

Original scientific paper

## Investigation of biopharmaceutical and physicochemical drug properties suitable for orally disintegrating tablets

Asami Ono\*, Takumi Tomono<sup>1</sup>, Takuo Ogihara<sup>1</sup>, Katsuhide Terada<sup>2,a</sup>, and Kiyohiko Sugano<sup>2</sup>

Asahi Kasei Pharma, 632-1 Mifuku, Izunokuni, Shizuoka 410-2321, Japan.

<sup>1</sup>Laboratory of Clinical Pharmacokinetics, Graduate School of Pharmaceutical Sciences, Takasaki University of Health and Welfare, 60 Nakaorui Takasaki, Gunma 370-0033, Japan.

<sup>2</sup>Department of pharmaceuticals, Faculty of pharmaceutical sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan.

<sup>a</sup>Present address: Laboratory of Molecular Pharmaceutics and Technology, Faculty of Pharmacy, Takasaki University of Health and Welfare, 60 Nakaorui Takasaki, Gunma 370-0033, Japan.

\*Corresponding Author: E-mail: [ono.ar@om.asahi-kasei.co.jp](mailto:ono.ar@om.asahi-kasei.co.jp); Tel.: +81-558-76-7061; Fax: +81-558-76-7137

Received: September 14, 2016; Revised: November 18, 2016; Published: December 26, 2016

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### Abstract

The purpose of this study was to evaluate the biopharmaceutical and physicochemical drug properties suitable for orally disintegrating tablets (ODTs). The molecular weight (MW), polar surface area (PSA), hydrogen bond donor (HBD) and acceptor (HBA) numbers, net charge at pH 7.4,  $\log D_{6.5}$ , the highest dose strength, solubility in water, dose number, and elimination  $t_{1/2}$  of 57 ODT drugs and 113 drugs of immediate-release (IR) formulations were compared. These drugs were classified according to the Biopharmaceutical Classification System (BCS). A lower dose strength and a longer elimination  $t_{1/2}$  have been observed as characteristic properties of ODTs. The proportion of basic drugs was higher in the ODTs than in the IR formulations. A significant difference was not observed between the ODT and the IR formulation for MW, PSA, HBD, HBA,  $\log D_{6.5}$ , solubility in water, and dose number. The distributions of the ODTs and IR formulations among each BCS class were similar, suggesting that an ODT can be developed regardless of the BCS class of a drug.

### Keywords

orally disintegrating tablet (ODT); bioequivalence; biopharmaceutics classification system (BCS).

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### Introduction

An orally disintegrating tablet (ODT) improves patient compliance because it can be taken without water, does not cause dysphagia, and can prevent patients from spitting out their medication [1,2]. Many pharmaceutical companies are working on the development of ODTs. An ODT should be bioequivalent to a corresponding standard formulation, e.g. an immediate-release (IR) formulation. An ODT disintegrates and dissolves rapidly in the oral cavity within 30 seconds. Therefore, the dissolution rate may differ significantly between ODTs and IR formulations. When the dissolution rates are different between the ODT and the IR formulation, the risk to fail in a bioequivalence (BE) study is high. Therefore, during the development of an ODT, it is important to assess the risk of failing in a clinical BE study. It is preferable to reduce the risk of failing a clinical BE study because such studies are expensive, time consuming, and a burden to healthy

volunteers.

However, there has been no research investigating the biopharmaceutical properties of drugs suitable to be an ODT. In the present study, several physicochemical and biopharmaceutical properties were selected and a survey was performed to compare the properties between the two types of oral dose formulations.

## Methods

### *Drug list*

The physicochemical and biopharmaceutical properties of drugs marketed as ODTs and IR formulations were compared in this study. Currently, the number of drugs developed as ODT is largest in Japan. In addition, all the ODT formulations approved in Japan were proved to be bioequivalent to the IR formulation with and without water intake. Therefore, the ODT formulations in Japanese market were selected in this study. The list of the ODT drugs was obtained from the Pharmaceuticals and Medicinal Devices Agency website ([http://www.info.pmda.go.jp/psearch/html/menu\\_tenpu\\_base.html](http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html)) (Supplement Table 1). The list of the IR formulations were selected from the top 200 pharmaceutical products in Japan (Supplement Table 2) [3]. Finally, 57 compounds for the ODT and 113 compounds for the IR formulation were selected and analysed. The 25 compounds were overlapping between the lists of the ODTs and IR formulations.

### *Biopharmaceutical drug properties*

The physicochemical and biopharmaceutical properties of drugs related to the formulation design and oral bioavailability were selected [4,5]. The molecular weight (MW), polar surface area (PSA), hydrogen bond donor (HBD) and acceptor (HBA) numbers, dissociation constants ( $pK_a$ ), and n-octanol/water distribution coefficients at pH6.5 ( $\log D_{6.5}$ ) were calculated using ACD Percepta (ACD/Labs Software V 14.0.0 (<http://www.acdlabs.com/products/percepta/predictors.php>)). The calculated  $pK_a$  and  $\log D$  were used for all drugs, as the experimental values were not available for some drugs.

Net charge (NC) at pH 7.4 was represented as the weighted sum of the charge of each species.

$$NC = (\pm 0) \cdot f_0 + (+1) \cdot f_+ + (-1) \cdot f_- + (+2) \cdot f_{++} + \dots \quad (1)$$

$$(f_0 + f_+ + f_- + f_{++} + \dots = 1)$$

where  $f_0$  is the fraction of the undissociated species,  $f_+$  is that of +1 charged species, etc. Each fraction was calculated by the  $pK_a$  and the pH (set to be 7.4 in this study) using the Henderson-Hasselbalch equation [6]. The NC equations for acids and bases containing up to three ionization centers are summarized in Supplement Table 3. When a drug was more than 50 % dissociated at pH 7.4, it was classified as an acid (NC < -0.5) or as a base (NC > 0.5).  $\log D$  was calculated at pH 6.5 to estimate the permeability, whereas NC was calculated at pH 7.4 to discuss the pharmacokinetics after the absorption. The solubility in water, the highest dose strength, and the elimination  $t_{1/2}$  were obtained from the prescription information. When a reliable solubility figure was unavailable, a solubility value was assigned based on the solubility category defined by the Japanese pharmacopeia (Supplement Table 4).

### *Provisional classification according to the Biopharmaceutical Classification System*

According to the Biopharmaceutical Classification System (BCS), drugs can be categorized into the four classes, i.e. high solubility/high permeability (class I), low solubility/high permeability (class II), high solubility/low permeability (class III), and low solubility/low permeability (class IV). Moreover, BCS class II drugs can be sub-classified into acid (class IIa), base (class IIb), and undissociated drugs (class IIc) [7].

In the previous studies, solubility in water and calculated  $\log D_{6.5}$  were used as the surrogates of solubility and permeability data to provide provisional BCS class [3,8]. The same approach was taken in this study. According to the official BCS guidance, the equilibrium solubility of a drug at the physiological gastrointestinal pH range (namely, pH 1.2 to pH 6.8 or 7.4) is required. However, the pH solubility profile data were not available for many drugs. Therefore, solubility in water reported in the prescription information was used in this study. The dose number (Do) is a dimensionless number expressed by the ratio of the dose and the maximum dissolved amount in the intestine. Do was calculated by using Eq. 2 [5]:

$$Do = \frac{M}{S \times V} \quad (2)$$

where  $S$  is the solubility of a drug in water,  $V$  is the intestinal fluid volume (set to be 250 mL in this study), and  $M$  is the highest dose strength. Drugs were defined as highly soluble when the Do was  $\leq 1$ .

According to the official BCS guidance, to classify the permeability category, the fraction of a dose absorbed (Fa%) in humans or Caco-2 permeability data is required. However, due to the limited availability of these data, the permeability was classified based on the calculated  $\log D_{6.5}$  in this study. The  $\log D_{6.5}$  value of metoprolol was chosen as the criteria for high permeability [Fa% in human, 95 % [9]; human effective permeability,  $1.26 \times 10^{-4}$  cm/s [9];  $\log D_{6.5}$ , -0.92 (ACD Percepta)].

#### Statistical analysis

A student's t-test was used to evaluate the significance of difference between the ODTs and IR formulations in MW, PSA, HBD, HBA, NC at pH 7.4,  $\log D_{6.5}$ , the highest dose strength, solubility in water, Do, and elimination  $t_{1/2}$ . One-way analysis of variance was used to evaluate the significance of difference between acids, bases, and undissociated drugs in elimination  $t_{1/2}$  for the ODTs and IR formulations, respectively. A minimum p value of 0.05 was used as the significance level for all tests. Microsoft Excel 2010 (Microsoft) was used for statistical analysis.

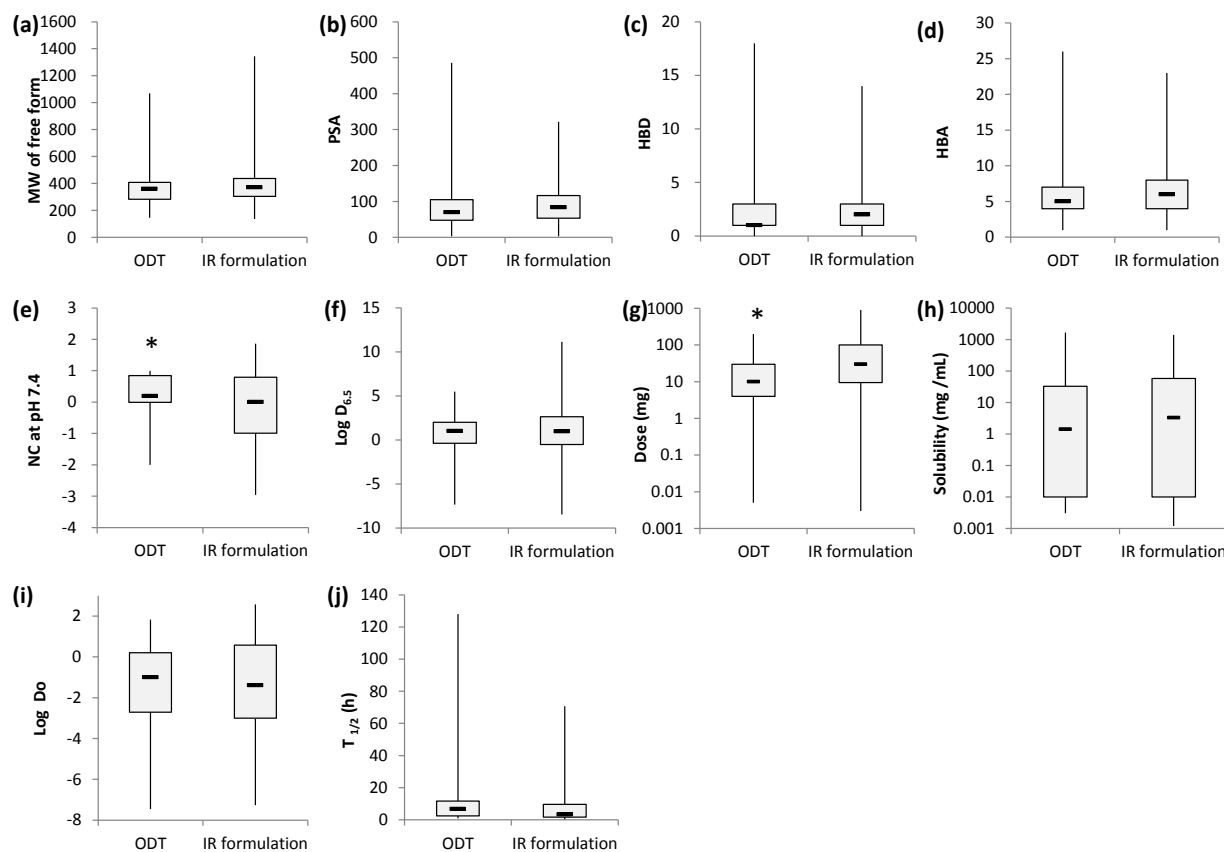
#### Results

MW of free form, PSA, HBD, HBA, NC at pH 7.4,  $\log D_{6.5}$ , the highest dose strength, solubility in water, Do, and elimination  $t_{1/2}$  are shown in Table 1. Some calculated  $pK_a$  and  $\log D_{6.5}$  might have a margin of error about 1 log unit (e.g.  $pK_a$ s of cetirizine (6.7 (B); 7.7 (B) [10]), domperidone (9.0 (B); 7.1 (B) [10]), glimepiride (5.1 (A); 6.2 (A) [11]),  $\log D_{6.5}$  of famotidine (-2.14; -1.3 [11]), glimepiride (1.51; 3.0 [11]) (calculated values; experimental values).

NC at pH 7.4 was significantly higher in the ODT than that for the IR formulation ( $p = 0.02$ ) (Figure 1e). The percentages of acid, base, and undissociated drugs for the ODTs were 13, 41 and 45 %, respectively (2 % unclassifiable). The corresponding percentages in the IR formulations were 30, 30 and 38 %, respectively (2 % unclassifiable). The highest dose strength of the ODTs was significantly lower than that of the IR formulations ( $p = 0.01$ ) (Figure 1g). The medians of the highest dose strength in the ODTs and IR formulations were 10 mg and 30 mg, respectively. The maximum values of the highest dose strength in the ODTs and IR formulations were 200 mg and 900 mg, respectively (Table 2). The elimination  $t_{1/2}$  of the ODTs tended to be longer than that of the IR formulations ( $p = 0.07$ ) (Figure 1j). The medians of  $t_{1/2}$  in the ODTs and IR formulations were 6.7 h, and 3.3 h, respectively (Table 2). A significant difference was not observed between the ODTs and the IR formulations for MW, PSA, HBD, HBA,  $\log D_{6.5}$ , solubility in water, and Do (Figure 1a, b, c, d, f, h, i).

The distribution of the ODTs and IR formulations among each BCS class were similar (Figure 2). The percentages of BCS class I, class II, class III, and class IV for the ODT were 52, 29, 20 and 0 %, respectively

(2 % unclassifiable). The corresponding percentages for the IR formulation were 48, 30, 16 and 4 %, respectively (2 % unclassifiable). The distribution of BCS II subclass was also similar (Figure 2). The percentages of BCS class IIa, class IIb, and class IIc for the ODT were 7, 12 and 9 %, respectively, whereas the corresponding percentages for the IR formulation were 10, 10 and 11 %, respectively.



**Figure 1.** Box and whisker plots of biopharmaceutical properties of ODT and IR formulation drugs ; the bottom and top of the box are the first and third quartiles, the band inside the box is the median, and the ends of the whiskers are the minimum and maximum. **(a)** MW of free form. **(b)** Polar surface area. **(c)** Hydrogen bond donor number. **(d)** Hydrogen bond acceptor number. **(e)** Net charge at pH 7.4. **(f)** Log  $D_{6.5}$ . **(g)** The highest dose strength. **(h)** Solubility in water. **(i)** Dose number. **(j)** Elimination  $t_{1/2}$ . \* $p < 0.05$ .

**Table 1.** MW of free form, PSA, HBD, HBA, NC at pH 7.4, log  $D_{6.5}$ , the highest dose strength, solubility in water,  $D_o$ , elimination  $t_{1/2}$ , and BCS class of drugs used in this study.

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log $D_{6.5}$ <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	$D_o$	$t_{1/2}$ (h) <sup>c</sup>	BCS class
<u>Acarbose</u> <sup>d,e</sup>	646	321	14	19	0.0	–	-4.88	100	1429	0.00028	3.2	3
Acetaminophen	151	49	2	3	0.0	–	0.40	500	10	0.2	2.9	1
Acetylsalicylic acid	180	64	1	4	-1.0	3.5 (A)	-1.39	100	3.33	0.12	0.4	3
Acyclovir	225	115	4	8	0.0	–	-1.23	400	1	1.6	2.4	4
Alendronate sodium hydrate	249	181	7	8	-2.0	1.7 (A), 2.7 (A), 6.1 (A), 10.3 (B)	-8.44	35	25.6	0.00546	1.5	3
Alfacalcidol	401	40	2	2	0.0	–	7.58	0.03	0.01	0.0012	17.6	1
Allopurinol	136	66	2	5	0.0	–	-0.70	100	0.1	4	1.6	2
<u>Ambroxol hydrochloride</u>	378	58	4	3	1.0	8.7 (B)	0.48	45	26.8	0.00672	11.2	1
<u>Amlodipine besylate</u>	409	100	3	7	1.0	9.0 (B)	1.09	10	2.22	0.018	36.2	1
<u>Aripiprazole</u>	448	45	1	5	0.6	7.7 (B)	4.42	24	0.01	9.6	59.6	2
Atenolol	266	85	4	5	1.0	9.4 (B)	-2.53	50	1	0.2	10.8	3
Atorvastatin calcium	559	112	4	7	-1.0	4.3 (A)	2.06	10	0.145	0.276	10.8	1
Azithromycin hydrate	749	180	5	14	1.8	8.2 (B), 8.6 (B)	-0.19	600	0.01	240	61.9	2
Azulene sulfonate sodium hydrate	278	63	1	3	-1.0	1.7 (A)	-2.03	2	10	0.0008	2.45	3
Benidipine hydrochloride	506	114	1	9	0.8	8.0 (B)	3.54	8	0.01	3.2	1.0	2
<u>Bepotastine besylate</u>	389	63	1	5	0.0	4.4 (A), 8.9 (B)	0.86	10	23.3	0.00172	2.5	1
Beraprost sodium	398	87	3	5	-1.0	4.8 (A)	1.42	0.04	833	$1.92 \times 10^{-7}$	1.1	1
<u>Bicalutamide</u>	430	116	2	6	0.0	–	2.53	80	0.01	32	4.9	2
Bisoprolol fumarate	325	60	2	5	1.0	9.4 (B)	-0.55	5	1250	$1.6 \times 10^{-5}$	8.6	1
<u>Brotizolam</u>	394	71	0	4	0.0	–	2.80	0.25	0.01	0.1	7	1
Cabergoline	452	72	2	7	1.0	9.4 (B)	0.40	1	0.01	0.4	43	1
Camostat mesylate	398	137	4	9	1.0	9.1 (B)	-0.53	100	45.5	0.0088	1.7	1
Candesartan cilexetil	440	119	2	9	-2.0	2.1 (A), 4.2 (A)	0.29	12	0.01	4.8	2.2	2

Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<i>Carvedilol</i>	406	76	3	6	0.9	8.2 (B)	2.20	20	0.01	8	7.7	2
<i>Cefcapene pivoxil hydrochloride</i>	594	257	3	16	0.0	5.9 (A), 9.0 (B)	-1.59	100	1.88	0.213	1.1	3
<i>Cefdinir</i>	395	212	5	10	-1.0	2.8 (A)	-3.92	100	0.381	1.05	1.6	4
<i>Cefditoren pivoxil</i>	621	257	3	13	-0.2	8.1 (A)	2.45	100	0.01	40	1.1	2
<i>Cefotiam hexetil hydrochloride</i>	696	276	3	16	0.8	8.0 (B)	-0.14	200	1000	0.0008	0.8	1
<i>Cetirizine hydrochloride</i>	389	53	1	5	-0.8	3.5 (A), 6.7 (B)	-0.09	10	1000	4.0 × 10 <sup>-5</sup>	7.5	1
<i>Cilostazol</i>	369	82	1	7	0.0	–	3.01	100	0.01	40	10.1	2
<i>Clarithromycin</i>	748	183	4	14	0.9	8.2 (B)	1.56	200	0.01	80	4.4	2
<i>Cyclosporin a</i>	1203	279	5	23	0.0	–	1.80	50	3.38	0.0592	1.6	1
<i>Desmopressin acetate hydrate</i>	1069	486	18	26	0.0	–	-7.34	0.24	33	2.9 × 10 <sup>-5</sup>	2	3
<i>Diclofenac sodium</i>	296	49	2	3	-1.0	4.2 (A)	2.17	25	17.2	0.0058	1.2	1
<i>Dienogest</i>	311	61	1	3	0.0	–	2.64	1	0.01	0.4	8.0	1
<i>Domperidone</i>	426	68	2	7	1.0	9.0 (B)	2.26	10	0.01	4	0.9	2
<i>Donepezil hydrochloride</i>	379	39	0	4	1.0	8.8 (B)	1.97	10	10	0.004	70.7	1
<i>Doxazosin mesylate</i>	451	112	2	10	0.1	6.5 (B)	1.20	4	1	0.016	11.8	1
<i>Doxifluridine</i>	246	99	3	7	-0.4	7.6 (A)	-1.13	200	33	0.0242	0.8 <sup>f</sup>	3
<i>Droxidopa</i>	213	124	6	6	-0.1	2.1 (A), 8.3 (B)	-3.57	200	2.4	0.333	2	3
<i>Ebastine</i>	470	30	0	3	0.9	8.2 (B)	5.49	10	0.01	4	17.6	2
<i>Enalapril maleate</i>	376	96	2	7	-1.0	3.1 (A)	-1.06	10	21	0.00191	6.1	3
<i>Epalrestat</i>	319	115	1	4	-1.0	3.6 (A)	-1.04	50	0.009	22.2	1.8	4
<i>Eperisone hydrochloride</i>	259	20	0	2	0.9	8.5 (B)	2.02	50	200	0.001	1.6	1
<i>Epinastine hydrochloride</i>	249	42	2	3	1.0	12.0 (B)	0.77	20	133	0.0006	9.2	1
<i>Ethyl icosapentate</i>	331	26	0	2	0.0	–	6.65	900	0.01	360	58.9	2
<i>Etizolam</i>	343	71	0	4	0.0	–	2.87	1	0.01	0.4	6.3	1

Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<i>Famotidine</i>	337	238	8	9	0.8	7.9 (B)	-2.14	20	0.741	0.108	3.1	3
<i>Fexofenadine hydrochloride</i>	502	81	3	5	0.0	4.4 (A), 9.4 (B)	2.43	60	1.43	0.168	19	1
<i>Fluconazole</i>	306	82	1	7	0.0	–	0.70	400	1	1.6	30	2
<i>Flurbiprofen</i>	244	37	1	2	-1.0	4.1 (A)	1.48	40	0.01	16	2.7	2
<i>Fluvastatin sodium</i>	411	83	3	5	-1.0	4.3 (A)	1.33	30	82.0	0.00146	1.3	1
<i>Fluvoxamine maleate</i>	318	57	2	4	1.0	9.4 (B)	0.36	75	14	0.0214	14.1	1
<i>Fursultiamine</i>	399	152	3	7	0.0	–	2.05	50	200	0.001	14.7	1
<i>Galantamine hydrobromide</i>	287	42	1	4	0.8	7.9 (B)	0.12	12	33	0.00145	6.8	1
<i>Gefitinib</i>	447	69	1	7	0.3	7.0 (B)	3.07	250	0.01	100	30.1	2
<i>Gimeracil</i>	146	53	2	3	0.1	6.5 (A), 12.6 (B)	-2.58	7.25	1.74	0.0167	3	3
<i>Glimepiride</i>	491	133	3	9	-1.0	5.1 (A)	1.51	3	0.01	1.2	5.8	2
<i>Granisetron hydrochloride</i>	312	50	1	5	1.0	10.5 (B)	-0.95	2	588	1.36 × 10 <sup>-5</sup>	5.3	3
<i>Hydrochlorothiazide</i>	298	135	4	7	0.0	–	0.01	12.5	0.1	0.5	9.1	1
<i>Imatinib mesylate</i>	494	86	2	8	0.6	7.6 (B)	2.00	200	1300	0.000615	15.9	1
<i>Imidafenacin</i>	319	61	2	4	0.6	7.6 (B)	1.68	0.1	0.01	0.04	3.1	1
<i>Imidapril hydrochloride</i>	405	116	2	9	-1.0	2.4 (A)	-2.51	10	49.3	0.000812	1.7	3
<i>Irsogladine maleate</i>	359	96	1	6	0.0	–	1.81	4	0.01	1.6	128	2
<i>Itraconazole</i>	706	101	0	12	0.1	6.5 (B)	4.67	200	0.01	80	27.9	2
<i>Ketoprofen</i>	254	54	1	3	-1.0	4.2 (A)	0.87	75	0.01	30	1.6	2
<i>Ketotifen fumarate</i>	309	49	0	2	1.0	8.8 (B)	1.79	1	1	0.004	6.7	1
<i>L-carbocysteine</i>	179	126	4	5	-1.0	2.1 (A), 3.8 (A), 8.8 (B)	-3.80	500	0.1	20	1.6	4
<i>Lafutidine</i>	432	104	1	7	0.4	7.2 (B)	0.56	10	0.01	4	1.6	2
<i>Lansoprazole</i>	369	87	1	5	0.0	–	2.40	30	0.0323	3.72	1.4	2

Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<i>Levofloxacin</i>	361	73	1	7	-0.5	5.2 (A), 7.4 (B)	-1.76	500	16.7	0.12	7.9	3
<i>Limaprost alfadex</i>	366	95	3	5	-1.0	4.6 (A)	0.85	0.005	370	5.4 × 10 <sup>-8</sup>	0.5	1
<u>Loratadine</u>	383	42	0	4	0.0	–	5.32	10	0.00303	13.2	20.1	2
<i>Losartan potassium</i>	423	93	2	7	-1.0	4.2 (A)	1.77	100	1000	0.0004	1.8	1
<i>Loxoprofen sodium hydrate</i>	246	54	1	3	-1.0	4.4 (A)	0.37	60	1000	0.00024	1.2	1
<i>Manidipine hydrochloride</i>	611	117	1	10	0.1	6.1 (B)	5.29	20	3.88	0.0206	1.5	1
<i>Mecobalamin</i>	1344	ND	ND	ND	–	ND	ND	0.5	12.5	0.00016	12.5	UC
<i>Meloxicam</i>	351	136	2	7	-1.0	4.5 (A)	0.29	10	0.01	4	27.6	2
<u>Memantine hydrochloride</u>	179	26	2	1	1.0	10.8 (B)	0.40	20	33	0.00242	53.6	1
<i>Menatetrenone</i>	445	34	0	2	0.0	–	9.55	15	0.01	6	3.9	2
<i>Mesalazine</i>	153	84	4	4	-1.0	1.9 (A)	-1.85	500	1	2	6.4	4
<i>Methylmethionine sulfonium chloride</i>	164	ND	ND	ND	–	ND	ND	25	1000	0.0001	3.2	UC
<i>Mexiletine hydrochloride</i>	179	35	2	2	0.9	8.6 (B)	0.39	100	833	0.00048	9.4	1
<u>Midodrine hydrochloride</u>	254	94	4	6	0.7	7.8 (B)	-1.24	2	138	5.80 × 10 <sup>-5</sup>	2.4	3
<u>Miglitol</u>	207	104	5	6	0.1	6.5 (B)	-2.27	75	791	0.000379	2.0	3
<i>Montelukast sodium</i>	586	96	2	4	-1.0	4.8 (A)	5.82	10	200	0.0002	4.3	1
<i>Mosapride citrate hydrate</i>	422	77	3	6	0.1	6.2 (B)	2.89	5	0.01	2	2	2
<u>Naftopizil</u>	393	45	1	5	0.2	6.9 (B)	3.65	75	0.01	30	11.2	2
<i>Nicardipine hydrochloride</i>	480	114	1	9	0.4	7.3 (B)	3.94	20	6	0.0133	1.5	1
<i>Nicergoline</i>	484	57	0	6	0.1	6.3 (B)	4.29	5	0.01	2	3.3	2
<i>Nicorandil</i>	211	97	1	7	0.0	–	0.93	5	10	0.002	0.8	1
<i>Nifedipine</i>	346	110	1	8	0.0	–	3.45	10	0.01	4	1.0	2
<i>Nilvadipine</i>	385	134	1	9	0.0	–	3.23	4	0.01	1.6	10.7	2
<i>Nizatidine</i>	331	140	2	7	0.5	7.3 (B)	-0.61	150	17.3	0.0347	1.7	1



Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<u>Olanzapine</u>	312	56	1	4	1.0	10.4 (B)	-0.35	10	0.01	4	30.6	2
<u>Olopatadine hydrochloride</u>	337	50	1	4	0.0	4.3 (A), 9.2 (B)	1.54	5	10	0.002	0.8	1
<u>Ondansetron</u>	293	40	0	4	0.6	7.5 (B)	1.76	4	0.01	1.6	4.5	2
<u>Oseltamivir phosphate</u>	312	91	3	6	1.0	8.8 (B)	-0.19	75	521	0.000576	7	1
<u>Oteracil potassium</u>	157	108	3	7	-1.0	-3.1 (A)	-5.54	24.5	7.42	0.0132	3	3
<u>Paroxetine hydrochloride hydrate</u>	329	40	1	4	1.0	9.7 (B)	0.84	20	2	0.04	13.6	1
<u>Pergolide mesylate</u>	314	44	1	2	0.8	8.0 (B)	2.39	0.25	5	0.0002	8.8	1
<u>Perindopril erbumine</u>	368	96	2	7	-1.0	3.2 (A)	0.07	4	500	3.2 × 10 <sup>-5</sup>	0.8	1
<u>Pilsicainide hydrochloride hydrate</u>	272	32	1	3	1.0	10.4 (B)	-0.12	50	100	0.002	4.4	1
<u>Pioglitazone hydrochloride</u>	356	94	1	5	-0.9	6.3 (A)	2.16	30	0.01	12	6.7	2
<u>Pitavastatin calcium</u>	421	91	3	5	-1.0	4.2 (A)	1.17	4	0.1	0.16	9.3	1
<u>Polaprezinc</u>	ND	ND	ND	ND	–	ND	ND	75	0.01	30	2.2	UC
<u>Pramipexole hydrochloride hydrate</u>	211	79	3	3	1.0	9.5(B)	-1.03	0.5	1000	2.0 × 10 <sup>-6</sup>	8.4	3
<u>Pranlukast hydrate</u>	482	119	2	9	-1.0	5.3 (A)	2.74	112.5	0.0012	375	1.2	2
<u>Pravastatin sodium hydrate</u>	425	124	4	7	-1.0	4.3 (A)	0.06	10	100	0.0004	2.7	1
<u>Procaterol hydrochloride</u>	290	82	4	5	1.0	9.4 (B)	-1.47	0.05	50	4.0 × 10 <sup>-6</sup>	3.8	3
<u>Propiverine hydrochloride</u>	367	39	0	4	0.7	7.8 (B)	4.10	20	124	0.000645	10.7	1
<u>Quetiapine fumarate</u>	384	74	1	5	0.2	6.7 (B)	1.92	200	3.38	0.2364	3.5	1
<u>Ramosectron hydrochloride</u>	279	51	1	4	0.4	7.3 (B)	1.80	0.005	575	3.48 × 10 <sup>-8</sup>	7	1
Ranitidine hydrochloride	314	112	2	7	0.9	8.4 (B)	-1.47	150	1429	0.00042	2.7	3
<u>Rebamipide</u>	371	96	3	6	-1.0	3.4 (A)	-0.75	100	0.006	66.7	1.9	2
<u>Risedronate sodium hydrate</u>	283	168	5	8	-3.0	1.4 (A), 2.4 (A), 6.0 (A)	-8.38	75	33	0.00909	1.5	3
<u>Risperidone</u>	410	62	0	6	0.8	8.1 (B)	0.99	2	0.01	0.8	0.3	1

Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<u>Rizatriptan benzoate</u>	269	50	1	5	1.0	9.5 (B)	-0.70	10	34	0.00118	1.7	1
<u>Sarpogrelate hydrochloride</u>	430	85	1	7	-0.2	4.3 (A), 8.1 (B)	1.37	100	1	0.4	0.8	1
<u>Selegiline hydrochloride</u>	187	3	0	1	0.6	7.5 (B)	1.81	2.5	1667	6.0 × 10 <sup>-6</sup>	5.3	1
<u>Sertraline hydrochloride</u>	306	12	1	1	1.0	9.5 (B)	2.45	100	2.70	0.148	25.1	1
<u>Sildenafil citrate</u>	475	118	1	10	0.0	–	1.85	50	1	0.2	1.6	1
<u>Simvastatin</u>	419	73	1	5	0.0	–	4.60	20	0.01	8	2.3	2
<u>Solifenacin succinate</u>	362	171	5	12	1.0	9.0 (B)	1.36	5	610	3.28 × 10 <sup>-5</sup>	46.5	1
<u>Sultamicillin tosilate</u>	595	216	3	13	0.2	6.8 (B)	-0.46	375	0.1	15	1.0	2
<u>Tacrolimus hydrate</u>	804	178	3	13	0.0	–	4.10	5	0.01	2	32.0	2
<u>Taltirelin hydrate</u>	405	171	5	12	0.2	6.7 (B)	-2.73	5	208	9.6 × 10 <sup>-5</sup>	2	3
<u>Tamoxifen citrate</u>	372	12	0	2	1.0	8.7 (B)	4.68	20	0.09	0.889	27.2	1
<u>Tamsulosin hydrochloride</u>	409	108	3	7	1.0	8.8 (B)	-0.06	0.2	11.8	6.76 × 10 <sup>-5</sup>	11.7	1
<u>Teqafur</u>	200	59	1	5	-0.4	7.6 (A)	-0.43	25	16.8	0.00595	1.9	1
<u>Temocapril hydrochloride</u>	477	149	2	7	-1.0	3.7 (A)	0.62	4	0.719	0.0223	0.2	1
<u>Teprenone</u>	331	17	0	1	0.0	–	7.40	50	8.32	0.0240	1.8	1
<u>Terbinafine hydrochloride</u>	291	3	0	1	0.2	6.9 (B)	5.45	125	5.07	0.0987	6.2	1
<u>Ticlopidine hydrochloride</u>	264	31	0	1	0.3	7.1 (B)	3.41	100	58.8	0.0068	1.6	1
<u>Tocopherol nicotinate</u>	536	48	0	4	0.0	–	11.14	200	0.01	80	4.3	2
<u>Tramadol hydrochloride</u>	263	33	1	3	1.0	9.6 (B)	-0.18	50	100	0.002	5.7	1
<u>Tulobuterol hydrochloride</u>	228	32	2	2	1.0	9.6 (B)	-0.17	1	714	5.6 × 10 <sup>-6</sup>	3.2	1
<u>Ursodeoxycholic acid</u>	393	78	3	4	-1.0	4.8 (A)	2.01	100	0.01	40	1.1	2
<u>Valacyclovir hydrochloride</u>	324	147	5	10	0.7	7.8 (B)	-1.78	500	100	0.02	3.0	3
<u>Valproate sodium</u>	144	37	1	2	-1.0	4.8 (A)	0.97	200	1000	0.0008	9.5	1
<u>Valsartan</u>	436	112	2	8	-2.0	3.6 (A), 4.2 (A)	-0.71	160	0.17	3.76	7.7	2

Table 1. (Continued)

Drug	MW (free form)	PSA <sup>b</sup>	HBD <sup>b</sup>	HBA <sup>b</sup>	NC <sup>a</sup> pH 7.4	pK <sub>a</sub> <sup>b</sup>	Log D <sub>6.5</sub> <sup>b</sup>	Highest dose strength (mg) <sup>c</sup>	Solubility in water (mg/mL) <sup>c</sup>	Do	t <sub>1/2</sub> (h) <sup>c</sup>	BCS class
<i>Voglibose</i>	267	154	8	8	0.2	6.8 (B)	-3.57	0.3	1000	1.2 × 10 <sup>-6</sup>	5.3	3
Zolmitriptan	287	57	2	5	1.0	9.5 (B)	-0.29	2.5	0.1	0.1	2.9	1
<i>Zolpidem tartrate</i>	307	38	0	4	0.2	6.8 (B)	2.78	10	8.9	0.00449	1.9	1
Zonizamide	212	95	2	5	0.0	–	0.45	25	0.270	0.37	119.1	1

ND = no data.

UC = unclassifiable.

<sup>a</sup> Net charge at pH 7.4 calculated by Eq. 1.

<sup>b</sup> Calculated value (ACD/Labs Software V 14.0.0).

<sup>c</sup> Data from prescription information (Supplement Tables 1 and 2) otherwise noted.

<sup>d</sup> Underscored drugs correspond to ODTs.

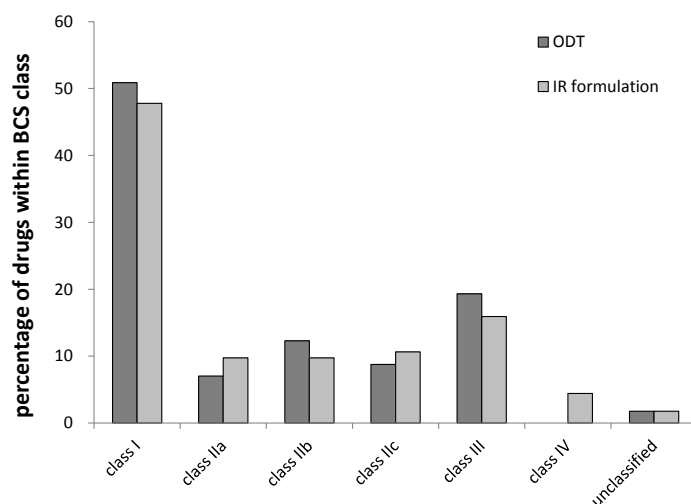
<sup>e</sup> Drugs in italics correspond to IR formulations.

<sup>f</sup> Reference [12]

**Table 2.** Minimum, maximum, and median of biopharmaceutical properties of ODT and IR formulation drugs.

Biopharmaceutical properties		ODT	IR formulation
MW of free form	n	56	113
	Median	359	371
	Min. – Max.	146 – 1069	136 – 1344
PSA	n	56	111
	Median	70	84
	Min. – Max.	3 – 486	3 – 321
HBD	n	56	111
	Median	1	2
	Min. – Max.	0 – 18	0 – 14
HBA	n	56	111
	Median	5	6
	Min. – Max.	1 – 26	1 – 23
NC <sup>a</sup> pH 7.4	n	56	111
	Median	0.2	0.0
	Min. – Max.	-2.0 – 1.0	-3.0 – 1.8
Log $D_{6.5}$	n	56	111
	Median	1.02	0.97
	Min. – Max.	-7.34 – 5.49	-8.44 – 11.14
The highest dose strength (mg)	n	57	113
	Median	10	30
	Min. – Max.	0.005 – 200	0.003 – 900
Solubility in water (mg/mL)	n	57	113
	Median	1.43	3.33
	Min. – Max.	0.003 – 1667	0.0012 – 1429
Do	n	57	113
	Median	0.1	0.04
	Min. – Max.	$3.48 \times 10^{-8}$ – 66.7	$5.4 \times 10^{-8}$ – 375
Elimination $t_{1/2}$ (h)	n	57	113
	Median	6.7	3.3
	Min. – Max.	0.9 – 128	0.2 – 70.7

<sup>a</sup> Net charge at pH 7.4 calculated by Eq. 1.

**Figure 2.** Provisional BCS classification of drugs in ODTs and IR formulations.

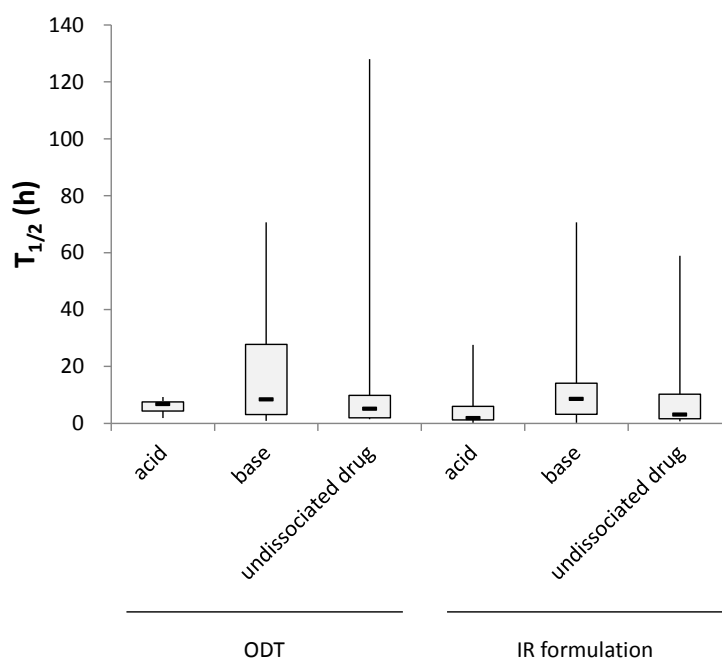
## Discussion

A significant difference was seen in the highest dose strength between the ODT and IR formulation. The ODT would have to have a feasible tablet size and drug loading [13,14]. Therefore, a drug with a high dose strength (>200 mg) would be less suitable as an ODT.

There was no significant difference in the solubility in water and  $D_{6.5}$  between the ODT and IR formulation. This result suggests that many drugs can be developed as an ODT regardless of their solubility and  $D_{6.5}$  (e.g., bicalutamide:  $S = 0.01$  mg/mL,  $D_{6.5} = 32$ , cilostazole:  $S = 0.01$  mg/mL,  $D_{6.5} = 40$ ). Furthermore, an ODT shows BE with a corresponding IR formulation with and without water intake. Therefore, even though it is counterintuitive, water intake may have little effect on the dissolution and oral absorption of low solubility drugs. Previously, Sumesen et al. reported that the oral absorption of danazol was not significantly altered when administered together with 1000 mL of water compared to when administered with 200 mL [15]. Danazol, which has poor water solubility (0.2  $\mu$ g/mL) and high permeability ( $\log D_{6.5} = 4.5$ ), is a typical BCS class II drug [16].

The drugs that have been developed as ODTs tended to have a longer elimination  $t_{1/2}$ . Previously, we reported that the elimination  $t_{1/2}$  of drugs influence the BE of  $C_{max}$  [17]. For the drugs with high permeability and short elimination  $t_{1/2}$ , BE of  $C_{max}$  between two formulations with different dissolution rates would become more difficult to prove. This point has been suggested by several articles [18-21]. A drug with a long elimination  $t_{1/2}$  might be suitable for an ODT.

The proportion of bases was larger in the ODT than in the IR formulation. It is well known that the basic lipophilic drugs have a large distribution volume, and a long elimination  $t_{1/2}$  due to wide tissue distribution [22]. A significant difference was seen in elimination  $t_{1/2}$  between acids, bases, and undissociated drugs in the IR formulation ( $p = 0.04$ ) (Figure 3).



**Figure 3.** Box and whisker plot of elimination  $t_{1/2}$  of acid, base, and undissociated drugs

The biowaiver schemes (BWS) has been discussed based on BCS proposed by Amidon et al. in 1995 [5]. In 2000, the US Food and Drug Administration (FDA) adopted the BCS-BWS [23]. The guideline allows BCS class I drugs which show rapid dissolution (>85 % dissolution in 30 min) to waive clinical BE studies. The World Health Organization (WHO) and other regulatory agencies followed the BCS-BWS [24-27]. However,

there are some differences among these guidelines, e.g. solubility pH range, criteria for high permeability, and definition of the dose used for the Do calculation [28]. One of the most significant differences is about the biowaiver for BCS class III drugs. WHO, European Union, and Canada accept biowaiver for BCS class III drugs which show very rapid dissolution (>85 % dissolution in 15 min), while only BCS class I drugs are eligible for biowaiver in the US FDA and Korea FDA guideline. However, there are several computer simulation and experimental studies on the biowaiver for BCS class III drugs, suggesting that BCS class III drugs are suitable for biowaiver [20,21,29-33]. In addition, it has been pointed out that many BCS class III drugs show BE even when the dissolution profiles are different between the test and reference drugs, for example famotidine, hydrochlorothiazide, and cimetidine [33,34]. Moreover, WHO adopts the possibility of biowaiver for BCS class IIa drugs with low solubility at acidic pH and high solubility at neutral pH that are absorbed completely. However, it was reported that, in the case of ibuprofen, the typically BCS class IIa drug, the BE of  $C_{max}$  is more sensitive to the difference of dissolution rates [35,36].

The BCS class distribution of ODTs and IR formulations may reflect their non-BE risk due to the difference of the dissolution rates. Based on the BCS-BWS, BE is most easily established for BCS class I drugs. However, no difference in the distribution of the BCS classes, including subclasses, between the ODTs and IR formulations was observed in this study. This result may suggest that a BCS class I drug would not necessarily be suitable to show BE. Ramirez et al. reported that in the 124 clinical BE studies there is no difference in the number of subjects in the BE study and the inter- and intra-subject variability for  $C_{max}$  or AUC between four BCS classes [37]. All the BCS classes drugs have the risk of non-BE. Their results also showed that all of the bioequivalent parameters in BCS class I drugs was  $C_{max}$ , but not AUC. The results of the present study suggest that the elimination  $t_{1/2}$  would affect the success rate of a BE study more significantly than the BCS class of a drug (e.g. ibuprofen).

In conclusion, drugs with a lower dose strength (<10 mg) and a longer elimination  $t_{1/2}$  (>6.5 h) were suggested to be more suitable for an ODT. However, the distributions of the ODT and IR formulation among each BCS class were similar, suggesting that the BCS classes are irrelevant to the development risk of ODTs.

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**Supplement Table 1.** ODT drug list used in this study

<b>Drug</b>	<b>Prescription information</b>
Acarbose	<a href="http://www.info.pmda.go.jp/go/interview/1/630004_3969003F3037_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/630004_3969003F3037_1_005_1F</a>
Ambroxol hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/300119_2239001G1039_1_061_1F">http://www.info.pmda.go.jp/go/interview/1/300119_2239001G1039_1_061_1F</a>
Amlodipine besylate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_2171022F1029_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_2171022F1029_2_1F</a> <a href="http://www.info.pmda.go.jp/go/interview/3/400093_2171022F1045_3_017_1F">http://www.info.pmda.go.jp/go/interview/3/400093_2171022F1045_3_017_1F</a>
Aripiprazole	<a href="http://www.info.pmda.go.jp/go/interview/1/180078_1179045F4022_1_012_1F">http://www.info.pmda.go.jp/go/interview/1/180078_1179045F4022_1_012_1F</a>
Bepotastine besylate	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_4490022F3022_1_090_1F">http://www.info.pmda.go.jp/go/interview/1/400315_4490022F3022_1_090_1F</a>
Bicalutamide	<a href="http://www.info.pmda.go.jp/go/interview/1/670227_4291009F1039_1_171_1F">http://www.info.pmda.go.jp/go/interview/1/670227_4291009F1039_1_171_1F</a>
Brotizolam	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_1124009F2025_1_14X_1F">http://www.info.pmda.go.jp/go/interview/1/650168_1124009F2025_1_14X_1F</a>
Cetirizine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/300119_4490020F1225_1_051_1F">http://www.info.pmda.go.jp/go/interview/1/300119_4490020F1225_1_051_1F</a>
Cilostazol	<a href="http://www.info.pmda.go.jp/go/interview/1/180078_3399002F3020_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/180078_3399002F3020_1_005_1F</a>
Desmopressin acetate hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/670666_2419001F1023_2_1F">http://www.info.pmda.go.jp/go/interview/1/670666_2419001F1023_2_1F</a>
Dienogest	<a href="http://www.info.pmda.go.jp/go/interview/1/790005_2499010F1023_1_M02_1F">http://www.info.pmda.go.jp/go/interview/1/790005_2499010F1023_1_M02_1F</a>
Domperidone	<a href="http://www.info.pmda.go.jp/go/interview/1/230124_2399005F3020_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/230124_2399005F3020_1_004_1F</a>
Donepezil hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_1190012F3029_1_028_1F">http://www.info.pmda.go.jp/go/interview/1/170033_1190012F3029_1_028_1F</a>
Doxazosin mesylate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_2149026F1026_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_2149026F1026_2_1F</a>
Droxidopa	<a href="http://www.info.pmda.go.jp/go/interview/2/400093_1169006C1039_2_009_1F">http://www.info.pmda.go.jp/go/interview/2/400093_1169006C1039_2_009_1F</a>
Ebastine	<a href="http://www.info.pmda.go.jp/go/interview/1/400093_4490019F1028_1_018_1F">http://www.info.pmda.go.jp/go/interview/1/400093_4490019F1028_1_018_1F</a>
Famotidine	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2325003F1024_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2325003F1024_1_1F</a>
Fexofenadine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/780069_4490023F1024_1_021_1F">http://www.info.pmda.go.jp/go/interview/1/780069_4490023F1024_1_021_1F</a>
Galantamine hydrobromide	<a href="http://www.info.pmda.go.jp/go/interview/1/800155_1190019F1028_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/800155_1190019F1028_1_005_1F</a>
Gimeracil	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F">http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F</a>
Glimepiride	<a href="http://www.info.pmda.go.jp/go/interview/1/780069_3961008F4070_1_020_1F">http://www.info.pmda.go.jp/go/interview/1/780069_3961008F4070_1_020_1F</a>
Hydrochlorothiazide	<a href="http://www.info.pmda.go.jp/go/interview/1/480235_2132004F1103_1_002_1F">http://www.info.pmda.go.jp/go/interview/1/480235_2132004F1103_1_002_1F</a>
Imidafenacin	<a href="http://www.info.pmda.go.jp/go/interview/1/230109_2590013F1027_1_a13_1F">http://www.info.pmda.go.jp/go/interview/1/230109_2590013F1027_1_a13_1F</a> <a href="http://www.info.pmda.go.jp/go/interview/1/180188_2590013F1035_1_009_1F">http://www.info.pmda.go.jp/go/interview/1/180188_2590013F1035_1_009_1F</a>
Irsogladine maleate	<a href="http://www.info.pmda.go.jp/go/interview/1/530263_2329020F3020_1_05F_1F">http://www.info.pmda.go.jp/go/interview/1/530263_2329020F3020_1_05F_1F</a>

Lafutidine	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_2325006F3020_1_04E_1F">http://www.info.pmda.go.jp/go/interview/1/400107_2325006F3020_1_04E_1F</a>
Lansoprazole	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_2329023F1020_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/400256_2329023F1020_1_006_1F</a>
Loratadine	<a href="http://www.info.pmda.go.jp/go/interview/1/170050_4490027F1022_1_015_1F">http://www.info.pmda.go.jp/go/interview/1/170050_4490027F1022_1_015_1F</a>
Memantine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/430574_1190018F1023_1_M09_1F">http://www.info.pmda.go.jp/go/interview/1/430574_1190018F1023_1_M09_1F</a>
Midodrine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/400059_2160002F2024_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/400059_2160002F2024_1_004_1F</a>
Miglitol	<a href="http://www.info.pmda.go.jp/go/interview/1/300297_39690A0F1026_1_001_1F">http://www.info.pmda.go.jp/go/interview/1/300297_39690A0F1026_1_001_1F</a>
Naftopizil	<a href="http://www.info.pmda.go.jp/go/interview/1/100898_2590009F4020_1_1F">http://www.info.pmda.go.jp/go/interview/1/100898_2590009F4020_1_1F</a>
Olanzapine	<a href="http://www.info.pmda.go.jp/go/interview/1/530471_1179044F4028_1_18F_1F">http://www.info.pmda.go.jp/go/interview/1/530471_1179044F4028_1_18F_1F</a>
Olopatadine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/230124_4490025F3026_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/230124_4490025F3026_1_006_1F</a>
Ondansetron hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/340278_2391006F1023_1_1F">http://www.info.pmda.go.jp/go/interview/1/340278_2391006F1023_1_1F</a>
Oteracil potassium	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F">http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F</a>
Paroxetine hydrochloride hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/480235_1179041F1254_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/480235_1179041F1254_1_005_1F</a>
Pioglitazone hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_3969007F3027_1_007_1F">http://www.info.pmda.go.jp/go/interview/1/400256_3969007F3027_1_007_1F</a>
Pitavastatin calcium	<a href="http://www.info.pmda.go.jp/go/interview/1/270072_2189016F4027_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/270072_2189016F4027_1_005_1F</a>
Polaprezinc	<a href="http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/380077_2329027F1029_1_04">http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/380077_2329027F1029_1_04</a>
Pramipexole hydrochloride hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/480235_1169012F3025_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/480235_1169012F3025_1_004_1F</a>
Ramosetron hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2399014F3029_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2399014F3029_1_1F</a> <a href="http://www.info.pmda.go.jp/go/interview/1/800126_2391004F1024_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2391004F1024_1_1F</a>
Rebamipide	<a href="http://www.info.pmda.go.jp/go/interview/1/530113_2329021F2028_1_002_1F">http://www.info.pmda.go.jp/go/interview/1/530113_2329021F2028_1_002_1F</a>
Risperidone	<a href="http://www.info.pmda.go.jp/go/interview/1/800155_1179038F5029_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/800155_1179038F5029_1_005_1F</a>
Rizatriptan benzoate	<a href="http://www.info.pmda.go.jp/go/interview/2/230109_2160006F1026_2_011_1F">http://www.info.pmda.go.jp/go/interview/2/230109_2160006F1026_2_011_1F</a>
Selegiline hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/170654_1169010F2020_1_S03_1F">http://www.info.pmda.go.jp/go/interview/1/170654_1169010F2020_1_S03_1F</a>
Sertraline hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_1179046F1028_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_1179046F1028_2_1F</a>
Sildenafil citrate	<a href="http://www.info.pmda.go.jp/go/interview/1/480235_259000AF3027_1_002_1F">http://www.info.pmda.go.jp/go/interview/1/480235_259000AF3027_1_002_1F</a>
Solifenacin succinate	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2590011F3020_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2590011F3020_1_1F</a>
Taltirelin hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_1190014F2021_1_050_1F">http://www.info.pmda.go.jp/go/interview/1/400315_1190014F2021_1_050_1F</a>
Tamsulosin hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2590008F1026_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2590008F1026_1_1F</a>
Tegafur	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F">http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F</a>

Tramadol hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/530263_1149038F1024_1_01F_1F">http://www.info.pmda.go.jp/go/interview/1/530263_1149038F1024_1_01F_1F</a>
Valsartan	<a href="http://www.info.pmda.go.jp/go/interview/1/300242_2149041F5026_5_DIO_1F">http://www.info.pmda.go.jp/go/interview/1/300242_2149041F5026_5_DIO_1F</a>
Voglibose	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_3969004F3023_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/400256_3969004F3023_1_006_1F</a>
Zolmitriptan	<a href="http://www.info.pmda.go.jp/go/interview/1/670227_2160004F2023_1_101_1F">http://www.info.pmda.go.jp/go/interview/1/670227_2160004F2023_1_101_1F</a>
Zolpidem tartrate	<a href="http://www.info.pmda.go.jp/go/interview/3/800126_1129009F1025_3_1F">http://www.info.pmda.go.jp/go/interview/3/800126_1129009F1025_3_1F</a>
Zonizamide	<a href="http://www.info.pmda.go.jp/go/interview/1/400093_1169015F2022_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/400093_1169015F2022_1_004_1F</a>

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**Supplement Table 2.** IR formulation drug list used in this study

<b>Drug</b>	<b>Prescription information</b>
Acarbose	<a href="http://www.info.pmda.go.jp/go/interview/1/630004_3969003F3037_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/630004_3969003F3037_1_005_1F</a>
Acetaminophen	<a href="http://www.info.pmda.go.jp/go/interview/3/671610_1141007F1063_3_15L_1F">http://www.info.pmda.go.jp/go/interview/3/671610_1141007F1063_3_15L_1F</a>
Acetylsalicylic acid	<a href="http://www.info.pmda.go.jp/go/interview/1/630004_3399007H1021_1_002_1F">http://www.info.pmda.go.jp/go/interview/1/630004_3399007H1021_1_002_1F</a>
Acyclovir	<a href="http://www.info.pmda.go.jp/go/interview/W/340278_6250002F1025_1_001_1F">http://www.info.pmda.go.jp/go/interview/W/340278_6250002F1025_1_001_1F</a>
Alendronate sodium hydrate	<a href="http://www.info.pmda.go.jp/go/interview/2/170050_3999018F1021_2_018_1F">http://www.info.pmda.go.jp/go/interview/2/170050_3999018F1021_2_018_1F</a>
Alfacalcidol	<a href="http://www.info.pmda.go.jp/go/interview/1/450045_3112001M1046_1_007_1F">http://www.info.pmda.go.jp/go/interview/1/450045_3112001M1046_1_007_1F</a>
Allopurinol	<a href="http://www.info.pmda.go.jp/go/interview/W/340278_3943001F1314_1_1F">http://www.info.pmda.go.jp/go/interview/W/340278_3943001F1314_1_1F</a>
Ambroxol hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_2239001N1135_1_148_1F">http://www.info.pmda.go.jp/go/interview/1/650168_2239001N1135_1_148_1F</a>
Amlodipine besylate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_2171022F1029_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_2171022F1029_2_1F</a>
Atenolol	<a href="http://www.info.pmda.go.jp/go/interview/3/670227_2123011F1155_1_131_1F">http://www.info.pmda.go.jp/go/interview/3/670227_2123011F1155_1_131_1F</a>
Atorvastatin calcium	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2189015F1023_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2189015F1023_1_1F</a>
Azithromycin hydrate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_6149004F1028_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_6149004F1028_2_1F</a>
Azulene sulfonate	<a href="http://www.info.pmda.go.jp/go/interview/1/530263_2323001F1225_1_04F_1F">http://www.info.pmda.go.jp/go/interview/1/530263_2323001F1225_1_04F_1F</a>
Benidipine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/230124_2171021F1024_1_001_1F">http://www.info.pmda.go.jp/go/interview/1/230124_2171021F1024_1_001_1F</a>
Beraprost sodium	<a href="http://www.info.pmda.go.jp/go/interview/1/480220_3399005F1021_1_A06_1F">http://www.info.pmda.go.jp/go/interview/1/480220_3399005F1021_1_A06_1F</a>
Bicalutamide	<a href="http://www.info.pmda.go.jp/go/interview/1/670227_4291009F1039_1_171_1F">http://www.info.pmda.go.jp/go/interview/1/670227_4291009F1039_1_171_1F</a>
Bisoprolol fumarate	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_2123016F1107_1_120_1F">http://www.info.pmda.go.jp/go/interview/1/400315_2123016F1107_1_120_1F</a>
Brotizolam	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_1124009F2025_1_14X_1F">http://www.info.pmda.go.jp/go/interview/1/650168_1124009F2025_1_14X_1F</a>
Cabergoline	<a href="http://www.info.pmda.go.jp/go/interview/4/671450_1169011F1028_4_1F">http://www.info.pmda.go.jp/go/interview/4/671450_1169011F1028_4_1F</a>
Camostat mesylate	<a href="http://www.info.pmda.go.jp/go/interview/1/180188_3999003F1297_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/180188_3999003F1297_1_005_1F</a>
Candesartan cilexetil	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_2149040F1026_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/400256_2149040F1026_1_004_1F</a>
Carvedilol	<a href="http://www.info.pmda.go.jp/go/interview/2/430574_2149032F1021_2_A13_1F">http://www.info.pmda.go.jp/go/interview/2/430574_2149032F1021_2_A13_1F</a>
Cefcapene pivoxil hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/340018_6132016F1023_1_011_1F">http://www.info.pmda.go.jp/go/interview/1/340018_6132016F1023_1_011_1F</a>
Cefdinir	<a href="http://www.info.pmda.go.jp/go/interview/3/800126_6132013M1029_3_1F">http://www.info.pmda.go.jp/go/interview/3/800126_6132013M1029_3_1F</a>
Cefditoren pivoxil	<a href="http://www.info.pmda.go.jp/go/interview/1/780009_6132015F1037_1_01A_1F">http://www.info.pmda.go.jp/go/interview/1/780009_6132015F1037_1_01A_1F</a>
Cefotiam hexetil hydrochloride	<a href="http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_6132012F1025_1_12">http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_6132012F1025_1_12</a>

Cetirizine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/2/820110_4490020F1020_2_013_1F">http://www.info.pmda.go.jp/go/interview/2/820110_4490020F1020_2_013_1F</a>
Cilostazol	<a href="http://www.info.pmda.go.jp/go/interview/1/180078_3399002F3020_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/180078_3399002F3020_1_005_1F</a>
Clarithromycin	<a href="http://www.info.pmda.go.jp/go/interview/1/400059_6149003F2038_1_028_1F">http://www.info.pmda.go.jp/go/interview/1/400059_6149003F2038_1_028_1F</a>
Cyclosporin a	<a href="http://www.info.pmda.go.jp/go/interview/2/300242_3999004M3021_2_NEO_1F">http://www.info.pmda.go.jp/go/interview/2/300242_3999004M3021_2_NEO_1F</a>
Diclofenac sodium	<a href="http://www.info.pmda.go.jp/go/interview/1/300242_1147002F1560_1_VOL_1F">http://www.info.pmda.go.jp/go/interview/1/300242_1147002F1560_1_VOL_1F</a>
Donepezil hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_1190012F3029_1_028_1F">http://www.info.pmda.go.jp/go/interview/1/170033_1190012F3029_1_028_1F</a>
Doxazosin mesylate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_2149026F1026_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_2149026F1026_2_1F</a>
Doxifluridine	<a href="http://www.info.pmda.go.jp/go/interview/2/450045_4223004M1027_2_004_1F">http://www.info.pmda.go.jp/go/interview/2/450045_4223004M1027_2_004_1F</a>
Ebastine	<a href="http://www.info.pmda.go.jp/go/interview/1/400093_4490019F1028_1_018_1F">http://www.info.pmda.go.jp/go/interview/1/400093_4490019F1028_1_018_1F</a>
Enalapril maleate	<a href="http://www.info.pmda.go.jp/go/interview/2/170050_2144002F1024_2_016_1F">http://www.info.pmda.go.jp/go/interview/2/170050_2144002F1024_2_016_1F</a>
Epalrestat	<a href="http://www.info.pmda.go.jp/go/interview/1/180188_3999013F1231_1_004_1F">http://www.info.pmda.go.jp/go/interview/1/180188_3999013F1231_1_004_1F</a>
Eperisone hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_1249009D1030_1_007_1F">http://www.info.pmda.go.jp/go/interview/1/170033_1249009D1030_1_007_1F</a>
Epinastine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_4490014F1025_1_119_1F">http://www.info.pmda.go.jp/go/interview/1/650168_4490014F1025_1_119_1F</a>
Ethyl icosapentate	<a href="http://www.info.pmda.go.jp/go/interview/1/790005_3399004M2022_1_M03_1F">http://www.info.pmda.go.jp/go/interview/1/790005_3399004M2022_1_M03_1F</a>
Etizolam	<a href="http://www.info.pmda.go.jp/go/interview/2/400315_1179025C1054_2_150_1F">http://www.info.pmda.go.jp/go/interview/2/400315_1179025C1054_2_150_1F</a>
Famotidine	<a href="http://www.info.pmda.go.jp/go/interview/1/800126_2325003F1024_1_1F">http://www.info.pmda.go.jp/go/interview/1/800126_2325003F1024_1_1F</a>
Fexofenadine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/780069_4490023F1024_1_021_1F">http://www.info.pmda.go.jp/go/interview/1/780069_4490023F1024_1_021_1F</a>
Fluconazole	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_6290002M1020_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_6290002M1020_2_1F</a>
Flurbiprofen	<a href="http://www.info.pmda.go.jp/go/interview/1/200022_1149011D1032_1_080_1F">http://www.info.pmda.go.jp/go/interview/1/200022_1149011D1032_1_080_1F</a>
Fluvastatin sodium	<a href="http://www.info.pmda.go.jp/go/interview/3/300242_2189012F1020_3_LOC_1F">http://www.info.pmda.go.jp/go/interview/3/300242_2189012F1020_3_LOC_1F</a>
Fluvoxamine maleate	<a href="http://www.info.pmda.go.jp/go/interview/1/780009_1179039F1028_1_1F">http://www.info.pmda.go.jp/go/interview/1/780009_1179039F1028_1_1F</a>
Fursultiamine	<a href="http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_3122007F2039_1_10">http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_3122007F2039_1_10</a>
Gefitinib	<a href="http://www.info.pmda.go.jp/go/interview/1/670227_4291013F1027_1_192_1F">http://www.info.pmda.go.jp/go/interview/1/670227_4291013F1027_1_192_1F</a>
Glimepiride	<a href="http://www.info.pmda.go.jp/go/interview/1/780069_3961008F4070_1_020_1F">http://www.info.pmda.go.jp/go/interview/1/780069_3961008F4070_1_020_1F</a>
Granisetron hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/450045_2391002C1037_1_010_1F">http://www.info.pmda.go.jp/go/interview/1/450045_2391002C1037_1_010_1F</a>
Imatinib mesylate	<a href="http://www.info.pmda.go.jp/go/interview/1/300242_4291011F1028_1_GLI_1F">http://www.info.pmda.go.jp/go/interview/1/300242_4291011F1028_1_GLI_1F</a>
Imidapril hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_2144008F1021_1_090_1F">http://www.info.pmda.go.jp/go/interview/1/400315_2144008F1021_1_090_1F</a>
Itraconazole	<a href="http://www.info.pmda.go.jp/go/interview/1/800155_6290004M1029_2_008_1F">http://www.info.pmda.go.jp/go/interview/1/800155_6290004M1029_2_008_1F</a>

Ketoprofen <sup>a</sup>	<a href="http://www.info.pmda.go.jp/go/interview/2/650208_1149700J1035_2_1F">http://www.info.pmda.go.jp/go/interview/2/650208_1149700J1035_2_1F</a>
Ketotifen fumarate	<a href="http://www.info.pmda.go.jp/go/interview/1/300242_4490003M1263_1_Z-C_1F">http://www.info.pmda.go.jp/go/interview/1/300242_4490003M1263_1_Z-C_1F</a>
L-carbocysteine	<a href="http://www.info.pmda.go.jp/go/interview/1/230109_2233002F1174_1_001_1F">http://www.info.pmda.go.jp/go/interview/1/230109_2233002F1174_1_001_1F</a>
Levofloxacin	<a href="http://www.info.pmda.go.jp/go/interview/1/430574_6241013C2024_1_c11_1F">http://www.info.pmda.go.jp/go/interview/1/430574_6241013C2024_1_c11_1F</a>
Limaprost alfadex	<a href="http://www.info.pmda.go.jp/go/interview/1/180188_3399003F1073_1_010_1F">http://www.info.pmda.go.jp/go/interview/1/180188_3399003F1073_1_010_1F</a>
Loratadine	<a href="http://www.info.pmda.go.jp/go/interview/1/170050_4490027F1022_1_015_1F">http://www.info.pmda.go.jp/go/interview/1/170050_4490027F1022_1_015_1F</a>
Losartan potassium	<a href="http://www.info.pmda.go.jp/go/interview/2/170050_2149039F1031_2_018_1F">http://www.info.pmda.go.jp/go/interview/2/170050_2149039F1031_2_018_1F</a>
Loxoprofen sodium hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/430574_1149019C1149_1_LO8_1F">http://www.info.pmda.go.jp/go/interview/1/430574_1149019C1149_1_LO8_1F</a>
Manidipine hydrochloride	<a href="http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_2149027F1020_1_09">http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_2149027F1020_1_09</a>
Mecobalamin	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_3136004C1038_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/170033_3136004C1038_1_006_1F</a>
Meloxicam	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_1149035F1020_1_156_1F">http://www.info.pmda.go.jp/go/interview/1/650168_1149035F1020_1_156_1F</a>
Menatetrenone	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_3160002M2028_1_008_1F">http://www.info.pmda.go.jp/go/interview/1/170033_3160002M2028_1_008_1F</a>
Mesalazine	<a href="http://www.info.pmda.go.jp/go/interview/1/230109_2399009F1149_1_015_1F">http://www.info.pmda.go.jp/go/interview/1/230109_2399009F1149_1_015_1F</a>
Methylmethionine sulfonium chloride	<a href="http://www.info.pmda.go.jp/go/interview/1/270072_2321001F1042_1_002_1F">http://www.info.pmda.go.jp/go/interview/1/270072_2321001F1042_1_002_1F</a>
Mexiletine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/650168_2129003M1021_1_14Y_1F">http://www.info.pmda.go.jp/go/interview/1/650168_2129003M1021_1_14Y_1F</a>
Montelukast sodium	<a href="http://www.info.pmda.go.jp/go/interview/1/230109_4490026F2040_1_035_1F">http://www.info.pmda.go.jp/go/interview/1/230109_4490026F2040_1_035_1F</a>
Mosapride citrate hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/400093_2399010B1034_1_020_1F">http://www.info.pmda.go.jp/go/interview/1/400093_2399010B1034_1_020_1F</a>
Nicardipine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/300119_2149019F1085_1_041_1F">http://www.info.pmda.go.jp/go/interview/1/300119_2149019F1085_1_041_1F</a>
Nicergoline	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_2190021B1095_1_100_1F">http://www.info.pmda.go.jp/go/interview/1/400315_2190021B1095_1_100_1F</a>
Nicorandil	<a href="http://www.info.pmda.go.jp/go/interview/1/450045_2171017F1028_1_009_1F">http://www.info.pmda.go.jp/go/interview/1/450045_2171017F1028_1_009_1F</a>
Nifedipine	<a href="http://www.info.pmda.go.jp/go/interview/1/630004_2171014M1104_1_001_1F">http://www.info.pmda.go.jp/go/interview/1/630004_2171014M1104_1_001_1F</a>
Nilvadipine	<a href="http://www.info.pmda.go.jp/go/interview/3/800126_2149022F1028_3_1F">http://www.info.pmda.go.jp/go/interview/3/800126_2149022F1028_3_1F</a>
Nizatidine	<a href="http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/380077_2325005F1031_1_06">http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/380077_2325005F1031_1_06</a>
Olanzapine	<a href="http://www.info.pmda.go.jp/go/interview/1/530471_1179044F4028_1_18F_1F">http://www.info.pmda.go.jp/go/interview/1/530471_1179044F4028_1_18F_1F</a>
Olopatadine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/230124_4490025F3026_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/230124_4490025F3026_1_006_1F</a>
Oseltamivir phosphate	<a href="http://www.info.pmda.go.jp/go/interview/1/450045_6250021M1027_1_026_1F">http://www.info.pmda.go.jp/go/interview/1/450045_6250021M1027_1_026_1F</a>
Paroxetine hydrochloride hydrate	<a href="http://www.info.pmda.go.jp/go/interview/2/340278_1179041F1025_1_018_1F">http://www.info.pmda.go.jp/go/interview/2/340278_1179041F1025_1_018_1F</a>

Pergolide mesylate	<a href="http://www.info.pmda.go.jp/go/interview/2/230124_1169008F1026_2_004_1F">http://www.info.pmda.go.jp/go/interview/2/230124_1169008F1026_2_004_1F</a>
Perindopril erbumine	<a href="http://www.info.pmda.go.jp/go/interview/3/230124_2144012F1028_3_001_1F">http://www.info.pmda.go.jp/go/interview/3/230124_2144012F1028_3_001_1F</a>
Pilsicainide hydrochloride hydrate	<a href="http://www.info.pmda.go.jp/go/interview/3/430574_2129008M1024_3_S10_1F">http://www.info.pmda.go.jp/go/interview/3/430574_2129008M1024_3_S10_1F</a>
Pioglitazone hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_3969007F3027_1_007_1F">http://www.info.pmda.go.jp/go/interview/1/400256_3969007F3027_1_007_1F</a>
Pranlukast hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/180188_4490017M1036_1_009_1F">http://www.info.pmda.go.jp/go/interview/1/180188_4490017M1036_1_009_1F</a>
Pravastatin sodium	<a href="http://www.info.pmda.go.jp/go/interview/2/430574_2189010C1032_2_M10_1F">http://www.info.pmda.go.jp/go/interview/2/430574_2189010C1032_2_M10_1F</a>
Procaterol hydrochloride hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/180078_2259004F2168_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/180078_2259004F2168_1_005_1F</a>
Propiverine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_2590007C1025_1_04L_1F">http://www.info.pmda.go.jp/go/interview/1/400107_2590007C1025_1_04L_1F</a>
Quetiapine fumarate	<a href="http://www.info.pmda.go.jp/go/interview/2/800126_1179042C1023_2_1F">http://www.info.pmda.go.jp/go/interview/2/800126_1179042C1023_2_1F</a>
Ranitidine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/340278_2325002F1194_1_009_1F">http://www.info.pmda.go.jp/go/interview/1/340278_2325002F1194_1_009_1F</a>
Rebamipide	<a href="http://www.info.pmda.go.jp/go/interview/1/180078_2329021D1020_1_013_1F">http://www.info.pmda.go.jp/go/interview/1/180078_2329021D1020_1_013_1F</a>
Risedronate sodium hydrate	<a href="http://www.info.pmda.go.jp/go/interview/2/111890_3999019F1026_2_016_1F">http://www.info.pmda.go.jp/go/interview/2/111890_3999019F1026_2_016_1F</a>
Risperidone	<a href="http://www.info.pmda.go.jp/go/interview/1/800155_1179038F5029_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/800155_1179038F5029_1_005_1F</a>
Sarpogrelate hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/3/400315_3399006C1020_3_15A_1F">http://www.info.pmda.go.jp/go/interview/3/400315_3399006C1020_3_15A_1F</a>
Simvastatin	<a href="http://www.info.pmda.go.jp/go/interview/2/170050_2189011F1025_2_022_1F">http://www.info.pmda.go.jp/go/interview/2/170050_2189011F1025_2_022_1F</a>
Sultamicillin tosilate hydrate	<a href="http://www.info.pmda.go.jp/go/interview/2/671450_6131008F1030_2_1F">http://www.info.pmda.go.jp/go/interview/2/671450_6131008F1030_2_1F</a>
Tacrolimus hydrate	<a href="http://www.info.pmda.go.jp/go/interview/3/800126_3999014D1022_3_1F">http://www.info.pmda.go.jp/go/interview/3/800126_3999014D1022_3_1F</a>
Taltirelin hydrate	<a href="http://www.info.pmda.go.jp/go/interview/1/400315_1190014F2021_1_050_1F">http://www.info.pmda.go.jp/go/interview/1/400315_1190014F2021_1_050_1F</a>
Tamoxifen citrate	<a href="http://www.info.pmda.go.jp/go/interview/1/670227_4291003F1163_1_012_1F">http://www.info.pmda.go.jp/go/interview/1/670227_4291003F1163_1_012_1F</a>
Tegafur	<a href="http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F">http://www.info.pmda.go.jp/go/interview/1/400107_4229101F1026_1_10E_1F</a>
Temocapril hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/3/430574_2144009F1026_3_C10_1F">http://www.info.pmda.go.jp/go/interview/3/430574_2144009F1026_3_C10_1F</a>
Teprenone	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_2329012C1026_1_009_1F">http://www.info.pmda.go.jp/go/interview/1/170033_2329012C1026_1_009_1F</a>
Terbinafine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/730012_6290005F1032_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/730012_6290005F1032_1_006_1F</a>
Ticlopidine hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/4/780069_3399001C1027_4_011_1F">http://www.info.pmda.go.jp/go/interview/4/780069_3399001C1027_4_011_1F</a>
Tocopherol nicotinate	<a href="http://www.info.pmda.go.jp/go/interview/1/170033_2190006C1037_1_008_1F">http://www.info.pmda.go.jp/go/interview/1/170033_2190006C1037_1_008_1F</a>
Tulobuterol hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/3/100159_2259002F1065_3_004_1F">http://www.info.pmda.go.jp/go/interview/3/100159_2259002F1065_3_004_1F</a>
Ursodeoxycholic acid	<a href="http://www.info.pmda.go.jp/go/interview/2/400315_2362001F1088_2_11A_1F">http://www.info.pmda.go.jp/go/interview/2/400315_2362001F1088_2_11A_1F</a>
Valacyclovir hydrochloride	<a href="http://www.info.pmda.go.jp/go/interview/1/340278_6250019F1020_1_013_1F">http://www.info.pmda.go.jp/go/interview/1/340278_6250019F1020_1_013_1F</a>

Valproate sodium	<a href="http://www.info.pmda.go.jp/go/interview/1/230124_1139004F1096_1_005_1F">http://www.info.pmda.go.jp/go/interview/1/230124_1139004F1096_1_005_1F</a>
Valsartan	<a href="http://www.info.pmda.go.jp/go/interview/1/300242_2149041F5026_5_DIO_1F">http://www.info.pmda.go.jp/go/interview/1/300242_2149041F5026_5_DIO_1F</a>
Voglibose	<a href="http://www.info.pmda.go.jp/go/interview/1/400256_3969004F3023_1_006_1F">http://www.info.pmda.go.jp/go/interview/1/400256_3969004F3023_1_006_1F</a>
Zolpidem tartrate	<a href="http://www.info.pmda.go.jp/go/interview/3/800126_1129009F1025_3_1F">http://www.info.pmda.go.jp/go/interview/3/800126_1129009F1025_3_1F</a>

<sup>a</sup> IR formulations of ketoprofen are no longer in production in Japan. The dose strengths of the IR formulations were from the FDA website (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>).



**Supplement Table 3.** Model equation for NC calculation by using the Henderson-Hasselbalch equation.

Compound type	Model equation
Mono acid	$NC = \frac{(-1) \times 10^{-pK_a}}{10^{-pK_a} + 10^{-pH}}$
Mono base	$NC = \frac{10^{-pH}}{10^{-pK_a} + 10^{-pH}}$
Di acid	$NC = \frac{(-1) \times 10^{-pK_{a1}} \times 10^{-pH} + (-2) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}}}{[10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}}}$
Di base	$NC = \frac{2 \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pH}}{[10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}}}$
Mono acid/mono base	$NC = \frac{[10^{-pH}]^2 + (-1) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}}}{[10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}}}$
Tri acid	$NC = \frac{(-1) \times 10^{-pK_{a1}} \times [10^{-pH}]^2 + (-2) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + (-3) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}{[10^{-pH}]^3 + 10^{-pK_{a1}} \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}$
Tri base	$NC = \frac{3 \times [10^{-pH}]^3 + 2 \times 10^{-pK_{a1}} \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH}}{[10^{-pH}]^3 + 10^{-pK_{a1}} \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}$
Di acid/mono base	$NC = \frac{[10^{-pH}]^3 + (-1) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + (-2) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}{[10^{-pH}]^3 + 10^{-pK_{a1}} \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}$
Mono acid/di base	$NC = \frac{2 \times [10^{-pH}]^3 + 10^{-pK_{a1}} \times [10^{-pH}]^2 + (-1) \times 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}{[10^{-pH}]^3 + 10^{-pK_{a1}} \times [10^{-pH}]^2 + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pH} + 10^{-pK_{a1}} \times 10^{-pK_{a2}} \times 10^{-pK_{a3}}}$

Supplement Table 4 Solubility Definitions

<b>Solubility definition</b>	<b>Parts of solvent required for 1 part of solute</b>	<b>Solubility range (mg/mL)</b>	<b>Solubility assigned (mg/mL)</b>
very soluble	<1	≥1000	1000
freely soluble	1-10	100-1000	100
soluble	10-30	33-100	33
sparingly soluble	30-100	10-33	10
slightly soluble	100-1000	1-10	1
very slightly soluble	1000-10000	0.1-1	0.1
practically insoluble	≥10000	<0.1	0.01