Impact of biorelevant media on apparent solubility and biopharmaceutical classification of poorly soluble compounds

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Aim

The purpose of this project was to measure the apparent solubility of a diverse series of poorly soluble compounds (fig. 1) in four different biorelevant dissolution media (BDM) simulating intestinal conditions to investigate potential consequences for an apparent BCS classification.

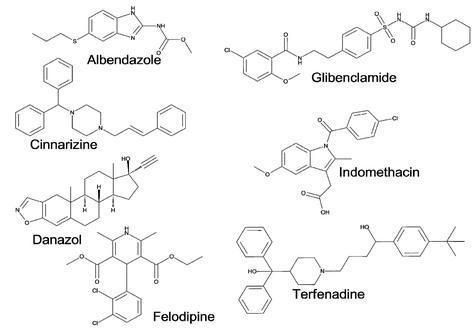

Figure 1: Chemical structures of the studied drugs.

Table 1: Physicochemical properties of the compounds.

COMPOUND	MW	T_m ℃	logP_{oct}	pK_a
Albendazole	265.3	178.1	3.5[a]	11.69,4.07[e]
Cinnarizine	365.5	120.2	6.1[a]	7.69[e]
Danazol	337.5	225.0	4.2[a]	*NA*
Felodipine	384.3	139.1	5.58[b]	*NA*
Glibenclamide	494.0	176.1	4.23[c]	5.75[d]
Indomethacin	357.8	159.8	3.51[d]	4.42[d]
Terfenadine	471.7	151.2	5.52[d]	9.86[d]

[a]calculated logP [b]Cammenisch *et al.* 2007, [c]Yalkowsky *et al.*1991, [d]pION, [e]Uppsala University, Department of Pharmacy.
All pK_a values were determined at 25 °C and 0.15 M ionic strength. NA= not applicable

Methods

The apparent solubility of three neutral, two basic and two acidic compounds with poor aqueous solubility[1] was measured in BDM: simulated intestinal fluid in fasted (FaSSIF pH 6.5 containing 3 mM sodium taurocholate and 0.75 lecithin) and fed state (FeSSIF pH 5.0 containing 15 mM sodium taurocholate and 3.75 lecithin) [2], and in their corresponding blank buffers ($FaSSIF_{blk}$ and $FeSSIF_{blk}$).

All measurements were performed using the µDiss Profiler*PLUS* (fig. 2)[3]. Each channel of the instrument was calibrated with its own standard curve prior to the experiment. Dissolution rate and solubility were measured (n≥3) at 37℃ and excess powder of the compound under investigation was present throughout the experiment. The dissolution media was stirred (100 rpm) and the concentration was measured at predefined time intervals until the solubility plateau was reached (fig. 3).

The apparent BCS classification was based on literature permeability values and the results from the solubility experiments. Dose number (D_0) was calculated based on the maximum oral dose given and a volume of 250 mL.

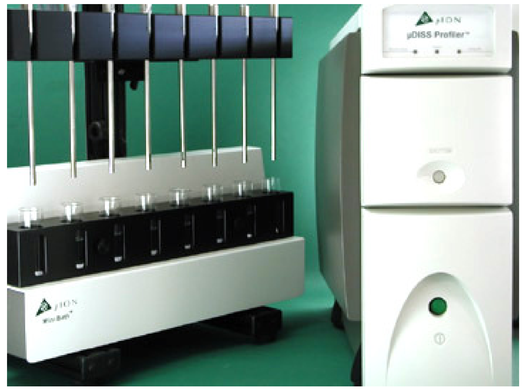

Figure 2: The equipment allows simultaneous assessment of dissolution rate and solubility in small volumes of BDM.

Results

The apparent solubility measured in the simulated intestinal fluids and their blank buffers ranged from below 0.1% (danazol in FaSSIFblk) to above 200% of the maximum oral dose (felodipine and terfenadine in FeSSIF). For four of the seven compounds the increase in the apparent solubility in FaSSIF and FeSSIF resulted in an apparent BCS class improvement from class II to class I (table 2).

The neutral compounds showed higher solubility in FeSSIF than FaSSIF and the largest effect was obtained for felodipine which was the most lipophilic compound. Bases displayed higher solubility in FeSSIF than FaSSIF, a result that was dependent on the inclusion of solubilizing agents and the pH. Finally the acidic compounds displayed clear pH dependence although the inclusion of solubilizing agents improved the solubility as well. All studied compounds exhibit higher solubility in the full simulated media compared to the corresponding blank buffers (fig. 4.)

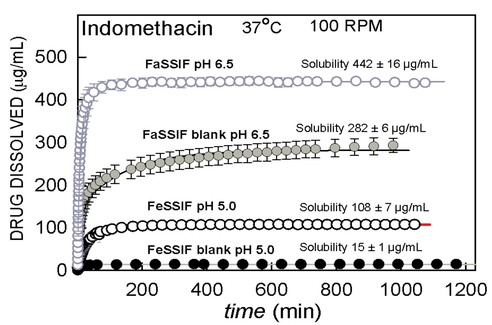

Figure 3: Example of dissolution profiles and solubility values in simulated intestinal fluids and corresponding blank buffers.

Conclusion

All seven compounds showed a higher solubility in FeSSIF than the corresponding blank buffer. The increased solubility in the BDM resulted in improved positioning in the BCS for four of the seven drugs studied.

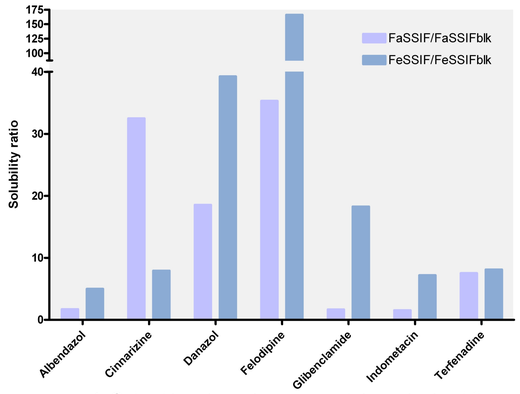

Figure 4: Solubility ratio between simulated intestinal fluids and corresponding blank buffers.

Table 2: Dose number and apparent BCS Class

COMPOUND	Media	Max Dose (mg)	D_0[a] (%)	Apparent BCS Class[b]
Albendazole	FaSSIF Blk	400	0.1	
	FeSSIF Blk		0.1	
	FaSSIF		0.1	
	FeSSIF		0.4	
Cinnarizine	FaSSIF Blk	30	0.3	
	FeSSIF Blk		12.5	
	FaSSIF		10.8	
	FeSSIF		99.2	I
Danazol	FaSSIF Blk	400	0.0	
	FeSSIF Blk		0.1	
	FaSSIF		0.7	
	FeSSIF		2.0	
Felodipine	FaSSIF Blk	20	1.9	
	FeSSIF Blk		2.0	
	FaSSIF		66.3	
	FeSSIF		332.5	I
Glibenclamide	FaSSIF Blk	20	3.1	
	FeSSIF Blk		0.5	
	FaSSIF		5.2	
	FeSSIF		8.5	
Indomethacin	FaSSIF Blk	100	70.5	
	FeSSIF Blk		3.8	
	FaSSIF		110.5	I
	FeSSIF		27.0	
Terfenadine	FaSSIF Blk	60	4.7	
	FeSSIF Blk		30.2	
	FaSSIF		35.4	
	FeSSIF		245.5	I

[a]Percentage of max dose possible to dissolve in 250 mL media. [a] All studied drugs are sorted as class II compounds based on literature permeability and aqueous solubility data.

References;

[1]Bergström C. A. S., Wassvik C. M., Johansson K., Hubatsch, I. Poorly soluble marketed drugs display solvation limited solubility. J Med Chem 2007, 50, 5858-62.

[2]Galia E., Nicolaides E., Hörter D., Löbenberg R., Reppas C., Dressman J.B. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res 1998, 15, 698-705.

[3]Tsinman K., Avdeef A., Tsinman O., Voloboy D. Powder dissolution method for estimating rotating disk intrinsic dissolution rates of low solubility drugs. Pharm Res 2009, 26, 2093-2100.

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