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Original scientific paper

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

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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).

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) (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.

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

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

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 ≤ 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, 1.26×10^{-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_as 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.

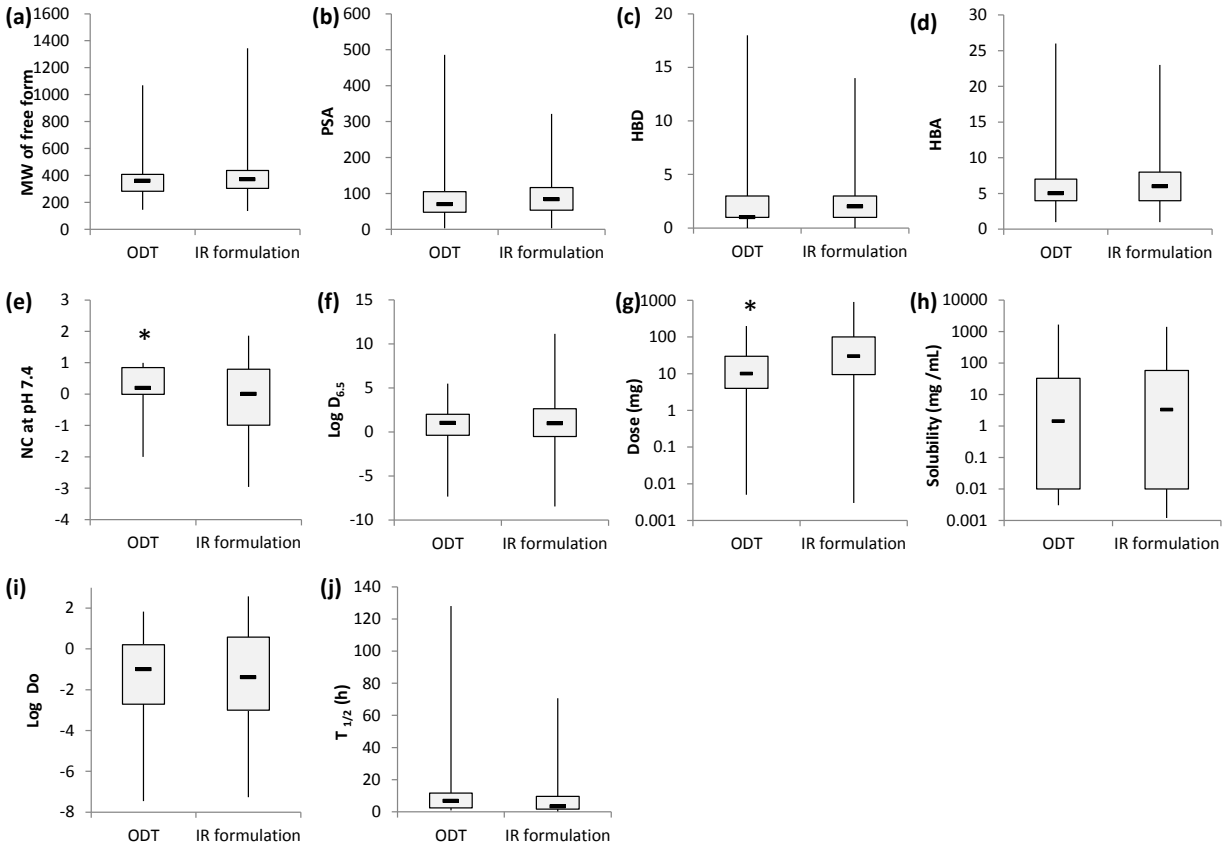

Figure 1. Box and whisker plots of biopharmaceutical properties of ODT and IR formulation drugs ; the bottom and top of the box are the first and third quartiles, the band inside the box is the median, and the ends of the whiskers are the minimum and maximum. **(a)** MW of free form. **(b)** Polar surface 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 [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	*D*o	$t_{1/2}$ (h) [c]	BCS class
Acarbose [d,e]	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
Ambroxol hydrochloride	378	58	4	3	1.0	8.7 (B)	0.48	45	26.8	0.00672	11.2	1
Amlodipine besylate	409	100	3	7	1.0	9.0 (B)	1.09	10	2.22	0.018	36.2	1
Aripiprazole	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
Bepotastine besylate	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	1.92×10^{-7}	1.1	1
Bicalutamide	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	1.6×10^{-5}	8.6	1
Brotizolam	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 [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	Do	$t_{1/2}$ (h) [c]	BCS class
Carvedilol	406	76	3	6	0.9	8.2 (B)	2.20	20	0.01	8	7.7	2
Cefcapene pivoxil hydrochloride	594	257	3	16	0.0	5.9 (A), 9.0 (B)	-1.59	100	1.88	0.213	1.1	3
Cefdinir	395	212	5	10	-1.0	2.8 (A)	-3.92	100	0.381	1.05	1.6	4
Cefditoren pivoxil	621	257	3	13	-0.2	8.1 (A)	2.45	100	0.01	40	1.1	2
Cefotiam hexetil hydrochloride	696	276	3	16	0.8	8.0 (B)	-0.14	200	1000	0.0008	0.8	1
Cetirizine hydrochloride	389	53	1	5	-0.8	3.5 (A), 6.7 (B)	-0.09	10	1000	4.0×10^{-5}	7.5	1
Cilostazol	369	82	1	7	0.0	–	3.01	100	0.01	40	10.1	2
Clarithromycin	748	183	4	14	0.9	8.2 (B)	1.56	200	0.01	80	4.4	2
Cyclosporin a	1203	279	5	23	0.0	–	1.80	50	3.38	0.0592	1.6	1
Desmopressin acetate hydrate	1069	486	18	26	0.0	–	-7.34	0.24	33	2.9×10^{-5}	2	3
Diclofenac sodium	296	49	2	3	-1.0	4.2 (A)	2.17	25	17.2	0.0058	1.2	1
Dienogest	311	61	1	3	0.0	–	2.64	1	0.01	0.4	8.0	1
Domperidone	426	68	2	7	1.0	9.0 (B)	2.26	10	0.01	4	0.9	2
Donepezil hydrochloride	379	39	0	4	1.0	8.8 (B)	1.97	10	10	0.004	70.7	1
Doxazosin mesylate	451	112	2	10	0.1	6.5 (B)	1.20	4	1	0.016	11.8	1
Doxifluridine	246	99	3	7	-0.4	7.6 (A)	-1.13	200	33	0.0242	0.8 [f]	3
Droxidopa	213	124	6	6	-0.1	2.1 (A), 8.3 (B)	-3.57	200	2.4	0.333	2	3
Ebastine	470	30	0	3	0.9	8.2 (B)	5.49	10	0.01	4	17.6	2
Enalapril maleate	376	96	2	7	-1.0	3.1 (A)	-1.06	10	21	0.00191	6.1	3
Epalrestat	319	115	1	4	-1.0	3.6 (A)	-1.04	50	0.009	22.2	1.8	4
Eperisone hydrochloride	259	20	0	2	0.9	8.5 (B)	2.02	50	200	0.001	1.6	1
Epinastine hydrochloride	249	42	2	3	1.0	12.0 (B)	0.77	20	133	0.0006	9.2	1
Ethyl icosapentate	331	26	0	2	0.0	–	6.65	900	0.01	360	58.9	2
Etizolam	343	71	0	4	0.0	–	2.87	1	0.01	0.4	6.3	1

Table 1. (Continued)

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

Table 1. (Continued)

Drug	MW (free form)	PSA [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	Do	$t_{1/2}$ (h) [c]	BCS class
Levofloxacin	361	73	1	7	-0.5	5.2 (A), 7.4 (B)	-1.76	500	16. 7	0.12	7.9	3
Limaprost alfadex	366	95	3	5	-1.0	4.6 (A)	0.85	0.005	370	5.4×10^{-8}	0.5	1
Loratadine	383	42	0	4	0.0	–	5.32	10	0.00303	13.2	20.1	2
Losartan potassium	423	93	2	7	-1.0	4.2 (A)	1.77	100	1000	0.0004	1.8	1
Loxoprofen sodium hydrate	246	54	1	3	-1.0	4.4 (A)	0.37	60	1000	0.00024	1.2	1
Manidipine hydrochloride	611	117	1	10	0.1	6.1 (B)	5.29	20	3.88	0.0206	1.5	1
Mecobalamin	1344	ND	ND	ND	–	ND	ND	0.5	12.5	0.00016	12.5	UC
Meloxicam	351	136	2	7	-1.0	4.5 (A)	0.29	10	0.01	4	27.6	2
Memantine hydrochloride	179	26	2	1	1.0	10.8 (B)	0.40	20	33	0.00242	53.6	1
Menatetrenone	445	34	0	2	0.0	–	9.55	15	0.01	6	3.9	2
Mesalazine	153	84	4	4	-1.0	1.9 (A)	-1.85	500	1	2	6.4	4
Methylmethionine sulfonium chloride	164	ND	ND	ND	–	ND	ND	25	1000	0.0001	3.2	UC
Mexiletine hydrochloride	179	35	2	2	0.9	8.6 (B)	0.39	100	833	0.00048	9.4	1
Midodrine hydrochloride	254	94	4	6	0.7	7.8 (B)	-1.24	2	138	5.80×10^{-5}	2.4	3
Miglitol	207	104	5	6	0.1	6.5 (B)	-2.27	75	791	0.000379	2.0	3
Montelukast sodium	586	96	2	4	-1.0	4.8 (A)	5.82	10	200	0.0002	4.3	1
Mosapride citrate hydrate	422	77	3	6	0.1	6.2 (B)	2.89	5	0.01	2	2	2
Naftopizil	393	45	1	5	0.2	6.9 (B)	3.65	75	0.01	30	11.2	2
Nicardipine hydrochloride	480	114	1	9	0.4	7.3 (B)	3.94	20	6	0.0133	1.5	1
Nicergoline	484	57	0	6	0.1	6.3 (B)	4.29	5	0.01	2	3.3	2
Nicorandil	211	97	1	7	0.0	–	0.93	5	10	0.002	0.8	1
Nifedipine	346	110	1	8	0.0	–	3.45	10	0.01	4	1.0	2
Nilvadipine	385	134	1	9	0.0	–	3.23	4	0.01	1.6	10.7	2
Nizatidine	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 [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	Do	$t_{1/2}$ (h) [c]	BCS class
Olanzapine	312	56	1	4	1.0	10.4 (B)	-0.35	10	0.01	4	30.6	2
Olopatadine hydrochloride	337	50	1	4	0.0	4.3 (A), 9.2 (B)	1.54	5	10	0.002	0.8	1
Ondansetron	293	40	0	4	0.6	7.5 (B)	1.76	4	0.01	1.6	4.5	2
Oseltamivir phosphate	312	91	3	6	1.0	8.8 (B)	-0.19	75	521	0.000576	7	1
Oteracil potassium	157	108	3	7	-1.0	-3.1 (A)	-5.54	24.5	7.42	0.0132	3	3
Paroxetine hydrochloride hydrate	329	40	1	4	1.0	9.7 (B)	0.84	20	2	0.04	13.6	1
Pergolide mesylate	314	44	1	2	0.8	8.0 (B)	2.39	0.25	5	0.0002	8.8	1
Perindopril erbumine	368	96	2	7	-1.0	3.2 (A)	0.07	4	500	3.2×10^{-5}	0.8	1
Pilsicainide hydrochloride hydrate	272	32	1	3	1.0	10.4 (B)	-0.12	50	100	0.002	4.4	1
Pioglitazone hydrochloride	356	94	1	5	-0.9	6.3 (A)	2.16	30	0.01	12	6.7	2
Pitavastatin calcium	421	91	3	5	-1.0	4.2 (A)	1.17	4	0.1	0.16	9.3	1
Polaprezinc	ND	ND	ND	ND	–	ND	ND	75	0.01	30	2.2	UC
Pramipexole hydrochloride hydrate	211	79	3	3	1.0	9.5(B)	-1.03	0.5	1000	2.0×10^{-6}	8.4	3
Pranlukast hydrate	482	119	2	9	-1.0	5.3 (A)	2.74	112.5	0.0012	375	1.2	2
Pravastatin sodium hydrate	425	124	4	7	-1.0	4.3 (A)	0.06	10	100	0.0004	2.7	1
Procaterol hydrochloride	290	82	4	5	1.0	9.4 (B)	-1.47	0.05	50	4.0×10^{-6}	3.8	3
Propiverine hydrochloride	367	39	0	4	0.7	7.8 (B)	4.10	20	124	0.000645	10.7	1
Quetiapine fumarate	384	74	1	5	0.2	6.7 (B)	1.92	200	3.38	0.2364	3.5	1
Ramosetron hydrochloride	279	51	1	4	0.4	7.3 (B)	1.80	0.005	575	3.48×10^{-8}	7	1
Ranitidine hydrochloride	314	112	2	7	0.9	8.4 (B)	-1.47	150	1429	0.00042	2.7	3
Rebamipide	371	96	3	6	-1.0	3.4 (A)	-0.75	100	0.006	66.7	1.9	2
Risedronate sodium hydrate	283	168	5	8	-3.0	1.4 (A), 2.4 (A), 6.0 (A)	-8.38	75	33	0.00909	1.5	3
Risperidone	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 [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	Do	$t_{1/2}$ (h) [c]	BCS class
Rizatriptan benzoate	269	50	1	5	1.0	9.5 (B)	-0.70	10	34	0.00118	1.7	1
Sarpogrelate hydrochloride	430	85	1	7	-0.2	4.3 (A), 8.1 (B)	1.37	100	1	0.4	0.8	1
Selegiline hydrochloride	187	3	0	1	0.6	7.5 (B)	1.81	2.5	1667	6.0×10^{-6}	5.3	1
Sertraline hydrochloride	306	12	1	1	1.0	9.5 (B)	2.45	100	2.70	0.148	25.1	1
Sildenafil citrate	475	118	1	10	0.0	–	1.85	50	1	0.2	1.6	1
Simvastatin	419	73	1	5	0.0	–	4.60	20	0.01	8	2.3	2
Solifenacin succinate	362	171	5	12	1.0	9.0 (B)	1.36	5	610	3.28×10^{-5}	46.5	1
Sultamicillin tosilate	595	216	3	13	0.2	6.8 (B)	-0.46	375	0.1	15	1.0	2
Tacrolimus hydrate	804	178	3	13	0.0	–	4.10	5	0.01	2	32.0	2
Taltirelin hydrate	405	171	5	12	0.2	6.7 (B)	-2.73	5	208	9.6×10^{-5}	2	3
Tamoxifen citrate	372	12	0	2	1.0	8.7 (B)	4.68	20	0.09	0.889	27.2	1
Tamsulosin hydrochloride	409	108	3	7	1.0	8.8 (B)	-0.06	0.2	11.8	6.76×10^{-5}	11.7	1
Tegafur	200	59	1	5	-0.4	7.6 (A)	-0.43	25	16.8	0.00595	1.9	1
Temocapril hydrochloride	477	149	2	7	-1.0	3.7 (A)	0.62	4	0.719	0.0223	0.2	1
Teprenone	331	17	0	1	0.0	–	7.40	50	8.32	0.0240	1.8	1
Terbinafine hydrochloride	291	3	0	1	0.2	6.9 (B)	5.45	125	5.07	0.0987	6.2	1
Ticlopidine hydrochloride	264	31	0	1	0.3	7.1 (B)	3.41	100	58.8	0.0068	1.6	1
Tocopherol nicotinate	536	48	0	4	0.0	–	11.14	200	0.01	80	4.3	2
Tramadol hydrochloride	263	33	1	3	1.0	9.6 (B)	-0.18	50	100	0.002	5.7	1
Tulobuterol hydrochloride	228	32	2	2	1.0	9.6 (B)	-0.17	1	714	5.6×10^{-6}	3.2	1
Ursodeoxycholic acid	393	78	3	4	-1.0	4.8 (A)	2.01	100	0.01	40	1.1	2
Valacyclovir hydrochloride	324	147	5	10	0.7	7.8 (B)	-1.78	500	100	0.02	3.0	3
Valproate sodium	144	37	1	2	-1.0	4.8 (A)	0.97	200	1000	0.0008	9.5	1
Valsartan	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 [b]	HBD [b]	HBA [b]	NC [a] pH 7.4	pK_a [b]	Log $D_{6.5}$ [b]	Highest dose strength (mg) [c]	Solubility in water (mg/mL) [c]	Do	$t_{1/2}$ (h) [c]	BCS class
Voglibose	267	154	8	8	0.2	6.8 (B)	-3.57	0.3	1000	1.2×10^{-6}	5.3	3
Zolmitriptan	287	57	2	5	1.0	9.5 (B)	-0.29	2.5	0.1	0.1	2.9	1
Zolpidem tartrate	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.
[a] Net charge at pH 7.4 calculated by Eq. 1.
[b] Calculated value (ACD/Labs Software V 14.0.0).
[c] Data from prescription information (Supplement Tables 1 and 2) otherwise noted.
[d] Underscored drugs correspond to ODTs.
[e] Drugs in italics correspond to IR formulations.
[f] 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 [a] 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.	3.48×10^{-8} – 66.7	5.4×10^{-8} – 375
Elimination $t_{1/2}$ (h)	n	57	113
	Median	6.7	3.3
	Min. – Max.	0.9 – 128	0.2 – 70.7

[a] Net charge at pH 7.4 calculated by Eq. 1.

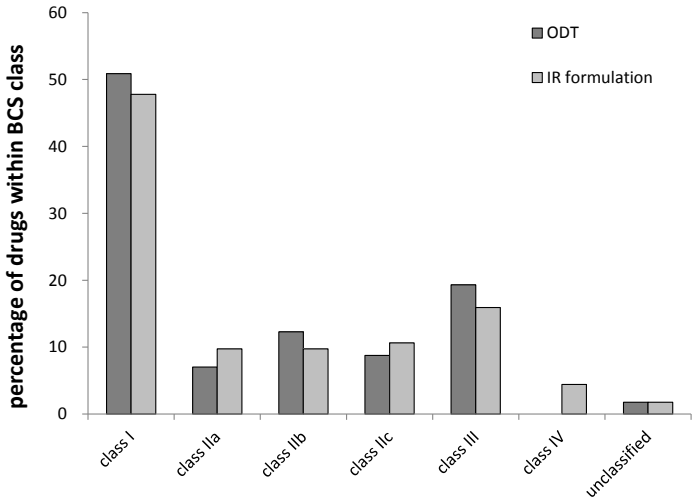

Figure 2. Provisional BCS classification of drugs in ODTs and IR formulations.

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 an ODT.

There was no significant difference in the solubility in water and Do between the ODT and IR formulation. This result suggests that many drugs can be developed as an ODT regardless of their solubility and Do (e.g., bicalutamide: S = 0.01 mg/mL, Do = 32, cilostazole: *S* = 0.01 mg/mL, Do = 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 μg/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 Cmax 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).

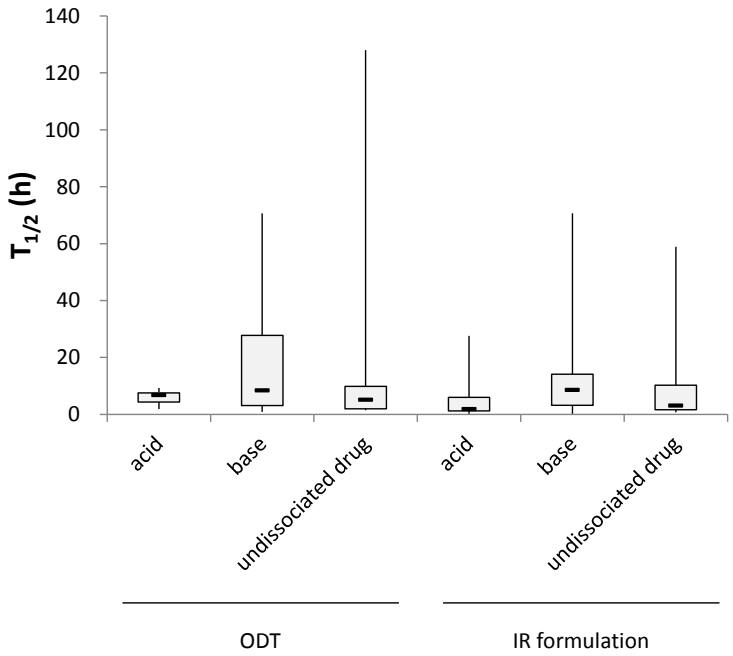

Figure 3. Box and whisker plot of elimination $t_{1/2}$ of acid, base, and undissociated drugs

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 Cmax 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 bioinequivalent 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

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

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

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

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

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

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

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

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

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

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

Supplement Table 4 Solubility Definitions

Solubility definition	**Parts of solvent required for 1 part of solute**	**Solubility range (mg/mL)**	**Solubility assigned (mg/mL)**
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