Dissolution Performance of Inhaled Products in Simulated Lung Fluid Using Novel Low Volume Assays

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Purpose

The aim of the study was to measure the dissolution characteristics of various active pharmaceutical ingredients used in inhalation products using novel low volume assays. Samples were compared in a standard phosphate buffer and in several simulated lung fluid (SLF) media.

Method

The dissolution performance of six samples used in inhalation products (budesonide, indacaterol, pranlukast, rofleponide, salmeterol and zafirlukast) was measured at 37°C.

SLFs (phosphate buffer) Conditions				
	Concentration (mM)	pH	Ionic Strength (M)	Temperature (°C)
Aqueous	50	7.4	0.17	37
0.5% SDS	10	7.4	0.15	37
0.025% DPPC	10	7.4	0.15	37
0.003% Curosurf	10	7.4	0.15	37

Table 1: Properties of the solutions used in this study.

Dissolution measurements were compared using standard phosphate buffer and three different simulated lung fluid media: 0.5% sodium dodecyl sulphate (SDS), 0.025% 1,2-dipalmitoyl-*ns*-glycero-3-phosphocholine (DPPC) and 0.003% Curosurf (see table 1).

The experiments were performed using two novel dissolution technologies. The SiriusT3 was set up to run powder dissolution assays in 2mL volumes with quantitation using in-situ UV fibre-optic probes. The Sirius SDI is a surface dissolution imaging system allowing direct measurement and visualization of dissolution events at or near the surface of the product in real-time. It uses a pixelated array to capture UV-light transmitted through a flow-cell where a compact of the sample is introduced to the flow.

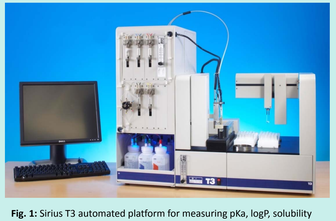


Fig. 1: Sirius T3 automated platform for measuring pKa, logP, solubility and dissolution properties.

Fig. 2: Above: Sirius SDI. Above right: Flow cell. Below right: press set with sample cups

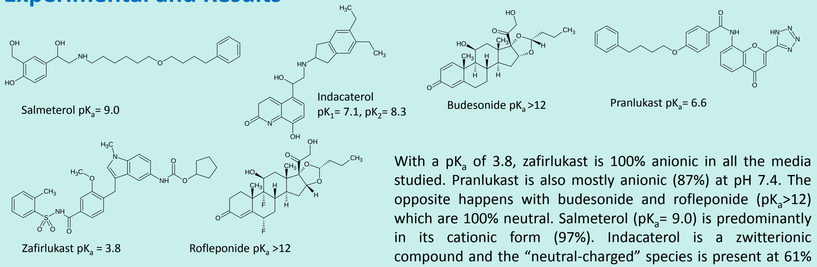
Conclusion

These novel low volume dissolution assays allowed comparison of release profiles of APIs used in inhalation products between standard phosphate buffer and several simulated lung fluid media containing SDS, DPPC and Curosurf. Direct imaging at the surface of a compact of the API showed that not all of the SLF studied improved the release characteristics of compounds, and different behaviour was observed between the SLF media. The biggest improvement in dissolution performance was observed for all compounds in 0.5% SDS.

References

- Ye F. et al. Eur. J. Pharm. Sci. 2012, 46, 72-78.
- Østergaard J. et al. Pharm. Res. 2010, 27, 2614-2623.

Experimental and Results



With a pK_a of 3.8, zafirlukast is 100% anionic in all the media studied. Pranlukast is also mostly anionic (87%) at pH 7.4. The opposite happens with budesonide and rofleponide (pK_a>12) which are 100% neutral. Salmeterol (pK_a= 9.0) is predominantly in its cationic form (97%). Indacaterol is a zwitterionic compound and the "neutral-charged" species is present at 61% at pH 7.4.

It should be noted that indacaterol and budesonide are the two compounds of the group studied that are not surface active, i.e., they do not reduce the surface tension of pH7.4 buffer at concentrations below their solubility values.

Dissolution studies (SiriusT3)

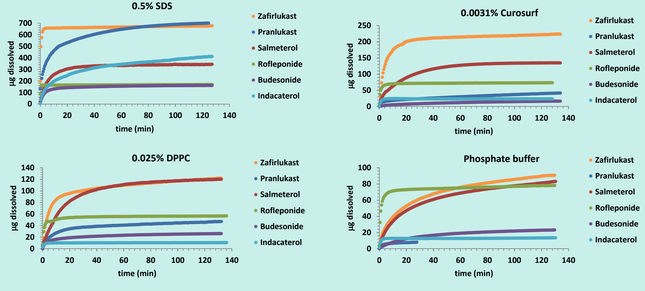


Fig. 3: SiriusT3 dissolution profiles showing the mass released *versus* time for the six drugs studied in the presence of the SLFs studied in comparison with the phosphate buffer media

Figure 3 displays the dissolution profiles of the drugs in SDS, DPPC and Curosurf media compared with phosphate buffer. Indacaterol, pranlukast and budesonide were the least soluble drugs studied in all the media with the exception of SDS. SDS improved the dissolution of all the drugs, with 100% released in the case of zafirlukast and pranlukast (see table 2), which are both ionised in the media studied. It should be noted that the steroids (budesonide and rofleponide) showed similar mass released in SDS. Curosurf improved the dissolution of salmeterol, indacaterol and zafirlukast, all three present in the media in different charged forms, when compared to DPPC and phosphate buffer. However, no significant changes were observed with rofleponide (fully neutral) in Curosurf. On the other hand, an increase in dissolution was observed in DPPC for pranlukast and budesonide when compared to phosphate buffer and Curosurf.

% Mass released				
Compounds with Surface Activity				
	Phosphate	**0.025% DPPC**	**0.003% Curosurf**	**0.5% SDS**
Zafirlukast	11.5%	19.4%	41.4%	100%
Pranlukast	1.1%	6.7%	6.0%	100%
Salmeterol	19.5%	23.9%	22.3%	70.4%
Rofleponide	14.0%	9.6%	12.5%	28.2%
Compounds without Surface Activity				
	Phosphate	**0.025% DPPC**	**0.003% Curosurf**	**0.5% SDS**
Indacaterol	3.1%	1.8%	4.1%	74.0%
Budesonide	4.6%	4.2%	2.5%	22.6%

Table 2: Percentage mass released observed at the end of the SiriusT3 dissolution experiments

Table 2 shows the increase of the amount of sample dissolved with the SLFs studied. All drugs showed an increase of dissolution in all of the SLF studied with the exception of indacaterol, budesonide and rofleponide, which did not see any improvement in DPPC and Curosurf. The largest increase in dissolution performance was found with SDS and this was observed for all compounds.

Dissolution studies (Sirius SDI)

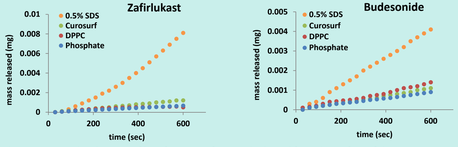


Fig. 4: Sirius SDI dissolution profiles of amount of material released from the surface of the compact.

Figure 4 shows the cumulative loss of material after 10 minutes in the Sirius SDI at a flow rate of 0.2mL/min for zafirlukast and budesonide. These results confirm the dissolution behaviour observed in figure 3 and table 2. Figure 5 shows the images of five of the drugs studied in the different media. Going from top to bottom, the snapshots represent the improvement of the dissolution of the same drug in the different media, i.e., lowest dissolution at top, highest dissolution in bottom image.

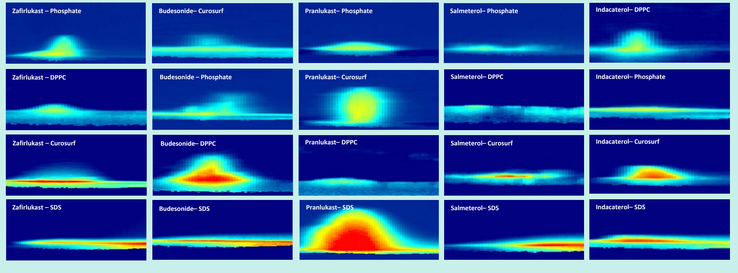


Fig. 5: Images of dissolution in the different media studied for five of the drugs. 10 min experiment with a flow rate of 0.2mL/min

Rofleponide

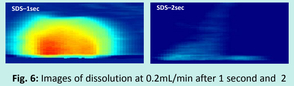


Fig. 6: Images of dissolution at 0.2mL/min after 1 second and 2 seconds. The snapshots show that SDS rapidly removes rofleponide compact from the holder, probably due to high

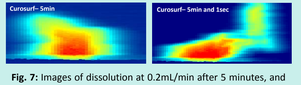


Fig. 7: Images of dissolution at 0.2mL/min after 5 minutes, and 5 minutes and one second in Curosurf. The snapshots show that rofleponide "bursts" away from the compact, probably due to

It should be noted that compacts of rofleponide showed "burst" effects in some of the media, which could be attributed to increased wettability.

Instrumentation
pKa, logP & logD,
Solubility, Supersaturation, Dissolution
Particle size and shape analysis

CRO Services
PhysChem properties – pK_a, logP, logD, solubility, supersaturation, dissolution
Formulation Excipient Studies
Parenteral Solubilisation Studies
Solid state assays – XRPD, DSC, TGA, Raman
Surface Tension – CMC, TSA, K_{AW}

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