Low volume dissolution assays – Comparison of disk and powder dissolution experiments for BCS Class II compounds

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Purpose

This poster describes recent work within the European funded OrBiTo project on the dissolution behaviour of BCS Class II (poorly soluble) compounds using disk and powder methods and the impact of different media on the dissolution performance.

Methods

Dissolution measurements were performed using the SiriusT3 platform (figure 1) with built-in pH measurement and UV fibre-optic spectroscopy. UV-visible absorption spectra were recorded via a fibre-optic dip probe with a diode array spectrophotometer. Spectra were recorded every 30 seconds for disc dissolution assays and every 10 seconds for powder dissolution assays for 2 hours.

Fig. 1 – SiriusT3 automated physchem platform for low volume dissoluion assays.

All compounds were supplied by EFPIA members of the OrBiTo project and used directly as powders or prepared as 3mm diameter disks using a tablet press with 80kg load force. The compounds were all BCS Class II covering a range of acidic, basic and neutral functionality. Acidic compounds included ibuprofen, valsartan and zafirlukast. Basic compounds studied were bromocriptine and carvedilol. Neutral compounds included felodipine, fenofibrate and tadalafil.

The dissolution media employed for the studies was FaSSIF version 1 (table 1) and phosphate buffer.

Ingredients of Phosphate buffer: pH 6.5 *	
Sodium taurocholate	0 mM
Lecithin	0 mM
NaH2PO4	3.95 g
NaCl	6.19 g
Purified water qs.	1000 mL

Ingredients of FaSSIF (Fasted State Simulated Intestinal Fluid) v1: pH 6.5 *	
Sodium taurocholate	3mM
Lecithin	0.75mM
NaH2PO4	3.95 g
NaCl	6.19 g
Purified water qs.	1000 mL

Table 1: Composition of media. *pH adjusted to final pH of 6.5 with NaOH. FaSSIF buffer was prepared from reconstitutable powder supplied by Biorelevant.com and based on published recipes [1].

Particle size measurements on the powders were carried out using a Mastersizer 2000 (Malvern, Worcester, UK).

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Results

Intrinsic dissolution rates (IDRs) from disc experiments are shown in table 2. IDRs were calculated from fitting to zero order profiles showing release from a constant surface area (3 mm disk, 0.07 cm^2) and is illustrated in figure 2 for ibuprofen.

Compound	IDR Phosphate pH 6.5 Sirius µg/min/cm^2	IDR Phosphate pH 6.5 Strathclyde µg/min/cm^2	IDR FaSSIF v1 pH 6.5 Sirius µg/min/cm^2	IDR FaSSIF v1 pH 6.5 Strathclyde µg/min/cm^2
Fenofibrate	0.08	0.7	0.6	1.3
Tadalafil	1.2	1.5	1.8	2.1
Felodipine	1.0	0.4	3.1	5.1
Bromocriptine	0.8	1.6	4.2	15.3
Zafirlukast	1.7	1.1	4.2	4.7
Carvedilol	8.5	6.3	14.4	15.1
Ibuprofen	255	220	453	335
Valsartan	599	551	677	623

Table 2: Comparison of disc IDR values obtained at Sirius and Strathclyde in phosphate and FaSSIF v1 buffers at pH 6.5.

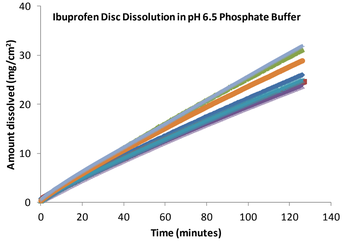

Figure 2: Ibuprofen disc IDR profiles.

Dissolution rates depended on the overall charge state of the compounds under study. For example, ibuprofen (pK_a 4.45) and valsartan (pK_{a1} 3.7, pK_{a2} 4.5) have good dissolution at pH 6.5 when they are negatively charged. Carvedilol (pK_a 8.02) is positively charged at pH 6.5.

The use of FaSSIF v1 increased dissolution performance significantly for zafirlukast, bromocriptine and felodipine.

Disk dissolution was challenging for the most poorly soluble compounds using in-situ UV spectroscopy due to the weak absorbance associated with low concentrations in solution. It does, however, provide a direct measurement of intrinsic dissolution rate (i.e., constant release from a constant surface area). It is important to note that when fabricating discs, the use of different tablet press designs may cause variation in data obtained between sites.

Powder dissolution experiments increased the UV absorbance levels compared to disk experiments but overall dissolution rates depended on the sample weight used due to an increase in surface area. In order to determine intrinsic dissolution rates from powder it was necessary to correct the results for particle size.

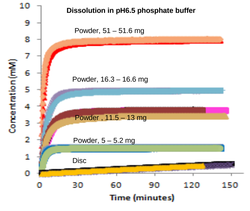

Figure 3: Ibuprofen disc and powder dissolution profiles.

Compound	Surface Weighted Mean Particle Size µm	Specific Surface Area m^2 / g	Powder IDR Phosphate pH 6.5 µg/min/cm^2	Powder IDR FaSSIF v1 pH 6.5 µg/min/cm^2
Tadalafil	25.9	0.232	4.6	9.5
Felodipine	121.6	0.049	0.2	1.0
Bromocriptine	14.7	0.408	0.7	3.9
Zafirlukast	6.3	0.955	0.7	19
Carvedilol	35.4	0.170	12.4	12.1
Ibuprofen	77.1	0.078	305	328
Valsartan	36.7	0.164	222	287

Table 3: IDR values in phosphate and FaSSIF v1 buffers at pH 6.5 obtained from powder dissolution experiments.

Increasing powder dissolution rate was observed with an increase in sample weight. Figure 3 shows the results for ibuprofen in pH 6.5 phosphate buffer. Figure 4a shows bromocriptine in pH 6.5 phosphate buffer and figure 4b shows bromocriptine in pH 6.5 FaSSIF v1. Note the improvement in dissolution of bromocriptine in the simulated intestinal fluid. IDRs from the powder experiments are shown in table 3 by correcting for surface weighted mean particle size and effective surface area as determined by the Malvern Mastersizer 2000.

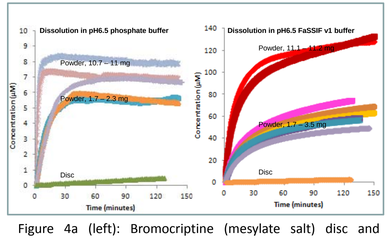

Figure 4a (left): Bromocriptine (mesylate salt) disc and powder dissolution profiles in pH 6.5 phosphate buffer.
Figure 4b (right): Bromocriptine (mesylate salt) disc and powder dissolution profiles in pH 6.5 FaSSIF v1 buffer.

Powder dissolution can be challenging even for highly soluble drugs since internal and external components of reflection and absorption affect UV spectroscopy when using large sample weights.

Conclusion

Experimental protocols have been optimised to successfully determine dissolution profiles using small quantities of material. The results of the study reveal increased dissolution performance in the presence of simulated intestinal fluids compared to aqueous buffer systems for most of the BCS Class II compounds.

References

[1] Kostewicz, E.S., Brauns, U., Becker, R., Dressman, J.B. Pharm. Res. 2002, 19(3), 345-349].

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