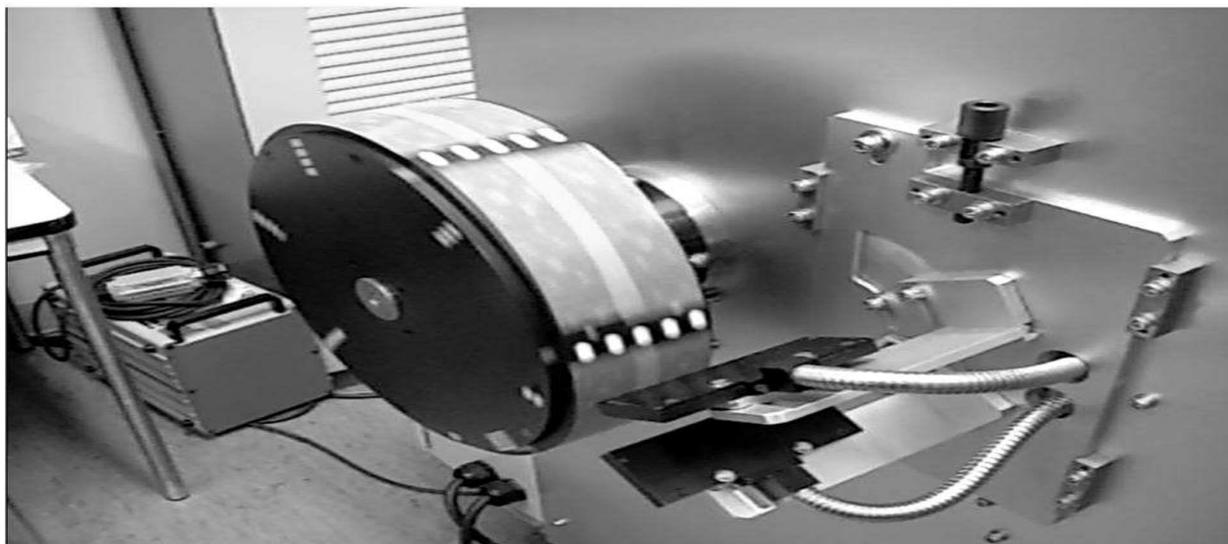
Table 1 List of Amlodipine pharmaceutical products.

Products	Lot. No.	Expiration date	Additives
Norvasc® 5 mg	11051103	2015.6	ferric microcrystalline cellulose, crospovidone, aminoalkyl methacrylate copolymer E, sodium lauryl sulfate, stearic acid, talc, dimethylpolysiloxane, silicon dioxide mixture, hydrated silicon dioxide, D-mannitol, sucralose, yellow, fragrance, magnesium stearate
A	VD011	2014.3	D-mannitol, hydrogen phosphate Ca, corn starch, hydroxypropyl cellulose, carmellose Ca, talc, stearic acid Mg, hypromellose, titanium dioxide, carnauba wax
B	022103	2013.11	crystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycolate, magnesium stearate, hypromellose, titanium oxide, talc, carnauba wax
C	1029	2014.6	D-mannitol, microcrystalline cellulose, sodium stearyl fumarate, aspartame (L-phenylalanine compound), hypromellose, Yellow No. 4 (Tartrazine) aluminum lake, l-menthol
D	VF251	2013.6	microcrystalline cellulose, calcium hydrogen phosphate dihydrate, hypromellose, magnesium stearate, titanium oxide, talc,
E	APMTH308	2014.3	crystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycolate, magnesium stearate, hypromellose, titanium oxide, talc, carnauba wax
F	T1FM09	2014.4	carnauba wax, sodium starch glycolate, microcrystalline cellulose, titanium oxide, magnesium stearate, talc, hypromellose, anhydrous calcium hydrogen phosphate
G	012060	2013.11	anhydrous calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, talc, carnauba wax
H	11501	2014.5	carnauba wax, microcrystalline cellulose, titanium oxide, stearic acid Mg, talc, starch glycolate Na, hypromellose, macrogol 6000, hydrogen phosphate Ca
I	10M081	2013.8	D-mannitol, microcrystalline cellulose, crospovidone, aspartame, l-menthol, magnesium stearate, Yellow No. 5
J	EN14A1	2014.5	cellulose, calcium hydrogen phosphate, anhydrous silicic acid, sodium carboxymethyl starch, magnesium stearate, hypromellose, macrogol, titanium oxide, talc, carnauba wax

The specifications for NIR-MX are as follows:

Near-infrared light source：Halogen lamp visceral IR filter

Optical lens measurement：25 mm F1.4

Measurement field：90 mm～210 mm

Spectral wavelength image：950 nm～1700 nm

NIR camera：Made in U.S.A, Goodrich Corp.

Image processing board：Made in U.S.A, National Instrument Co., Ltd.

Maximum testing capacity：75 msec / inspection

The drum of this machine is composed of 6 rows. Each row accommodates five tablets, thus it is capable of testing 30 tablets per test. The drum rotates 30 revolutions per minute. During rotation, near-infrared rays are irradiated to the total of the 30 test tablets at once, followed by spectroscopic analysis of the reflection wave for each tablet. Then, the data derived from spectroscopic analysis is submitted for Principal Component Analysis (PCA). [7] When mutual correlations were found through statistical data, PCA was used to locate a niche of integrated features.

Data for 375 trials was taken at 2nm intervals in the wavelength range of 950 ~ 1700 nm for each tablet. Next, of the 375 trials, 33 characteristics were selected and factor scores (the first and second principal component) for each tablet were calculated using PCA. The center circle of the graph was plotted on the basis of the factor scores (the first and second principal component), while taking into account the variation of the constant of the brand-name drug. The units for the horizontal and vertical axes of the graph are indicated as σ_1 (sigma) and σ_2 (sigma) respectively, which represent factor scores for the first and second principal components. These calculations are done automatically by "Pirouette[8]", which is the PCA calculation software that is included in the NIR-MX device.

In the first phase of this experiment, five tablets were randomly selected from each generic formulation, and loaded onto the drum, while 25 tablets of Norvasc[®], were placed on the drum as a control as illustrated in Figure 2.

Originally, the role of the NIR-MX device is to screen for content uniformity of the heterogeneous tablets during production. In this experiment, we used the NIR-MX device to examine whether the ten generic formulations of the drug Amlodipine were similar or not to Norvasc[®].

Fig. 2 Locations of tablets on the absorption drum:
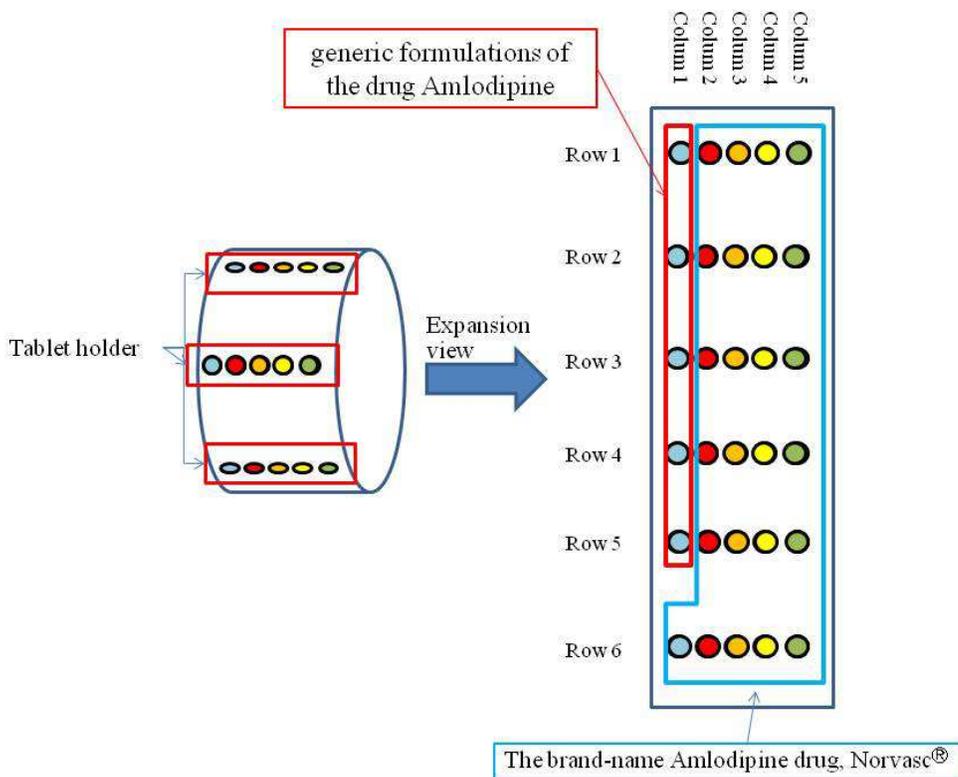
Comparison of Amlodipine content by NIR spectra

Near infrared absorption spectroscopy was performed on generic formulations and Norvasc® using Spectrometer-SPM-002 (NIR-1700) purchased from Photon Control Inc., Canada (Fig.3). The content of Amlodipine was evaluated by NIR absorbance at the peak wavelength of 1510.5 nm of the Amlodipine standard. The significant difference for each generic formulation versus Norvasc® was calculated by Dunnett's multiple comparison test.

Results

Similarity test of generic formulations versus Norvasc® using NIR-MX

Figure 4 shows the graphs for the discrimination tests of the tablets. The horizontal axis that runs through the center of the graph represents the score of the first component obtained from NIR spectra. The vertical axis running through the center of the graph represents the second component of NIR spectra. Results for the generic formulations were illustrated by a closed triangle. The outer circle in the center of the graph shows the mean discrimination area calculated on the basis of NIR spectra for 25 tablets of Norvasc®. The 25 open squares in the center circle indicate Norvasc®. In the case of Fig. 4-A, four tablets of generic formulation as illustrated by a closed triangle were located

outside of the circle and one closed triangle was located inside, thus a determination as to whether they are heterogeneous or not can not be made by NIR-MX. In the case of Fig. 4-B, all five closed triangles were located inside of the circle, thus they are not detected as heterogeneous tablets by NIR-MX. In the case of Fig. 4-C, all five closed triangles were located outside of the circle, thus they are detected as heterogeneous tablets by NIR-MX.

Fig.3 Results for the discrimination test for each generic formulation using a near-infrared spectroscopy tablet discrimination device.
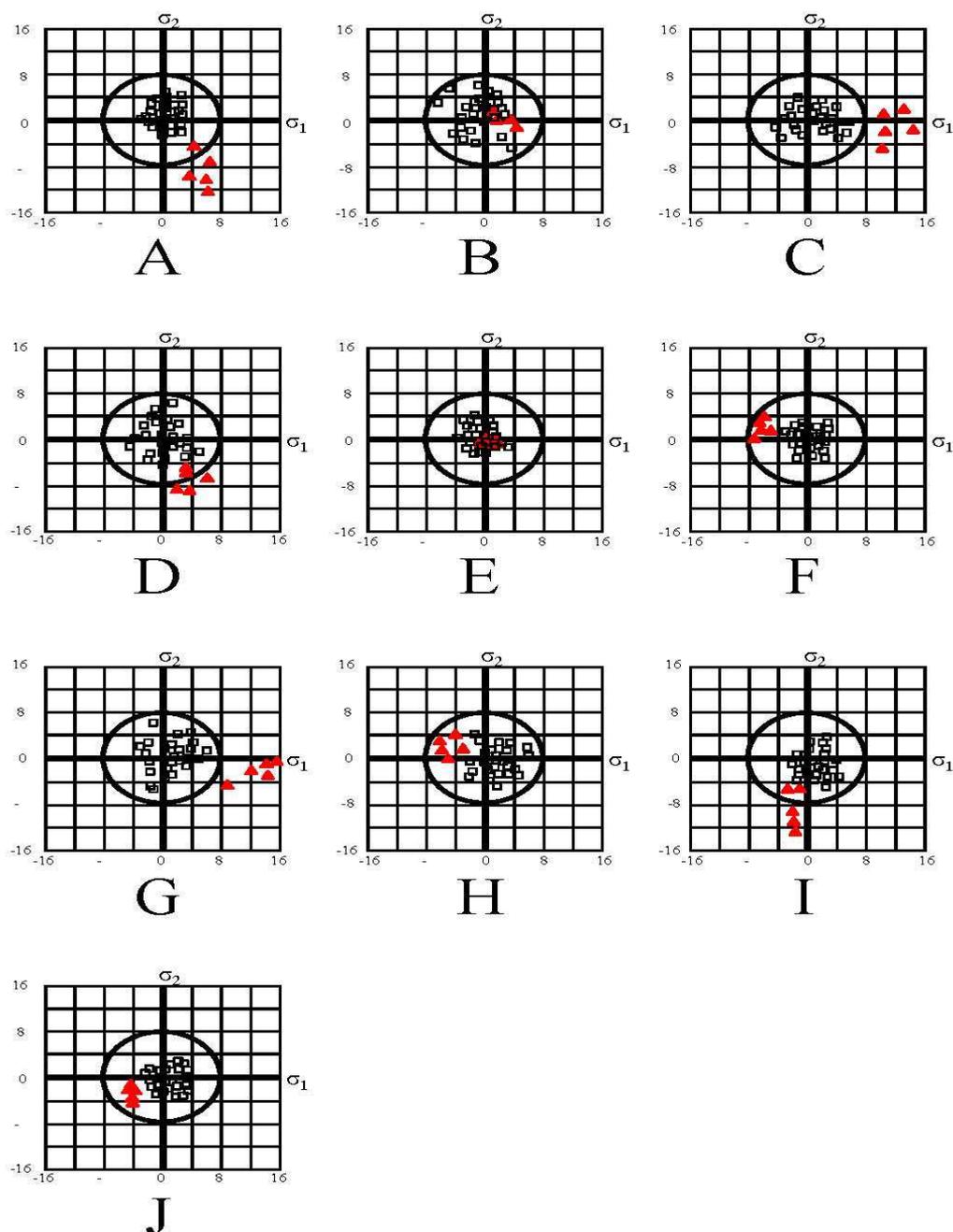
Table 2 shows the number of generic formulation tablets out of five that were identified as heterogeneous tablets. All five of the tablets for generic formulations C and G were detected as heterogeneous tablets. On the other hand, all five tablets for generic formulations B, E, F, H and J were not detected as heterogeneous tablets.

Table 2 Summary of the discrimination tests for each generic formulation using a near-infrared spectroscopy tablet discrimination deviceComparison of Amlodipine content by NIR spectra.

Products	Detection rate
A	4/5
B	0/5
C	5/5
D	2/5
E	0/5
F	0/5
G	5/5
H	0/5
I	3/5
J	0/5

Fig. 4 Near-infrared absorbance of each tablet in a stationary state at the peak wavelength (1510.1 nm) of Amlodipine.
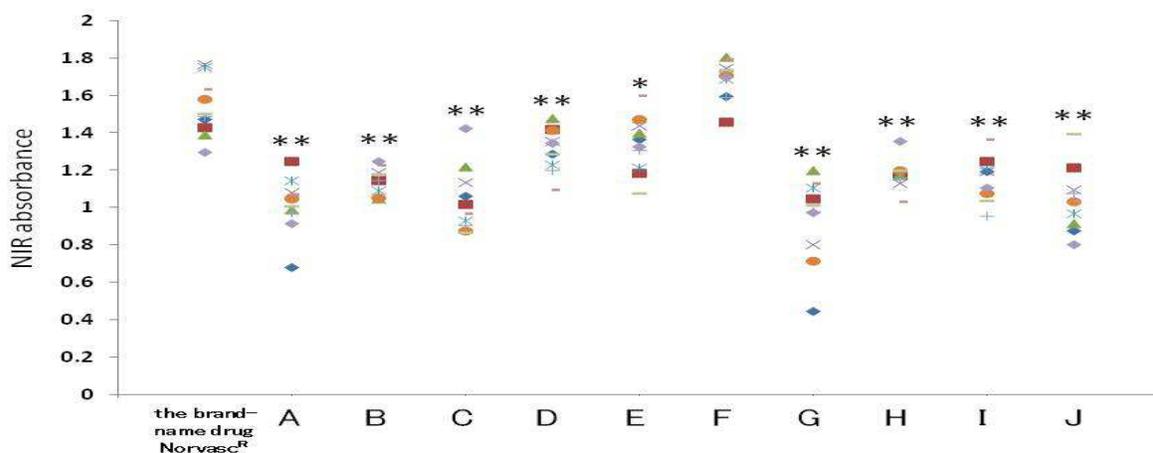

Fig. 4: *; $p<0.05$,**; $p<0.01$, Based on Dunnett's multiple comparison test, NIR spectra significantly decreased as compared to Norvasc[®].

Figure 5 showed the absorbance of Norvasc® and ten generic formulations at the peak wavelength (1510.5 nm) of the Amlodipine standard. Data for ten tablets was plotted for each formulation. The differences in absorbance of NIR spectra at a wave length of 1510.5 nm for the nine generic formulations, except F, were statistically significant compared to Norvasc®.

Discussion

NIR spectra has been attracting attention as a new method of quick and non-destructive instrumental analysis of drugs.[9] Especially, NIR spectra is suitable for evaluating labile compounds such as dihydropyridie   calcium channel blockers[10]). In our study, we performed a quantitative test to evaluate drug formulation using near-infrared absorption spectrums to profile generic formulations of amlodipine. We also employed qualitative chemometric methodology using NIR spectra.

For the discrimination of generic formulations using an NIR spectra heterogeneous differentiation tablet device (NIR-MX), all five of the tablets for generic formulations C and G were detected as heterogeneous. Therefore, it is considered that generic formulations C and G are not similar to Norvasc®. On the other hand, all five tablets of generic formulations B, E, F, H and J were detected as similar to Norvasc®. In addition, some tablets were located outside and some were located in the circle for generic formulations A, D and I, thus a determination as to whether they were heterogeneous or not could not be made by NIR-MX. Therefore, compositions of generic formulations A, D and I were considered varied. This test can not, however, identify which components of the generic formulations are different from the components of the brand-name formulation of Norvasc®.

At the peak wavelength of 1510.5 nm of the Amlodipine standard, only generic formulation F showed a high spectroscopy absorbance similar to Norvasc®. The nine other generic formulations showed significantly lower absorbance than Norvasc®. These results show that the Amlodipine content of the nine generic formulations, except F, is less than Norvasc®. One factor for this difference is that the size and the shape of the tablet might influence absorbance.[11] In this study, only three generic formulations D, G, and J had a larger volume than Norvasc®, and their volume difference was less than 4% (Volume＝(Radius of the tablet)^2×π×the thickness of the tablet).

The results of this study showed that of the ten generic formulations subjected to NIR spectra analysis, generic formulation F was the most similar to Norvasc®.

As stated previously, it is not the intention of this study to evaluate whether a generic formulation is inferior in quality, unreliable or not safe for use. The experiment is designed to show similarity of generic formulations to Norvasc®. In the future, we would like to clarify the reliability of using near-infrared spectroscopy for the evaluation of generic formulations by taking into consideration the composition of each generic formulation and how that formulation affects NIR spectra analysis. This will provide manufacturers and researchers with more comprehensive data that is related to Japanese Good Manufacturing Practice (GMP).

Conclusion

This study successfully determined generic formulations that are similar to Norvasc®. It also confirms that NIR spectroscopy is an effective way to evaluate the pharmaceutically similarity of drugs during the manufacturing process.

Acknowledgment

Declaration of Interest

The authors report no declaration of interest.

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