Solubility Estimation for Drugs Treated with the Simple Suspension Method Using Available Dissolution Test Profiles

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The simple suspension method (SSM) is a method of administering drugs via feeding or gastrostomy tubes to those who have difficulty swallowing. In the SSM, solid formulations (*eg*, tablets, capsules) are immersed in hot (55°C) water. This promotes the disintegration and dissolution of the drugs and changes their solubility. However, pharmaceutical companies have not issued test results on the solubility and dissolution behaviors of suspended drugs prepared according to the SSM.

For this study, we chose 10 drugs, 8 listed and 2 not listed in the Japanese Orange Book, to compare the dissolution behaviors of each drug, treated vs untreated with the SSM. Dissolution was classified into three patterns: rapid (gliclazide and famotidine), moderate (propranolol, pindolol, metoprolol), and slow (furosemide, ibuprofen, glimepiride). The initial dissolution rates of the moderate-dissolution drugs increased markedly by employing the SSM. In this study, hydroxyzine capsules and phenytoin tablets, neither of which is listed in the Japanese Orange Book, were compared with different dosage/administration forms of those drugs listed in the book (*ie* hydroxyzine tablets and phenytoin-phenobarbital combination tablets). The dissolution behavior of these drugs was not estimated from the dissolution profiles of different forms available in the book. Nevertheless, it seemed that the available data on the dissolution of drugs will be useful when pharmacists estimate the dissolution behavior of drugs administered using the SSM.

Key words — simple suspension method, dissolution behavior, Japanese Orange Book, drug information

Introduction

In today's medical practice, oral solid formulations (tablets and capsules) are excellent in portability and ingestibility. However, such formulations cannot be administered to patients who have difficulty swallowing. For those patients, medical preparations are more likely to be administered via gastrostomy tube, as liquid nutritional supplements and pharmaceutical suspensions. Kurata *et al* developed the simple suspension method (SSM) to administer drugs to those who are fed by gastrostomy tube.¹⁾ The SSM does not require specific equipment or a specific process. It involves immersing tablets or capsules in hot (55°C)

water for 10 min so that the formulations are sufficiently disintegrated and suspended to administer via a gastrostomy tube to the stomach. Today, the SSM is commonly applied at many hospitals in Japan,²⁾ proving that the method may contribute to efficient medical practice.³⁻⁵⁾

The advantages include the prevention of drug loss from tablet crush and easy referring for administered drugs.¹⁾ Nonetheless, the SSM is inappropriate for formulations that may clog feeding tubes due to their poor dispersability and for sustained-release formulations with modified designs. The SSM employability for oral formulations was summarized in a database by Kurata *et al*,¹⁾ which serves as a guideline for clinical medi-

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The employability of the SSM and the stability of SSM-administered drugs have been discussed in many studies. Yano *et al*⁶⁾ compared proprietary and generic pravastatin products, while Miyamoto *et al*⁷⁾ compared amantadine and 5 other proprietary and generic products, to point out that treatment of the SSM resulted in a significant difference in tube permeability between some of proprietary and generic products. Yano *et al*⁸⁾ confirmed that 8 types of suspended drugs, including phenytoin and digoxin, were found to be stable. Suryani *et al*⁹⁾ demonstrated that suspended ester prodrugs (acemetacin, cefpodoxime proxetil) are stable individually, although their ester bond is cut when they are mixed with magnesium oxide.

Pharmaceutical companies are obliged to test developed formulations prior to their distribution on the market. However, the tests do not cover the administration of drug suspensions in hot (55°C) water. Accordingly, there are no data accessible or reported on the dissolution behavior of suspended formulations in the SSM.

In previous studies, we examined the solubility of poorly water-soluble tablets (phenytoin and ibuprofen) in the SSM.¹⁰⁾ We found that the SSM promotes the immediate dissolution of phenytoin to the saturated concentration, whereas it promotes the gentle dissolution of ibuprofen. This might suggest that drugs which dissolve immediately when suspended may have enhanced solubility for the major ingredients in the drugs, and thus, the absorbability of the drug by the digestive canal may be affected. However, no details have been confirmed. This necessitates further studies on the passability of suspended drugs through gastrostomy tubes as well as on the solubility of those drugs, which will thus be used to determine whether the SSM can be used for the administra-

tion of each drug.

Studies on the applicability of the SSM to commercially available individual oral formulations require a lot of time; thus they are impractical. The Japanese Orange Book lists dissolution test data for 688 pharmaceutical ingredients that are orally administered (as of January 10, 2015). However these data are the dissolution profile of the intact drug (untreated with the SSM), thus it is not possible to apply the estimation for drugs treated with the SSM directly. In this study, we focused on the data in the Japanese Orange Book and on interview forms, both of which report dissolution profiles of oral formulations, for the purpose of comparing treated vs untreated drugs with the SSM in terms of dissolution behavior.

Moreover, the data does not cover some ingredients, such as hydroxyzine pamoate and phenytoin. Hydroxyzine pamoate is only listed for tablets and not capsules, and phenytoin tablets are included as a combined drug with phenobarbital, but are not listed independently. We also discuss the validity of the data on one form of ingredient with respect to a different form.

Materials & Methods

1. Reagent

Gliclazide tablets (20 mg, Glimicron® HA) and phenytoin (100 mg, Aleviatin®) tablets were purchased from the Dainippon Sumitomo Pharma Co, Ltd (Osaka, Japan). Famotidine tablets (10 mg, Gaster®) were purchased from Astellas Pharma Inc (Tokyo, Japan). Propranolol hydrochloride tablets (10 mg, Inderal®) and metoprolol tartrate tablets (20 mg, Seloken®) were purchased from AstraZeneca KK (Osaka, Japan). Pindolol tablets (5 mg, Carvisken®) were purchased from Alfresa Pharma Co (Osaka, Japan). Furosemide tablets

(20 mg, Lasix®) were purchased from Nichi-Iko Pharmaceutical Co, Ltd (Toyama, Japan). Ibuprofen tablets (100 mg, Brufen®) were purchased from Kaken Pharmaceutical Co, Ltd (Tokyo, Japan). Glimepiride tablets (1 mg, Amaryl®) were purchased from Sanofi KK (Tokyo, Japan). Hydroxyzine pamoate capsules (25 mg, Atarax®-P) were purchased from Pfizer Japan Inc (Tokyo, Japan).

Famotidine was purchased from MP Bio Japan KK (Tokyo, Japan). *dl*-Propranolol hydrochloride, pindolol, gliclazide, glimepiride and phenytoin were purchased from Wako Pure Chemical Inc, Ltd (Osaka, Japan). Metoprolol tartrate was purchased from LKT Laboratories (St Paul, MC, USA). Furosemide and ibuprofen sodium salt were purchased from Sigma-Aldrich Co, LLC (Tokyo, Japan). Hydroxyzine pamoate was purchased from Alfa Aesar (Heysham, UK). All other reagents used were either of GR grade or HPLC grade.

2. Information gathering by Japanese Orange Book

The Japanese Orange Book provides online the profiles of drug dissolution behavior (<http://www.jp-orangebook.gr.jp/index.html>, April 24, 2015). We downloaded a PDF document to use as the data for the dissolution tests. The tests provided lead times of 5, 10, 15, 30, 45 and 60 min; for each of these, we visually measured the solubility of the drug.

3. Simple suspension method (SSM)

The simple suspension method, employed in accordance with the procedure suggested by Kurata *et al.*¹⁾ was as follows: A drug was immersed in a disposable syringe (50 mL, Terumo® syringe SS-50ESZ, Terumo Co, Tokyo, Japan)

with 20 mL of purified water heated to 55°C; the solution was left at room temperature for 10 min and then mixed by inverting the syringe 15 times.

4. Dissolution test

In accordance with the Japanese Pharmacopoeia 16th Edition (JP), we performed dissolution tests of the drugs by employing the paddle method (DT600, Erweka GmbH, Heusenstamm, Germany). Each drug was subject to comparison between treated and untreated (the control). 900 mL of 1st fluid (pH 1.2, specified for the JP dissolution test) was used for the test, and the temperature of the fluid was kept at $37 \pm 0.5^\circ\text{C}$. The paddle rotation speed was set as 50 rpm. The drug suspension treated with the SSM was injected into the dissolution test vessel, and the syringe was rinsed two times with 1st fluid in the vessel. For the control, 20 mL of purified water heated to 55°C was added to the fluid and left at room temperature for 10 min. Fluid was sampled at 5, 10, 15, 30, 45 and 60 min. Purified water was added subsequently to fill in the sampled portion of the fluid. Sampled fluid (1 mL) was filtered by Millex®-LH (pore size 0.45 µm, Merck Millipore, Billerica, MA, USA), and it was diluted to 5 times with purified water to analyze the drug concentrations by HPLC. In the experiment of famotidine and gliclazide, sampled fluid was diluted using 2nd fluid specified for the JP dissolution test (pH 6.8) to prevent acid hydrolysis.

5. HPLC analysis conditions

Analysis was made by using the Shimadzu HPLC system (Kyoto, Japan), which consists of a LC-20AD pump, a SPD-20A UV detector, a SIL-20A auto-sampler, a CTO-20A column oven, a DGU-20A₃ degasser and a C-R8A chromatopac integrator. The columns used were Inertsil-ODS

Table 1 HPLC conditions

Drug	HPLC Column	Wavelength	Mobile phase
gliclazide	ODS	228 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 40 : 60
famotidine	ODS	254 nm	10 mM 1-pentanesulfonate sodium salt/acetic acid (pH 3.0) : acetonitrile : methanol = 780 : 190 : 30
propranolol	ODS	289 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 70 : 30
pindolol	ODS	215 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 85 : 15
metoprolol	ODS	222 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 80 : 20
furosemide	ODS	229 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 80 : 20
ibuprofen	C8	225 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 70 : 30
glimepiride	C8	228 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 40 : 60
hydroxyzine	ODS	231 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 50 : 50
phenytoin	ODS	229 nm	50 mM KH ₂ PO ₄ (pH 6.0) : acetonitrile = 80 : 20

ODS: Inertsil ODS-4, C8: Inertsil C8-4.

(4.6 mm × 150 mm, 5 µm, GL Sciences Inc, Tokyo, Japan) and Inertsil-C8-4 (4.6 mm × 150 mm, 5 µm, GL Sciences Inc). The flow rate was 0.8 to 1.0 mL/min. The column temperature was kept at 55°C. The column types, detected wavelengths and mobile phases of each drug are shown in **Table 1**. The conditions of HPLC analysis were slightly modified from those of JP and the Japanese Orange Book.

6. Statistical analysis

All data were presented as the mean value ± standard deviation (SD). The difference in solubility of treated vs untreated drugs with the SSM was evaluated by Student's *t*-test, and significance was defined as $P < 0.05$.

Results

1. Dissolution behavior of drugs listed in Japanese Orange Book

Table 2 shows the eye-measured solubility values of tested drugs, which are listed on the Japanese Orange Book website (<http://www.jp-orangebook.gr.jp/index.html>, April 24, 2015). According to **Table 2**, more than 80% of gliclazide and the famotidine dissolved within 10 min, less than 50% of the propranolol, the pindolol and the metoprolol dissolved within 10 min, and most of them dissolved in 60 min. Furosemide, ibuprofen and glimepiride dissolved very slowly, with less than 50% dissolution in 60 min.

From the data, the drugs tested for this study

Table 2 Cumulative solubility (%) of drugs from the dissolution test (1st fluid for dissolution test)

Drug	5 min	10 min	15 min	30 min	45 min	60 min
gliclazide tablet (20 mg)	68	88	96	98	> 99	> 99
famotidine tablet (10 mg)	37	81	89	96	98	> 99
propranolol HCl tablet (10 mg)	28	43	54	84	98	98
pindolol tablet (5 mg)	18	31	42	67	84	94
metoprolol tartrate tablet (20 mg)	10	28	45	94	97	> 99
furosemide tablet (20 mg)	5	15	19	30	34	39
ibuprofen tablet (100 mg)	0	0	2	12	18	23
glimepiride tablet (1 mg)	0	0	0	1	2	3

Data were measured visually in the dissolution profile from the jp-orangebook homepage (<http://www.jp-orangebook.gr.jp/index.html>, April 24, 2015).

can be categorized into three groups by dissolution pattern: those that dissolved rapidly (the rapid-dissolution group), those that dissolved moderately and most of the formulations dissolved in the end (the moderate-dissolution group), and those that dissolved slowly (the slow-dissolution group).

2. Change in dissolution behavior of SSM-treated drugs

Next, we analyzed the dissolution behaviors of treated vs untreated drugs with the SSM for the rapid-dissolution group, the moderate-dissolution group and the slow-dissolution group. In the rapid-dissolution group, treated gliclazide was found to have a slightly greater solubility than untreated gliclazide (**Fig 1A**). Treated famotidine was found to have double the solubility of untreated famotidine at 5 min, the behavior became similar between the two in 10 min (**Fig 1B**).

In the moderate-dissolution group, treated propranolol dissolved rapidly for the first 15 min, which showed a significant difference from untreated propranolol (**Fig 2A**). Treated pindolol also dissolved rapidly. A significant difference was recognized between treated and untreated pindolol in the first 5 min, and that difference re-

mained the same at 45 min (**Fig 2B**). In addition, metoprolol showed a great difference in solubility within 15 min, although most of the drug dissolved in 30 min whether or not it was treated with the SSM (**Fig 2C**).

In the slow-dissolution group, less than 20% of treated furosemide dissolved within 5 min, which was still more than double that for untreated furosemide (**Fig 3A**). Whether or not it was treated with the SSM, furosemide continued to dissolve at a constant rate, and the difference in solubility between treated and untreated drugs remained approximately 10%. The solubility of treated ibuprofen was approximately 3 percentage points greater than untreated ibuprofen in 10 min, and the difference remained the same subsequently (**Fig 3B**). The solubility of glimepiride was approximately 2 percentage points different for treated vs untreated at 5 min, the difference narrowing eventually to nil at 30 min (**Fig 3C**).

3. Data of formulations unlisted in Japanese Orange Book

In the dissolution profile of untreated hydroxyzine pamoate capsule (**Fig 4A**), less than 40% of the hydroxyzine dissolved in 10 min and most of them dissolved in 60 min. Therefore this drug be-

Fig 1 Dissolution profiles of gliclazide in Glimicron®-HA tablet 20 mg (A) and famotidine in Gaster® tablet 10 mg (B). Data are shown as the mean $\pm$ SD ($n = 4$). Most error bars are not shown when the SD values fall within the symbols. Closed circles (●) and open circle (○) means treated and untreated with the SSM, respectively. * $P < 0.05$, ** $P < 0.01$: Significantly different compared to SSM untreated. Student's t -test.

Fig 2 Dissolution profiles of propranolol in Inderal® tablet 10 mg (A), pindolol in Carvisken® tablet 5 mg (B) and metoprolol in Seloken® tablet 20 mg (C)

Data are shown as the mean $\pm$ SD ($n = 4$). Some error bars are not shown when the SD values fall within the symbols. Closed circles (●) and open circle (○) means treated and untreated with the SSM, respectively. * $P < 0.05$, ** $P < 0.01$: Significantly different compared to SSM untreated. Student's *t*-test.

longs to the moderate-dissolution group. Treated hydroxyzine pamoate capsule dissolved rapidly same as other moderate-dissolution drugs. According to the Japanese Orange Book, hydroxyzine pamoate tablet (25 mg) hardly dissolves in 15 min, while gradually dissolving approximately 44% of the tablet in 60 min (**Fig 4A**, dashed line). Given the same conditions, the dissolution behavior of hydroxyzine pamoate capsule (25 mg) was found to significantly differ from that of hydroxyzine pamoate tablet: The capsule dissolved faster than the tablet.

In the dissolution profile of untreated phenytoin tablet (**Fig 4B**), less than 15% of phenytoin dissolved in 10 min, and it was almost saturated in the solution at 30 min. This result suggests that the phenytoin tablet belongs to the slow-dissolution group. Treated phenytoin tablet was rapidly

dissolved within 5 min, but the difference of solubility between treated and untreated with the SSM was reduced same as the dissolution profile of glimepiride (**Fig 3C**). On the other hand, a combined tablet of phenytoin (67 mg) and phenobarbital (33 mg) dissolved faster than a single tablet of phenytoin (100 mg): the combination tablet dissolved more than 80% at 60 min (**Fig 4B**, dashed line), the single tablet dissolved only 25% (**Fig 4B**, solid line).

Discussion

In previous studies, we examined the solubility of poorly water-soluble drugs that were treated with the SSM, and we reported that phenytoin and pranlukast¹⁰⁾ dissolved in the suspension to the saturated solubility. This suggests that the SSM

Fig 3 Dissolution profiles of furosemide in Lasix® tablet 20 mg (A), ibuprofen in Brufen® tablet 100 mg (B) and glimepiride in Amaryl® tablet 1 mg (C)

Data are shown as the mean $\pm$ SD ($n = 4$). Some error bars are not shown when the SD values fall within the symbols. Closed circles (●) and open circle (○) means treated and untreated with the SSM, respectively. * $P < 0.05$, ** $P < 0.01$: Significantly different compared to SSM untreated. Student's t -test.

Fig 4 Dissolution profiles of hydroxyzine in Atarax®-P capsule 25 mg (A) and phenytoin in Aleviatin® tablet 100 mg (B)

Data are shown as the mean $\pm$ SD ($n = 4$). Some error bars are not shown when the SD values fall within the symbols. Closed circles (●) and open circle (○) means treated and untreated with the SSM, respectively. Dashed lines indicate the dissolution profiles of hydroxyzine pamoate tablet (25 mg) (A) and phenytoin (67 mg) / phenobarbital (33 mg) combination tablet (B) in 1st fluid, covered in the Japanese Orange Book. * $P < 0.05$, ** $P < 0.01$: Significantly different compared to SSM untreated. Student's t -test.

may help increase the initial drug concentrations in the stomach, which seems unlikely by oral tablet/capsule administration, and may affect the absorbability of those drugs by the body. Nevertheless, the dissolution behavior of treated drugs

with the SSM has not been confirmed. In this study, we compared the dissolution behavior of 10 drugs, treated vs untreated.

To determine whether to use the SSM to administer drugs to patients, pharmacists working

for hospitals usually refer to guidebooks¹⁾ on the disintegrability of suspended drugs, though they rarely search for the dissolution behavior of those drugs. This study found that the SSM significantly enhanced the dissolution rate for most of the tested drugs in 5 min, with various degrees of enhancement. Notably, the SSM treatment significantly increased the dissolution rate of the beta-blockers, propranolol and metoprolol. Their elevated dissolution rates may increase the drug absorption rate, thereby excessively lowering the blood pressure.

It is impractical to perform dissolution tests for each drug. Thus, we used existing dissolution profiles found in interview forms and the Japanese Orange Book to consider the estimability of the effect of the SSM on the dissolution of each drug.

Figure 1 indicates that drugs in the rapid-dissolution group show similar dissolution behavior between treated and untreated with the SSM. The SSM promotes the disintegration and subsequent dissolution of the drugs, and it was clarified from the drug dissolution that the disintegration and dissolution of untreated drugs were also promoted in the solution as rapidly as for the treated drugs. The cumulative solubility of gliclazide and famotidine was found to become lower over time. This is probably because gliclazide and famotidine were decomposed in the 1st fluid with a pH of 1.2: They are known to be highly likely to be hydrolyzed in a strongly acid solution (http://www2.jp-orangebook.gr.jp/data/06/06_02/06_02_Gliclazide.pdf, April 24, 2015, http://www2.jp-orangebook.gr.jp/data/06/06_06/06_06_Famotidine.pdf, April 24, 2015).

Figure 2 shows that drugs in the moderate-dissolution group were greatly affected by the SSM in the initial stage (0–5 min) of disintegration and dissolution; thus, the solubility of treated and

untreated drugs was found to significantly differ between 5 and 15 min. Furthermore, a significant difference was recognized between treated and untreated pindolol until 45 min (**Fig 2B**). The difference of dissolution behavior between treated and untreated drugs was greater for pindolol than for propranolol and metoprolol, probably because of the dissolution profile of the untreated drug: Only 67% of untreated pindolol dissolved in 30 min (**Table 2**).

Figure 3 shows that drugs in the slow-dissolution group were recognized as being little affected by the SSM in terms of solubility. The solubility of treated furosemide and ibuprofen was approximately 10 and 3 percentage points greater than untreated each drug in 10 min, and the difference remained the same subsequently. The solubility of treated glimepiride was significantly greater than untreated glimepiride at 5 and 10 min, however the difference disappeared after 15 min. Such a difference profile of these drugs was recognized because furosemide and ibuprofen did not dissolve completely in 60 min, whereas glimepiride, which is very poorly soluble, was almost saturated in the solution at 30 min.

It should be noted that these findings are only comparisons of data on dissolution profiles; hence, it is too early to discuss the absorbability and adverse reactions of those drugs. There are few reports on variations in drug concentration in the blood for drugs administered by the SSM. Miyazaki *et al*¹¹⁾ measured the tegafur concentrations in the blood of a patient who was treated with tegafur, gimeracil and oteracil potassium (TS-1[®] combination capsule), and reported that the drug absorbability and maximum blood concentrations were higher for the SSM treatment form than for orally administered capsules (Hirata *et al*¹²⁾). The dissolution profiles of TS-1[®]

capsules, not listed on the Japanese Orange Book website, are listed on the interview forms of TS-1[®]'s generic drugs, including that of Esueewan[®] capsules. According to the interview forms, the solubilities of tegafur from a TS-1[®] capsule (25 mg) and an Esueewan[®] capsule (25 mg) in a solution (pH 1.2, 50 rpm) are both approximately 80% in 5 min and 90% in 10 min. Most of the formulations dissolved in 15 min. Similar progress was recognized in gimeracil and oteracil potassium. From these results, it is estimated that the TS-1[®] capsule falls in the rapid-dissolution group. The solubility of tegafur in water is regarded as 1.68 g / 100 mL at 20°C (Interview Form of TS-1[®] combination capsule, revised 21st ed, ed by Taiho Pharmaceutical Co, Ltd, Tokyo, July 2014, http://www.info.pmda.go.jp/go/interview/1/400107_4229101D1025_1_10E_1F, April 24, 2015) ; therefore, tegafur in TS-1[®] capsule form is considered to almost completely dissolve via the SSM, similarly to gliclazide (**Fig 1A**).

Using the SSM to suspend drugs omits the process of disintegration and initial dissolution of the formulation within the stomach. In this light, absorbability by digestive canal is seemingly affected more by tube-administered suspended drugs than by orally-administered solid formulations. In this study, we examined only several kinds of drugs about the rapid-, moderate- and slow-dissolution group, so it is necessary to examine the dissolution profile of more drugs. However, when suspended drugs that are categorized as the rapid- or the moderate-dissolution groups are administered, the patients' body conditions should be carefully monitored. Adverse reactions (*eg*, hypotension after the administration of beta-blocker drugs) might occur by blood drug concentration increase.

As of January 10, 2015 the dissolution profiles

for 688 pharmaceutical ingredients are provided in the Japanese Orange Book. Although the book covers a few thousand formulations/products, including different dosages and forms (*eg*, tablet, granule, powder) of the same ingredient, some newly developed drugs and some available drugs have yet to be listed. For example, hydroxyzine pamoate, commonly used clinically, is covered in the forms of tablet and dry syrup, but not capsule. According to the book, tablets of hydroxyzine pamoate hardly dissolved within 30 min, and do not start to gently dissolve until afterwards. From this, hydroxyzine tablets belong to the slow-dissolution group. In contrast, 40% of hydroxyzine pamoate capsule dissolved in 10 min and 100% in 60 min (**Fig 4A**), from which hydroxyzine capsule belongs to the moderate-dissolution group. The SSM enhanced the dissolution of hydroxyzine, whose solubility was double that of untreated hydroxyzine at 15 min. Such solubility increase continued to 45 min.

An antiepileptic drug, phenytoin is listed only as a combination of phenytoin and phenobarbital, or as a combination of phenytoin, phenobarbital and caffeine-sodium benzoate. This study examined single-tablet phenytoin and compared its solubility with a phenobarbital-combined drug. Phenobarbital-combined phenytoin tablet was found to be more soluble, and to dissolve more rapidly, than phenytoin tablet (**Fig 4B**). It is thought that 0.3% polysorbate 80 added as a solubilizer to the test solution stimulates dissolution (http://www2.jp-orangebook.gr.jp/data/07/07_06/07_06_Phenytoin_Phenobarbital.pdf, April 24, 2015).

From those findings, it must be noted that the dissolution behavior may not conform to the behavior in the 1st fluid for dissolution test, particularly in cases where formulations (*eg*, tablet, capsule, combination) unlisted in the book are

administered via the SSM or where a solution contains some solubilizer.

This study pointed out for the first time that the dissolution behaviors of 10 drugs treated with the SSM can be estimated from the dissolution profiles listed in the Japanese Orange Book. The number of drug we examined is not enough, and it may still be difficult to estimate the blood drug concentrations of patients administered using the SSM, as well as the efficacy and safety. Nevertheless, it is safe to suggest that, when analyzing the possibility of the SSM treatment, pharmacists should be aware of drug dissolution profiles, consider every possible effect of regular drug administration on blood drug concentrations and pharmacological action, and regularly monitor the patients' conditions for adverse reactions.

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Conflict of Interest

The authors indicated no conflicts of interest.

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