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Review

A review of drug solubility in human intestinal fluids: Implications for the prediction of oral absorption

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ABSTRACT

The purpose of this paper is to collate all recently published solubility data of orally administered drugs in human intestinal fluids (HIF) that were aspirated from the upper small intestine (duodenum and jejunum). The data set comprises in total 102 solubility values in fasted state HIF and 37 solubility values in fed state HIF, covering 59 different drugs. Despite differences in the protocol for HIF sampling and subsequent handling, this summary of HIF solubilities provides a critical reference data set to judge the value of simulated media for intestinal solubility estimation. In this regard, the review includes correlations between the reported solubilizing capacity of HIF and fasted or fed state simulated intestinal fluid (FaSSIF/FeSSIF). Correlating with HIF solubilities enables the optimal use of solubility measurements in simulated biorelevant media to obtain accurate estimates of intestinal solubility during drug development. Considering the fraction of poorly soluble new molecular entities in contemporary drug discovery, adequate prediction of intestinal solubility is critical for efficient lead optimization, early candidate profiling, and further development.

1. Introduction

Intestinal drug absorption is a key process for determining oral bioavailability and systemic drug exposure. In conjunction with the permeability of the intestinal mucosa, the drug concentration in the intestinal fluids determines the rate (and extent) of oral drug absorption. For poorly soluble drugs, intraluminal concentrations and, hence, intestinal absorption may be limited by the drug solubility in the gastrointestinal (GI) environment (Dressman et al., 2007). Even when absorption is not solubility-limited, the intestinal solubility remains an important parameter, which affects the rate of dissolution and, in case of supersaturation, precipitation.

Since the 1990s, the average lipophilicity of new molecular entities (NMEs) has continuously increased, as a result of the lipophilic nature of new targets and the rise of modern drug discovery strategies based on combinatorial chemistry and high throughput screening (Gribbon and Sewing, 2005; Lipinski, 2000; Walters et al., 2011; Wenlock et al., 2003). As a consequence of this evolution, some authors estimate that up to 90% of current NMEs suffer from low solubility according to the Biopharmaceutics Classification System (Benet et al., 2011). Since limited solubility may compromise absorption and thus drug-likeliness, it is important to identify potential solubility issues in the lead optimization and candidate selection process (Stegemann et al., 2007). In order to measure solubility at these stages, analytical procedures should be throughput efficient and resources for sample preparation and separation should be minimal (Kerns, 2001). As a consequence, high throughput solubility testing using simple aqueous buffer systems is common practice for screening drug candidates (Alsenz and Kansy, 2007). However, it should be emphasized that aqueous solubility, as determined in the screening process, is not necessarily an adequate measure of intestinal solubility. Indeed, the intestinal solubility not only depends on the intrinsic aqueous solubility of the drug but is affected by multiple intraluminal factors, including pH (possibly affecting the drug's ionization behavior) and the presence of mixed micelles consisting of bile acids, phospholipids and lipid digestion products (Dressman et al., 2007). Since micelles have proven their efficiency in increasing the solubility of lipophilic drugs (Bakatselou et al., 1991; Naylor et al., 1993; Wiedmann and Kamel, 2002), screening solubility in simple aqueous media tends to underpredict the solubilizing capacity of the intestinal environment for many lipophilic drugs and drug candidates (Sunesen et al., 2005).

Thus, to make informed decisions on compound selection based on solubility profiling, it is necessary to choose an appropriate solvent system, i.e. one that reflects the solubilizing capacity of human intestinal fluid (HIF). Although the aspiration and use of HIF itself is obviously not suited for routine solubility assessment,

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reference data in HIF is necessary to judge the value of simulating intestinal media (Dressman et al., 2007). Therefore, the present review summarizes the available solubility data in HIF that can be used as reference to rationalize media selection for solubility profiling.

2. Methodological aspects of solubility assessment in HIF

Tables 1 and 2 list the solubility values of different drugs in fasted and fed state HIF (FaHIF and FeHIF), respectively, as reported by several research groups. Since a standardized protocol is lacking (Dressman et al., 2007), substantial differences exist in the collection and handling procedures of HIF (see Table 1). In all studies, HIF was aspirated from healthy volunteers. Using the Loc-I-Gut catheter with two inflatable balloons, HIF is collected from an open, half-open or closed segment of the jejunum. Alternatively, standard double-lumen naso- or oroduodenal sampling tubes have been used to collect HIF from the duodenum in an open segment setup. Positioning of the catheters is checked by means of fluoroscopy. To correspond with typical pharmacokinetic studies, 200–250 ml of water is usually administered prior to sampling. Fed state conditions are simulated with a liquid meal (nutritional drink or homogenized meal, see Table 2). Obviously, the composition of the drink/meal may affect the solubilizing capacity of the aspirated HIF. Instead of standard oral or gastric administration, water or a nutritional drink may also be perfused (2 ml/min) into the jejunum during aspiration of HIF using the Loc-I-Gut catheter. Immediately upon collection of HIF samples on ice, the pH is measured. In the further handling of HIF aspirates, care should be taken to limit exposure to atmospheric CO_2, since this may affect the pH of the poorly buffered aspirates (Kalantzi et al., 2006; Perez de la Cruz Moreno et al., 2006). To maintain the original composition of the HIF aspirates, digestion (especially in fed state conditions) is discontinued by addition of enzyme inhibitors (e.g. the lipase inhibitor Orlistat or a cocktail of lipase and protease inhibitors (Vertzoni et al., 2012)). Until solubility assessment, HIF samples are deep-frozen (−20 °C or lower).

In a typical aspiration procedure, HIF samples are collected for a few hours after intake of water and/or a liquid meal. Depending on the aim of the study, drug solubility has been measured in individual and time-dependent HIF aspirates, in 'volunteer pools' (i.e. combining different time fractions from a single volunteer), or in 'population pools' (i.e. combining aspirates from different volunteers). For the actual solubility assessment, a variant of the 'shake-flask' method has always been applied, attempting to determine the equilibrium solubility. Minor differences in the methodology of solubility determination are reported in Table 3.

3. Reported drug solubility in HIF

Based on literature information, solubility values of 59 different drugs in FaHIF and 28 different drugs in FeHIF are summarized in Tables 1 and 2, respectively. The reported values represent either the solubility measured in a population pool or the mean solubility measured from different volunteers. For some drugs, the solubility has been assessed by multiple research groups.

3.1. Intersubject variability in solubility

When solubilities were measured in different volunteers (Annaert et al., 2010; Clarysse et al., 2009, 2011; Pedersen et al., 2000a, 2000b), the standard deviation reported in Tables 1 and 2 reflects the interindividual variability. The median interindividual coefficients of variation amount to 30% in the fasted state (from 3% (hydrochlorothiazide) to 132% (fenofibrate), excluding the extreme cinnarizine) and to 34% in the fed state (from 3% (hydrochlorothiazide) to 94% (glipizide)). Based on these limited data sets, no clear correlations can be observed between the extent of variability and the absolute solubility or the nature of the compound (size, pK_a and/or $\log D$).

3.2. Correlations between composition and solubilizing capacity of HIF

Since most studies report solubilities in a single pool of HIF, attempts to correlate the solubilizing capacity of HIF with its composition, have been sparse. For some ionizable compounds, a relation between the pH of HIF and its solubilizing capacity can be put forward, as illustrated in Fig. 1 for the weak acid indomethacin. A correlation ($R^2 = 0.86$) was established between the solubility of indomethacin and the pH in fasted, fed and fat-enriched state HIFs (Clarysse et al., 2009).

Attempts to correlate the solubility of lipophilic compounds with the presence of bile acids and phospholipids in HIF have been less successful. Fig. 2 depicts the solubility of a neutral compound, danazol, in fasted, fed and fat-enriched state HIFs in function of the total concentration of phospholipids (Fig. 2a) and bile salts (Fig. 2b). No significant correlation was observed for any of these parameters. Psachoulias and colleagues observed a weak, linear correlation between the total bile salt concentration of time-dependent individual intestinal aspirates and the solubilility of both ketoconazole ($R^2 = 0.78$) and dipyridamole ($R^2 = 0.74$) (Psachoulias et al., 2011).

3.3. Food effect on drug solubility

As expected, postprandial conditions tend to increase the solubilizing capacity of HIF: of the 28 compounds listed in Table 2, only 4 compounds (glibenclamide, glipizide, indomethacin, and sulfasalazine) have lower solubilities in fed versus fasted state conditions. Since these four compounds are classified as weak acids, the observed negative food effect on solubility is presumably caused by the decreased pH of FeHIF (ranging between 5.5 and 6.6, Table 1) as compared to FaHIF (ranging from 6.3 to 7.5, Table 1).

3.4. Age and intestinal solubility

As far as reported in literature, all solubility values listed in Tables 1 and 2 have been measured in HIF from young to middle-aged, healthy volunteers. Annaert and colleagues did not find any statistical differences in the solubility of 10 model drugs in FaHIF aspirated from young (18–25 years) versus old volunteers (62–72 years) (Annaert et al., 2010).

3.5. Inter-study variability in HIF solubility data

For a number of the drugs listed in Table 1, the solubility has been assessed in multiple independent studies. Although a systematic analysis has not been performed here, it is apparent that for some drugs, the inter-study variability in HIF solubility data is limited (e.g. griseofulvin) whereas for others (e.g. ketoconazole), it is quite high. This may be related to protocol differences in the collection and pooling of HIF. In addition, the small number of HIF aspirates in most studies (small sample size) may compromise the use of mean solubility values as representative of the average solubility for some drugs. Illustrative in this case is the solubility assessment of ketoconazole and dipyridamole in more than 100 separate aspirates (Psachoulias et al., 2011), collected upon administration of drug solutions to different volunteers. Mean equilib-

Table 1
Overview of drug solubilities in fasted state simulated and human intestinal fluid (FaSSIF, FaHIF), as reported in literature.

Drug	MW (g/mol)	pK_a[a]	Class[b]	Log $D_{(pH6.5)}$[a]	Position (sampling segment)	Number of volunteers (Pooled[c])	Age	pH fasted HIF	Solubility in FaHIF (SD)		Solubility FaSSIF (SD)		Reference
									(μM)	(μg/ml)	(μM)	(μg/ml)	
Amiodarone	645	8.4	B	5.68	Jejunum (half open)	NA (Y)	NA	6.5–7.5	582.7 (157.3)	376.0 (101.5)	543.9 (54.4)	351.0 (35.1)	Söderlind et al. (2010)
Amprenavir	506	2.4	B	2.43	Duodenum (open)	1 (N)	20–30	6.3	160.1 (0.5)	81.0 (0.3)	NA (NA)	NA (NA)	Brouwers et al. (2007)
Antipyrine	188	/	N	1.22	Duodenum (open)	5 (Y)	24–39	6.2	34596.7 (NA)	6512.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Aprepitant	534	3.1	B	5.68	Jejunum (half open)	NA (Y)	NA	6.5–7.5	24.3 (5.4)	13.0 (2.9)	43.0 (0.9)	23.0 (0.5)	Söderlind et al. (2010)
Atenolol	266	9.7	B	−2.48	Duodenum (open)	5 (Y)	24–39	6.2	112827.4 (NA)	30050.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011
Atovaquone	367	8.2	A	4.99	Jejunum (half open)	NA (Y)	NA	6.5–7.5	0.9 (0.0)	0.3 (0.0)	5.2 (0.0)	1.9 (0.0)	Söderlind et al. (2010)
AZD0865	366	6.1[d]	B	NA	Jejunum (closed)	15 (Y)	NA	6.9	14.9 (1.3)	5.4 (0.5)	15.7 (2.9)	5.7 (1.1)	Calert et al. (2010)
AZD8055	NA	6.2[d]	B	NA	NA (NA)	NA (NA)	NA	NA	71.0 (NA)	NA (NA)	39.0 (NA)	NA (NA)	Dickinson et al. (2012)
Beclomethasone dipropionate	521	/	N	4.43	Duodenum (open)	5 (Y)	24–39	6.2	1.2 (NA)	0.6 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Carbamazepine	236	/	N	2.77	Duodenum (open)	8 (N)	18–25	5.4–7.1	1422.0 (75.6)	336.0 (17.9)	1080.0 (40.0)	255.2 (9.5)	Annaert et al. (2010)
Carbamazepine	236		N	2.77	Duodenum (open)	6 (N)	20–29	6.5–7.3	1294.0 (288.0)	305.7 (68.0)	1126.0 (133.0)	266.0 (31.4)	Clarysse et al. (2011)
Carbamazepine	236		N	2.77	Duodenum (open)	5 (Y)	24–39	6.2	719.5 (NA)	170.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Carbamazepine	236		N	2.77	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1197.8 (24.0)	283.0 (5.7)	998.9 (5.0)	236.0 (1.2)	Söderlind et al. (2010)
Carvedilol	406	8.8	B	1.22	Jejunum (half open)	NA (Y)	NA	6.5–7.5	88.6 (1.2)	36.0 (0.5)	334.6 (8.7)	136.0 (3.5)	Söderlind et al. (2010)
Cinnarizine	369	8.4	B	3.99	Duodenum (open)	6 (N)	20–29	6.5–7.3	32.0 (304.0)	11.8 (112.0)	47.3 (1.0)	17.4 (0.4)	Clarysse et al. (2011)
Cyclosporine	1202	/	N	3.64	Jejunum (half open)	12 (Y)	24–40	7.5	10.8 (NA)	13.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Cyclosporine	1202		N	3.64	Jejunum (half open)	NA (Y)	NA	6.5–7.5	2.9 (0.3)	3.5 (0.4)	4.7 (0.4)	5.7 (0.5)	Söderlind et al. (2010)
Danazol	337	/	N	3.46	Duodenum (open)	8 (N)	18–25	5.4–7.1	19.7 (4.2)	6.7 (1.4)	17.0 (0.5)	5.7 (0.2)	Annaert et al. (2010)
Danazol	337		N	3.46	Duodenum (open)	6 (N)	20–29	6.5–7.3	26.1 (15.5)	8.8 (5.2)	20.0 (2.3)	6.8 (0.8)	Clarysse et al. (2011)
Danazol	337		N	3.46	Duodenum (open)	5 (N)	21–37	NA	39.1 (41.8)	13.2 (14.1)	16.0 (1.0)	5.4 (0.3)	Clarysse et al. (2009)
Danazol	337		N	3.46	Jejunum (NA)	10 (N)	NA	6.7	6.1 (4.3)	2.0 (1.5)	NA (NA)	NA (NA)	Pedersen et al. (2000)
Danazol	337		N	3.46	Jejunum (half open)	12 (Y)	24–40	7.5	26.7 (NA)	9.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Danazol	337		N	3.46	Jejunum (half open)	NA (Y)	NA	6.5–7.5	14.5 (3.2)	4.9 (1.1)	25.8 (2.8)	8.7 (1.0)	Söderlind et al. (2010)
Darunavir	548	2.4	B	2.82	Duodenum (open)	1 (N)	NA	5.7	392.0 (16.0)	214.7 (8.8)	397.0 (15.0)	217.4 (8.2)	Holmstock et al. (2010)
Diazepam	285	3	B	3.08	Duodenum (open)	8 (N)	18–25	5.4–7.1	473.0 (67.6)	134.7 (19.2)	369.0 (2.0)	105.1 (0.6)	Annaert et al. (2010)
Diazepam	285		B	3.08	Duodenum (open)	6 (N)	20–29	6.5–7.3	520.0 (162.0)	148.1 (46.1)	195.0 (21.0)	55.5 (6.0)	Clarysse et al. (2011)

Diazepam	285		B	3.08	Duodenum (open)	5 (N)	21–37	NA	834.4 (647.0)	237.8 (184.4)	355.0 (4.0)	101.1 (1.1)	Clarysse et al. (2009)
Diazepam	285		B	3.08	NA (NA)	NA (NA)	NA	NA	105.4 (NA)	30.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Diclofenac	296	4	A	1.79	Jejunum (half open)	NA (Y)	NA	6.5–7.5	3012.0 (39.2)	892.0 (11.6)	2573.0 (41.2)	762.0 (12.2)	Söderlind et al. (2010)
Diclofenac	296		A	1.79	Duodenum (open)	5 (Y)	24–39	6.2	37751.3 (NA)	11180.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Diethylstilbestrol	268	9.2	A	5.19	Jejunum (half open)	NA (Y)	NA	6.5–7.5	141.6 (43.9)	38.0 (11.8)	149.1 (4.9)	40.0 (1.3)	Söderlind et al. (2010)
Dipyridamole	505	6.6	B	1.8	Duodenum (NA)	12 (Y)	NA	6.7	44.6 (4.0)	22.5 (2.0)	19.8 (1.0)	10.0 (0.5)	Kalantzi et al. (2006)
Dipyridamole	505		B	1.8	Jejunum (half open)	NA (Y)	NA	6.5–7.5	57.5 (0.8)	29.0 (0.4)	37.7 (0.8)	19.0 (0.4)	Söderlind et al. (2010)
Etravirine	435	4	B	5.53	Duodenum (open)	5 (Y)	20–30	6.7	3.4 (0.5)	1.5 (0.2)	2.3 (0.0)	1.0 (0.0)	Bevernage et al. (2010)
Felodipine	384	5.4	B	3.41	Jejunum (half open)	12 (Y)	24–40	7.5	36.4 (NA)	14.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Felodipine	384		B	3.41	Jejunum (half open)	NA (Y)	NA	6.5–7.5	36.4 (0.1)	14.0 (0.0)	137.9 (4.3)	53.0 (1.6)	Söderlind et al. (2010)
Fenofibrate	361		N	5.28	Duodenum (open)	6 (N)	20–29	6.5–7.3	54.6 (71.9)	19.7 (25.9)	26.6 (3.8)	9.6 (1.4)	Clarysse et al. (2011)
Fexofenadine	502	/	Z	0.82	NA (NA)	NA (NA)	NA	NA	996.7 (NA)	500.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Flufenamic acid	281	3.8	A	2.68	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1521.9 (3.0)	428.0 (0.9)	3310.5 (288.0)	931.0 (81.0)	Söderlind et al. (2010)
Furosemide	331	4.2	A	−0.48	Duodenum (open)	6 (N)	20–29	6.5–7.3	5862.0 (1712.0)	1938.8 (566.2)	8054.0 (102.0)	2663.8 (33.7)	Clarysse et al. (2011)
Furosemide	331		A	−0.48	Duodenum (open)	5 (Y)	24–39	6.2	11616.2 (NA)	3842.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Gefitinib	447	6.8	B	3.24	NA	NA (Y)	NA	7	190.2 (NA)	85.0 (NA)	NA (NA)	NA (NA)	Bergman et al. (2007)
Glibenclamide	494	4.3	A	2.87	Duodenum (open)	8 (N)	18–25	5.4–7.1	31.2 (7.6)	15.4 (3.8)	6.5 (0.2)	3.2 (0.1)	Annaert et al. (2010)
Glibenclamide	494		A	2.87	Duodenum (open)	6 (N)	20–29	6.5–7.3	18.7 (22.2)	9.2 (11.0)	6.9 (0.9)	3.4 (0.5)	Clarysse et al. (2011)
Glipizide	446	4.3	A	0.51	Duodenum (open)	8 (N)	18–25	5.4–7.1	648.5 (136.4)	288.9 (60.8)	70.9 (4.3)	31.6 (1.9)	Annaert et al. (2010)
Glipizide	446		A	0.51	Duodenum (open)	6 (N)	20–29	6.5–7.3	415.0 (454.0)	184.9 (202.3)	69.7 (7.5)	31.1 (3.3)	Clarysse et al. (2011)
Glipizide	446		A	0.51	Jejunum (half open)	NA (Y)	NA	6.5–7.5	94.3 (2.1)	42.0 (0.9)	130.2 (7.4)	58.0 (3.3)	Söderlind et al. (2010)
Griseofulvin	353	/	N	2.17	Duodenum (open)	8 (N)	18–25	5.4–7.1	69.7 (7.1)	24.6 (2.5)	87.7 (1.4)	30.9 (0.5)	Annaert et al. (2010)
Griseofulvin	353		N	2.17	Jejunum (half open)	12 (Y)	24–40	7.5	62.3 (NA)	22.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Griseofulvin	353		N	2.17	Jejunum (half open)	NA (Y)	NA	6.5–7.5	48.2 (3.8)	17.0 (1.3)	56.7 (2.5)	20.0 (0.9)	Söderlind et al. (2010)
Hydrochlorothiazide	298	9.4	A	−0.58	Duodenum (open)	6 (N)	20–29	6.5–7.3	3560.0 (101.0)	1060.0 (30.1)	2986.0 (49.0)	889.0 (14.6)	Clarysse et al. (2011)
Hydrochlorothiazide	298		A	−0.58	Duodenum (open)	5 (Y)	24–39	6.2	2485.4 (NA)	740.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Hydrocortisone	362	/	N	1.28	Jejunum (NA)	9 (N)	NA	6.1	1379.5 (82.8)	500.0 (30.0)	NA (NA)	NA (NA)	Pedersen et al. (2000)
Ibuprofen	206	4.8	A	2.19	Duodenum (open)	5 (Y)	24–39	6.2	9647.0 (NA)	1990.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Indinavir	613	7.2	B	1.89	Duodenum (open)	4 (Y)	19–35	7.5	84 (3)	51.5 (1.8)	79 (1)	48.4 (0.6)	Holmstock et al. (2013)
Indomethacin	358	3.8	A	0.89	Duodenum (open)	8 (N)	18–25	5.4–7.1	2151.0	769.6	1060.0	379.3	Annaert et al. (2010)

(*continued on next page*)

Table 1 (*continued*)

Drug	MW (g/mol)	pK_a[a]	Class[b]	Log $D_{(pH6.5)}$[a]	Position (sampling segment)	Number of volunteers (Pooled[c])	Age	pH fasted HIF	Solubility in FaHIF (SD)		Solubility FaSSIF (SD)		Reference
									(μM)	(μg/ml)	(μM)	(μg/ml)	
									(422.1)	(151.0)	(16.0)	(5.7)	
Indomethacin	358		A	0.89	Duodenum (open)	6 (N)	20–29	6.5–7.3	2301.0 (1094.0)	823.3 (391.4)	1218.0 (94.0)	435.8 (33.6)	Clarysse et al. (2011)
Indomethacin	358		A	0.89	Duodenum (open)	5 (N)	21–37	NA	2368.0 (1877.0)	847.7 (672.0)	1376.0 (8.0)	492.3 (2.9)	Clarysse et al. (2009)
Indomethacin	358		A	0.89	NA (NA)	NA (NA)	NA	NA	1677.0 (NA)	600.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Indomethacin	358		A	0.89	Duodenum (open)	5 (Y)	24–39	6.2	6657.6 (NA)	2382.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Irbesartan	429	4.2/7.4	A/B	5.48	Jejunum (half open)	NA (Y)	NA	6.5–7.5	287.0 (8.6)	123.0 (3.7)	261.4 (7.8)	112.0 (3.4)	Söderlind et al. (2010)
Irbesartan	429		A/B	5.48	NA (NA)	NA (NA)	NA	NA	466.7 (NA)	200.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Itraconazole	706	3.9	B	7.31	Duodenum (open)	5 (Y)	20–30	6.7	8.8 (1.3)	6.2 (0.9)	0.5 (0.0)	0.3 (0.0)	Bevernage et al. (2010)
Ketoconazole	531	6.8	B	3.91	Duodenum (open)	8 (N)	18–25	5.4–7.1	209.4 (92.2)	111.3 (49.0)	71.5 (0.8)	38.0 (0.4)	Annaert et al. (2010)
Ketoconazole	531		B	3.91	Duodenum (open)	6 (N)	20–29	6.5–7.3	193.0 (144.0)	102.6 (76.5)	49.2 (1.9)	26.1 (1.0)	Clarysse et al. (2011)
Ketoconazole	531		B	3.91	Duodenum (open)	5 (N)	21–37	NA	614.7 (689.2)	326.4 (366.0)	73.0 (5.0)	38.8 (2.7)	Clarysse et al. (2009)
Ketoconazole	531		B	3.91	Duodenum (NA)	12 (Y)	NA	6.7	54.2 (5.7)	28.8 (3.0)	15.1 (0.2)	8.0 (0.1)	Kalantzi et al. (2006)
Ketoconazole	531		B	3.91	Jejunum (half open)	NA (Y)	NA	6.5–7.5	105.4 (8.0)	56.0 (4.3)	48.9 (9.8)	26.0 (5.2)	Söderlind et al. (2010)
Ketoprofen	254	3.8	A	1.05	Duodenum (open)	5 (Y)	24–39	6.2	12592.4 (NA)	3202.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Loviride	351	/	Z	4.18	Duodenum (open)	8 (N)	18–25	5.4–7.1	18.1 (2.7)	6.4 (1.0)	11.5 (0.8)	4.0 (0.3)	Annaert et al. (2010)
Loviride	351		Z	4.18	Duodenum (open)	5 (Y)	20–30	6.7	15.4 (2.1)	5.4 (0.7)	8.5 (0.2)	3.0 (0.1)	Bevernage et al. (2010)
Loviride	351		Z	4.18	Duodenum (open)	6 (N)	20–29	6.5–7.3	13.4 (4.4)	4.7 (1.6)	11.9 (2.1)	4.2 (0.7)	Clarysse et al. (2011)
Mesalazine	153	/	Z	−1.18	Jejunum (half open)	15 (Y)	NA	6.3	10448.3 (NA)	1600.0 (NA)	NA (NA)	NA (NA)	Fadda et al. (2010)
Metoprolol	267	9.6	B	−1.14	Duodenum (open)	5 (Y)	24–39	6.2	1121187.3 (NA)	299765.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Naproxen	230	4.2	A	0.7	Duodenum (open)	5 (Y)	24–39	6.2	7148.5 (NA)	1646.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Nifedipine	346	5.4	B	1.79	Duodenum (open)	8 (N)	18–25	5.4–7.1	116.8 (21.6)	40.5 (7.5)	80.3 (1.8)	27.8 (0.6)	Annaert et al. (2010)
Nifedipine	346		B	1.79	Duodenum (open)	6 (N)	20–29	6.5–7.3	66.7 (18.2)	23.1 (6.3)	41.6 (0.8)	14.4 (0.3)	Clarysse et al. (2011)
Nifedipine	346		B	1.79	Duodenum (open)	5 (N)	21–37	NA	111.7 (69.4)	38.6 (24.0)	68.0 (2.0)	23.6 (0.7)	Clarysse et al. (2009)
Nifedipine	346		B	1.79	NA (NA)	NA (NA)	NA	NA	28.9 (NA)	10.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Nimesulide	308	6.8	A	1.65	Jejunum (half open)	NA (Y)	NA	6.5–7.5	275.7 (74.4)	85.0 (23.0)	116.8 (12.8)	36.0 (4.0)	Söderlind et al. (2010)
Nitrendipine	360	5.4	B	2.14	NA (NA)	NA (NA)	NA	NA	11.1 (NA)	4.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Piroxicam	331	6.4	A	−0.87	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1198.1 (12.0)	397.0 (4.0)	1204.2 (24.1)	399.0 (8.0)	Söderlind et al. (2010)

Piroxicam	331		A	−0.87	NA (NA)	NA (NA)	NA	NA	2453.6 (NA)	813.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Posaconazole	701	4	B	5.41	Duodenum (open)	5 (Y)	20–32	6.7	5.1 (0.2)	3.6 (0.1)	6.8 (1.2)	4.8 (0.8)	Brouwers et al. (2011)
Prazosin	383	7.2	B	0.87	NA (NA)	NA (NA)	NA	NA	260.8 (NA)	100.0 (NA)	NA (NA)	NA (NA)	McGinnity et al. (2007)
Prednisolone	360	/	N	1.27	Jejunum (half open)	15 (Y)	NA	6.3	1636.9 (NA)	590.0 (NA)	NA (NA)	NA (NA)	Fadda et al. (2010)
Prednisolone	360		N	1.27	Duodenum (open)	6 (N)	20–29	6.5–7.3	1337.0 (129.0)	481.9 (46.5)	1086.0 (78.9)	391.4 (28.4)	Clarysse et al. (2011)
Probenecid	285	3.6	A	−0.42	Jejunum (half open)	NA (Y)	NA	6.5–7.5	2586.2 (124.1)	738.0 (35.4)	5719.1 (537.6)	1632.0 (153.4)	Söderlind et al. (2010)
Probucol	516	/	N	10.57	Jejunum (half open)	12 (Y)	24–40	7.5	1.9 (NA)	1.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Probucol	516		N	10.57	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1.8 (0.9)	0.9 (0.5)	6.6 (0.5)	3.4 (0.3)	Söderlind et al. (2010)
Propranolol (HCl)	259	9.6	B	−0.32	Duodenum (open)	5 (Y)	24–39	6.24	419251.1 (NA)	108730.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Quinidine	324	9	B	0.01	Duodenum (open)	6 (N)	20–29	6.5–7.3	1977.0 (447.0)	641.4 (145.0)	6972.0 (293.0)	2261.8 (95.1)	Clarysse et al. (2011)
Rifampicin	823	/	Z	2.56	Duodenum (open)	5 (Y)	24–39	6.2	7218.0 (NA)	5940.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Rimonabant	464	1.6	A	5.91	Jejunum (half open)	NA (Y)	NA	6.5–7.5	11.6 (0.6)	5.4 (0.3)	23.7 (1.4)	11.0 (0.6)	Söderlind et al. (2010)
Ritonavir	721	2.6	B	5.22	Duodenum (open)	6 (N)	20–29	6.5–7.3	48.0 (60.8)	34.6 (43.8)	9.1 (0.7)	6.6 (0.5)	Clarysse et al. (2011)
Spironolactone	417	/	N	3.64	Jejunum (half open)	NA (N)	NA	NA	79.2 (NA)	33.0 (NA)	NA (NA)	NA (NA)	Bonlokke et al. (2001)
Spironolactone	417		N	3.64	Duodenum (open)	5 (Y)	24–39	6.2	480.1 (NA)	200.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Sulfasalazine	398	/	A	1	Duodenum (open)	6 (N)	20–29	6.5–7.3	5041.0 (1430.0)	2008.3 (569.7)	3483.0 (221.0)	1387.6 (88.0)	Clarysse et al. (2011)
Sulfasalazine	398		A	1	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1365.5 (491.6)	544.0 (195.8)	1910.2 (439.3)	761.0 (175.0)	Söderlind et al. (2010)
Trimethoprim	290	7.2	B	0.6	Duodenum (open)	5 (Y)	24–39	6.2	2824.5 (NA)	820.0 (NA)	NA (NA)	NA (NA)	Heikkilä et al. (2011)
Ubiquinone	863	/	N	17.16	Jejunum (half open)	12 (Y)	24–40	7.5	1.2 (NA)	1.0 (NA)	NA (NA)	NA (NA)	Persson et al. (2005)
Warfarin	308	6.4	A	2.35	Jejunum (half open)	NA (Y)	NA	6.5–7.5	1015.2 (32.5)	313.0 (10.0)	1436.8 (21.6)	443.0 (6.6)	Söderlind et al. (2010)

Abbreviations: MW – molecular weight; NA – not available; FaSSIF – fasted state simulated fluid; FaHIF – fasted state human intestinal fluid.

[a] pK_a and Log$D_{(pH6.5)}$ were predicted using Marvin Sketch.

[b] Drug ionization behavior: acid (A), base (B), neutral (N), zwitterion (Z).

[c] Pooled: yes (Y) or no (N).

[d] pK_a of AZD0865 and AZD8055 were adopted from literature.

Table 2
Overview of drug solubilities in fed state simulated and human intestinal fluid, as reported in literature.

Drug	Log$D_{(pH5)}$[a]	Type of meal[b]	pH fed HIF	Solubility in fed HIF (SD)		FeHIF/FaHIF	Solubility FeSSIF (SD)		FeSSIF/FaSSIF	Reference
				(μM)	(μg/ml)		(μM)	(μg/ml)		
Carbamazepine	2.77	Ensure Plus®	5.9–6.6	1981.0 (314.0)	468.0 (74.2)	1.5	2218.0 (106.0)	524.0 (25.0)	2.0	Clarysse et al. (2011)
Cinnarizine	2.73	Ensure Plus®	5.9–6.6	478.0 (266.0)	176.1 (98.0)	14.9	878.0 (18.0)	323.6 (6.6)	18.6	Clarysse et al. (2011)
Cyclosporine	3.64	Nutriflex®	6.1	199.7 (NA)	240.0 (NA)	18.5	NA (NA)	NA (NA)	NA	Persson et al. (2005)
Danazol	3.46	Ensure Plus®	5.9–6.6	121.0 (41.0)	40.8 (13.8)	4.6	67.8 (2.4)	22.9 (0.8)	3.4	Clarysse et al. (2011)
Danazol	3.46	Ensure Plus®	NA	86.1 (45.7)	29.0 (15.4)	2.2	52.0 (1.0)	17.5 (0.3)	3.3	Clarysse et al. (2009)
Danazol	3.46	Nutriflex®	6.1	281.9 (NA)	95.0 (NA)	10.6	NA (NA)	NA (NA)	NA	Persson et al. (2005)
Danazol[c]	3.46	Homogenized meal	NA	118.4 (127.0)	39.9 (42.8)	NA	83.1 (NA)	28 (NA)	NA	Vertzoni et al. (2012)
Darunavir	2.82	Ensure Plus®	5.5	494.0 (41.0)	270.5 (22.5)	1.3	321.0 (18.0)	175.8 (9.9)	0.8	Holmstock et al. (2010)
Diazepam	3.07	Ensure Plus®	5.9–6.6	1687.0 (432.0)	480.4 (123.0)	3.2	727.0 (35.0)	207.0 (10.0)	3.7	Clarysse et al. (2011)
Diazepam	3.07	Ensure Plus®	NA	1796.0 (1534.0)	511.9 (437.2)	2.2	909.0 (4.0)	258.8 (1.1)	2.6	Clarysse et al. (2009)
Dipyridamole	1.6	Ensure Plus®	6.5	329.6 (NA)	166.3 (NA)	7.4	485.5 (1.0)	245.0 (0.5)	24.5	Kalantzi et al. (2006)
Etravirine	5.48	Ensure Plus®	6.2	9.4 (0.2)	4.1 (0.1)	2.8	14.3 (0.6)	6.2 (0.2)	6.3	Bevernage et al. (2010)
Felodipine	2.9	Nutriflex®	6.1	1080.0 (NA)	415.0 (NA)	29.6	NA (NA)	NA (NA)	NA	Persson et al. (2005)
Fenofibrate	5.28	Ensure Plus®	5.9–6.6	409.0 (165.0)	147.6 (59.5)	7.5	112.0 (8.0)	40.4 (2.9)	4.2	Clarysse et al. (2011)
Furosemide	0.93	Ensure Plus®	5.9–6.6	6384.0 (2967.0)	2111.5 (981.3)	1.1	1582.0 (26.0)	523.2 (8.6)	0.2	Clarysse et al. (2011)
Glibenclamide	3.22	Ensure Plus®	5.9–6.6	6.6 (3.0)	3.3 (1.5)	0.4	4.4 (0.4)	2.2 (0.2)	0.6	Clarysse et al. (2011)
Glipizide	0.85	Ensure Plus®	5.9–6.6	38.6 (36.2)	17.2 (16.1)	0.1	9.7 (0.6)	4.3 (0.2)	0.1	Clarysse et al. (2011)
Griseofulvin	2.17	Nutriflex®	6.1	170.0 (NA)	60.0 (NA)	2.7	NA (NA)	NA (NA)	NA	Persson et al. (2005)
Hydrochlorothiazide	−0.58	Ensure Plus®	5.9–6.6	4313.0 (139.0)	1284.1 (41.4)	1.2	2982.0 (100.0)	887.9 (29.8)	1.0	Clarysse et al. (2011)
Indinavir	0.46	Ensure Plus®	6	517 (94)	316.9 (57.6)	6.2	2214 (196)	1357.2 (120.1)	28.0	Holmstock et al. (2013)
Indomethacin	2.31	Ensure Plus®	5.9–6.6	1953.0 (1492.0)	698.8 (533.8)	0.8	377.0 (8.0)	134.9 (2.9)	0.3	Clarysse et al. (2011)
Indomethacin	2.31	Ensure Plus®	NA	1815.0 (2170.0)	649.8 (776.9)	0.8	402.0 (8.0)	143.8 (2.9)	0.3	Clarysse et al. (2009)
Itraconazole	7.28	Ensure Plus®	6.2	17.5 (2.7)	12.3 (1.9)	2.0	1.0 (0.0)	0.7 (0.0)	2.2	Bevernage et al. (2010)
Ketoconazole	3.58	Ensure Plus®	5.9–6.6	2047.0 (617.0)	1087.8 (327.9)	10.6	759.0 (31.0)	403.4 (16.5)	15.4	Clarysse et al. (2011)
Ketoconazole	3.58	Ensure Plus®	NA	1463.0 (1239.0)	776.9 (657.9)	2.4	1420.0 (30.0)	754.6 (15.9)	19.5	Clarysse et al. (2009)
Ketoconazole	3.58	Ensure Plus®	6.5	1715.3 (NA)	911.6 (NA)	31.7	940.9 (0.4)	500.0 (0.2)	62.5	Kalantzi et al. (2006)
Loviride	4.17	Ensure Plus®	6.2	44.8	15.7	2.9	26.6	9.4	3.1	Bevernage et al. (2010)

				(6.3)	(2.2)		(0.1)	(0.0)		
Loviride	4.17	Ensure Plus®	5.9–6.6	35.0 (7.1)	12.3 (2.5)	2.6	21.0 (0.6)	7.4 (0.2)	1.8	Clarysse et al. (2011)
Nifedipine	1.32	Ensure Plus®	5.9–6.6	126.0 (24.2)	43.6 (8.4)	1.9	133.0 (3.0)	46.1 (1.0)	3.2	Clarysse et al. (2011)
Nifedipine	1.32	Ensure Plus®	NA	185.6 (133.4)	64.1 (46.2)	1.7	173.0 (7.0)	59.9 (2.4)	2.5	Clarysse et al. (2009)
Posaconazole	5.37	Ensure Plus®	6.2	53.9 (18.8)	37.8 (13.2)	10.5	14.5 (0.5)	10.2 (0.4)	2.1	Brouwers et al. (2011)
Prednisolone	1.27	Ensure Plus®	5.9–6.6	1690.0 (146.0)	609.2 (52.6)	1.3	1409.0 (41.0)	507.9 (14.8)	1.3	Clarysse et al. (2011)
Probucol	10.57	Nutriflex®	6.1	48.4 (NA)	25.0 (NA)	25.0	NA (NA)	NA (NA)	NA	Persson et al. (2005)
Quinidine	−0.92	Ensure Plus®	5.9–6.6	3834.0 (1577.0)	1243.8 (511.6)	1.9	7977.0 (600.0)	2587.9 (194.7)	1.1	Clarysse et al. (2011)
Ritonavir	5.22	Ensure Plus®	5.9–6.6	159.0 (52.0)	114.6 (37.5)	3.3	23.1 (0.6)	16.7 (0.4)	2.5	Clarysse et al. (2011)
Sulfasalazine	2.47	Ensure Plus®	5.9–6.6	3372.0 (2475.0)	1343.4 (986.0)	0.7	606.0 (15.0)	241.4 (6.0)	0.2	Clarysse et al. (2011)
Ubiquinone	17.16	Nutriflex®	6.1	40.6 (NA)	35.0 (NA)	35.0	NA (NA)	NA (NA)	NA	Persson et al. (2005)

Abbreviations: FaHIF – fasted state human intestinal fluid; FaSSIF – fasted state simulated intestinal fluid; FeHIF – fed state human intestinal fluid; FeSSIF – fed state simulated intestinal fluid; NA – not available.

[a] Log$D_{(pH5.0)}$ was predicted using Marvin Sketch.

[b] Ensure Plus®: 2526 kJ (29% lipids, 54% carbohydrates, 17% proteins); Nutriflex®: 577 kJ; homogenized meal: 3138 kJ (73% lipids, 13% carbohydrate, 14% protein).

[c] Danazol: solubility determined in the micellar phase of fed state human intestinal aspirates collected from the duodenum (8 volunteers, 22–34 years old).

Table 3
Methodology of solubility determination.

Reference	FaSSIF[a]	FeSSIF[b]	Separation	Time (h)	Temperature (°C)	Amount of solids/volume
Annaert et al. (2010)	Crude[c]		Centrifugation	24	37	0.5 mg/500 µl
Bergman et al. (2007)	V1[c]		NA[d]	NA	NA	NA
Bevernage et al. (2010)	Crude	Crude	Centrifugation	24	37	2 mg/500 µl
Bevernage et al. (2011)	Crude	Crude	Centrifugation	24	37	2 mg/500 µl
Bønløkke et al. (2001)			Centrifugation	48	37	5 mg/mL
Brouwers et al. (2007)			Centrifugation	24	37	2 mg/2 ml
Brouwers et al. (2011)	Crude	Crude	Centrifugation	24	37	1 mg/0.5 ml
Carlert et al. (2010)	V1		Centrifugation	24	37	NA/5 ml
Clarysse et al. (2009)	Crude	Crude	Centrifugation	24	37	1 mg/300 µl
Clarysse et al. (2011)	Crude	Crude	Centrifugation	24	37	1 mg/300 µl
Dickinson et al. (2012)	V1		NA	NA	NA	NA
Fadda et al. (2010)			Centrifugation	5	37	NA/200 µl
Heikkilä et al. (2011)			Centrifugation	30	23	NA/250 µl
Holmstock et al. (2010)	Crude	Crude	Centrifugation	24	37	2 mg/500 µl
Holmstock et al. (2013)	Crude	Crude	Centrifugation	24	37	1 mg/500 µl
Kalantzi et al. (2006)	Crude	Crude	Centrifugation	5	37	45 mg, 135 mg/25 ml
McGinnity et al. (2007)			NA	NA	NA	NA
Pedersen et al. (2000a, 2000b)			Centrifugation	17	37	3 mg/5 ml
Persson et al. (2005)		V1	Centrifugation	24	37	1 mg/ml
Söderlind et al. (2010)	V1, V2[c]		Centrifugation	24	37	1 mg/ml
Vertzoni et al. (2012)		V2	Centrifugation	4	37	1 mg/ml

[a] FaSSIF: fasted state simulated intestinal fluid.
[b] FeSSIF: fed state simulated intestinal fluid.
[c] FaSSIF and FeSSIF are based on either crude taurocholate from ox bile ('crude') or pure taurocholate (version 1, 'V1' and version 2, 'V2').
[d] NA: not available.

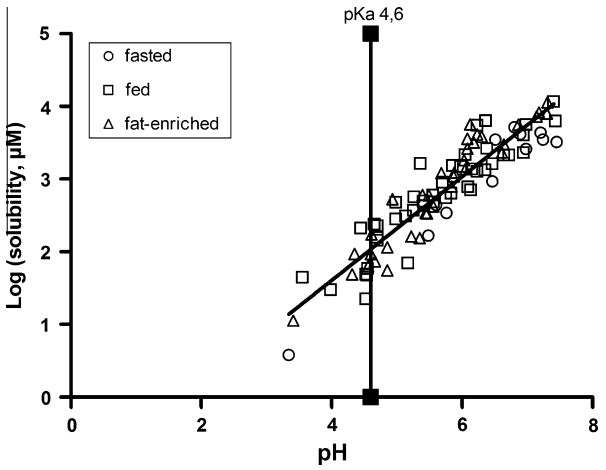

Fig. 1. Correlation between the pH of fasted and fed state HIF and its solubilizing capacity for the weak acid indomethacin. Data from Clarysse et al. (2009).

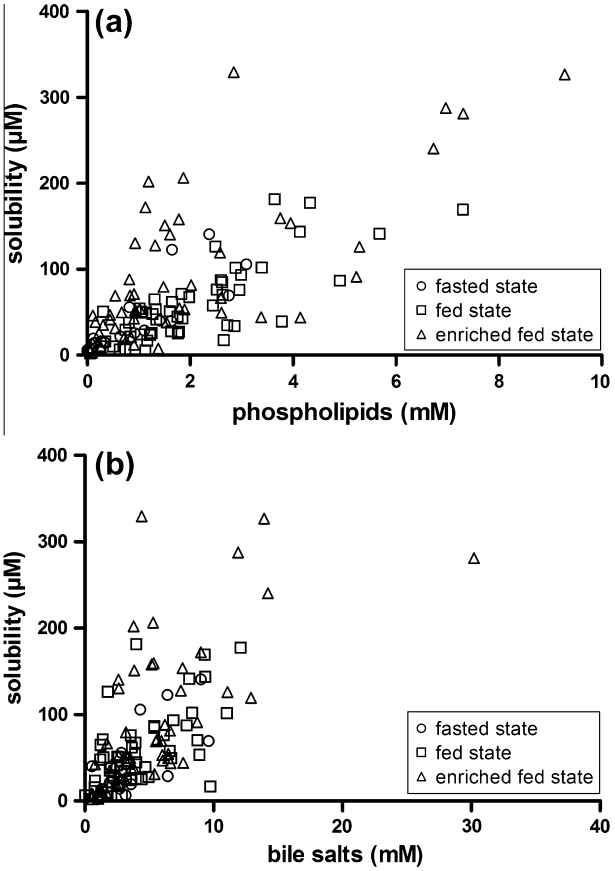

Fig. 2. Correlation between the danazol solubility in HIF and the total concentration of phospholipids (a) and bile acids (b).

um solubility values were 5–12 times higher than median values, indicating a skewed distribution in HIF solubility for these weakly basic drugs.

4. Predictive value of simulated intestinal fluids for solubility assessment

Since HIF is obviously not suited as a solvent system for routine use in drug development, alternatives to aspirated intestinal fluids have been proposed. In the late nineties, two media containing bile salts and lecithin were introduced to simulate fasted and fed state intestinal fluids (FaSSIF and FeSSIF) (Galia et al., 1998). Recently, an instant powder for reconstitution has become available to facilitate the preparation of FaSSIF and FeSSIF, and their use in high-throughput settings (Biorelevant.com, Surrey, UK). Meanwhile, revised versions of FaSSIF (FaSSIFv2) and FeSSIF (FeSSIFv2, early FeSSIF, middle FeSSIF, late FeSSIF) have been introduced to compensate for the absence of lipid degradation products and to concede to different phases of digestion (Jantratid et al., 2008). In addition, different investigators have tried to define even more

precisely optimized media to accurately simulate the human gastrointestinal conditions (Boni et al., 2007; Psachoulias et al., 2012; Rupp et al., 2010; Söderlind et al., 2010).

It is important to note, however, that simulating media for solubility screening purposes in early drug development should reflect the solubilizing capacity of HIF, rather than having an identical composition. This means that functional relevance prevails over compositional biorelevance, implying that media to be used for intestinal solubility estimation require a thorough functional validation. To allow such a validation, the solubility data that have been measured in HIF and are summarized in this review, are of critical importance.

Based on literature data of simultaneously assessed solubilities in human and simulating intestinal fluids (Tables 1 and 2), we have investigated the correlation between the solubilizing capacity of FaSSIF versus FaHIF (Fig. 3) and FeSSIF versus FeHIF (Fig. 4). In the fasted state, a statistically significant ($p < 0.0001$) and relatively strong correlation ($R^2 = 0.85$) can be observed. It appears that the correlation of FaHIF with FaSSIF is better at high (e.g. >100 μM in FaSSIF) solubility and worse at low solubility (e.g. <10 μM in FaSSIF). Considering the compounds' ionization behavior, the best correlation between FaSSIF and FaHIF is clearly obtained for neutral molecules. This demonstrates the complicating influence of the variable intestinal pH on drug solubility and the importance of considering pH-dependency for ionizable compounds.

Also for the fed state, the solubilizing capacities of simulated and real intestinal fluids (FeSSIF versus FeHIF) are correlated ($p < 0.0001$, $R^2 = 0.83$). In contrast to the fasted state, however, a systematic trend towards underprediction can be observed (deviation from the 1:1 prediction). While the use of FeSSIFv2, containing monoglycerides and free fatty acids, may theoretically improve this prediction, insufficient solubility data in FeSSIFv2 are currently available. It should further be noted that fed state simulating media usually aim to represent the micellar phase of intestinal fluids, while solubility data are often measured in total aspirates.

Alternatively, it may be worthwhile to investigate approaches to 'correct' measured solubilities in simulating media using the observed correlation with HIF to obtain improved estimates of intestinal solubility without further complicating the composition of the biorelevant media. Using such a correlation approach, Clarysse and colleagues previously demonstrated that even simple aqueous media containing a single surfactant (e.g. D-α-tocopheryl-polyethylene glycol 1000 succinate) may provide adequate estimates of intestinal drug solubility (Clarysse et al., 2011).

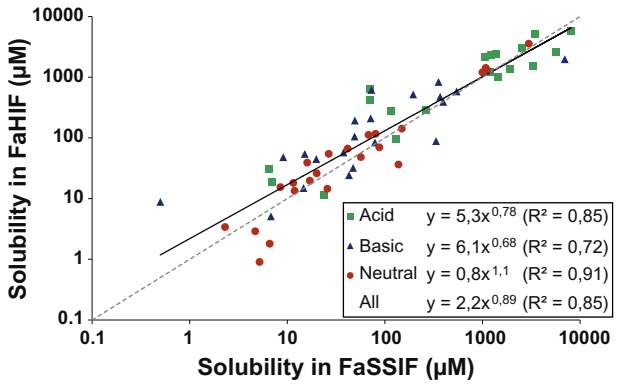

Fig. 3. Overall correlation between solubility in FaHIF and FaSSIF (based on data from Table 1). Regression equations for neutral, acidic, basic and all compounds are reported on the graph. The dotted gray line indicates the $y = x$ relation.

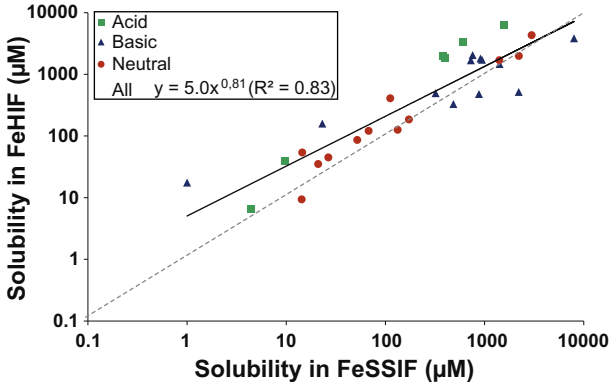

Fig. 4. Overall correlation between solubility in FeHIF and FeSSIF (based on data from Table 2, FeSSIFv1 or based on crude taurocholate). The regression equation including all compounds is reported on the graph. Due to the limited data set, no separate regressions for neutral, acidic and basic compounds are reported. The dotted gray line indicates the $y = x$ relation.

5. Implications for the prediction of intestinal absorption

For the prediction of oral absorption, in particular when the aqueous solubility of drugs and drug candidates is poor, reliable estimation of intestinal solubility is essential. Solubility assessment in HIF could be considered the "gold standard" measure. Unfortunately, HIF is not readily available and its collection and use suffer from practical concerns, including the need for ethical approval and qualified people for aspiration, the use of biological samples in a highly regulated industry setting, and analytical issues. Therefore, the use of simulated media is attractive, especially for the characterization of drug solubility in lead optimization and early development.

Based on the observed correlations between FaHIF/FeHIF and FaSSIF/FeSSIF, we advocate an approach that emphasizes correlating solubility in simulating media with reported HIF solubility as a simple but effective way of getting adequately accurate estimates of intestinal solubility. With this approach, the required complexity of the simulating media will be less than for a medium that needs to mimic as closely as possible the exact composition of HIF.

It is possible to envisage how the concept of using a simple correlation between simulated and real intestinal fluid could be extended as more HIF solubility data is generated and our knowledge of the gastrointestinal environment increases. For instance, it may be possible to use measurements in relatively simple simulated media to predict how the intestinal solubility of a drug varies according to the region of the small intestine, and/or how it varies within the normal range of bile salt and phospholipid concentrations, pH, and buffer capacity in the human small intestine. Correlations of this kind could be incorporated into PBPK (physiologically based pharmacokinetic) modelling approaches as a powerful tool for characterizing the solubility component of oral absorption prediction based on relatively straightforward experimental measurements in simple simulating media.

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