Faster dissolution methods for the early-stage screening of pharmaceutical salts

Darren Matthews[1], Brian Stockton[1], George Butcher[1], Jon Mole[2]

[1] Sirius Analytical Ltd. Forest Row, RH18 5DW, UK. [2] Sirius Analytical Inc., Beverly, MA, USA.

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Purpose

To evaluate three dissolution methodologies used for characterizing the dissolution properties of two pharmaceutical salts of a weak base.

Methods

The dissolution of two forms of a basic drug (pK_a 5.09, L-tartrate and hydrogen sulfate salts) was compared using three methodologies. In method 1, dissolution was performed on the Sirius inForm. Free powders of the two salts were added to 40 mL of an acetate buffer adjusted to pH 2.5; after 1 hour the pH was adjusted to pH 6.5 and a FaSSIF concentrate added. The amount of dissolved API was determined at fixed time intervals by *in-situ* UV detection. Method 2 was performed on a SiriusT3 automatic titration instrument. Compacts of API were held in a fixed position in vials holding 20 mL of stirred solution. Amounts in solution were determined from multi-wavelength UV absorption measured using an *in-situ* dip probe. Method 3 was performed on a Sirius SDI (Surface Dissolution Imaging) instrument. Prepared compacts were held in fixed position inside a flow cell; buffer was pumped at 0.2 mL/min across the compact surface. The concentration gradient was measured downstream of the dissolving sample by UV absorption at 214 nm. Experiments on the SiriusT3 and the Sirius SDI were conducted in buffer solutions at pH 6.5.

Results

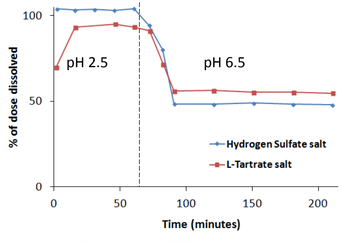
Method 1 showed subtle differences between the dissolution rates of the two salts, but it was difficult to determine the reasons for these differences. Method 2 allowed the intrinsic dissolution to be determined without the need for large amounts of each compound. From these data it was possible to determine that the differences in dissolution rate were not related to dissimilarities in the particle size distribution. Method 3 produced images and movies showing the shape of the dissolving plumes, from which distinct differences in the surface behaviour were determined. Using a different wavelength (550 nm) and a digital camera it was possible to determine the formation of second layer above the compact surface for both salts, and to observe disintegration of the hydrogen sulfate salt compact.

Conclusion

Each dissolution method investigated in this study yields different, but complementary data. The scientist can decide whether, for example, to investigate the influence of particle size or to exclude it. By visualising the dissolution process using the Sirius SDI, an insight into the possible dissolution mechanism of the salts can be gained.

Method 1 – Sirius inForm

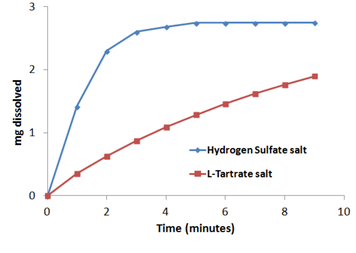
The hydrogen sulfate salt dissolved rapidly in the pH 2.5 buffer, and reached 100% of the added dose by the start of data collection. The L-tartrate salt, however, required a further 16 minutes to reach approximately 100% of the added dose. The pH of the solution decreased in the presence of the hydrogen sulfate salt (pH 2.0) and increased (pH 3.0) in the presence of the L-tartrate salt. Upon transition to FaSSIF (pH 6.5), the API rapidly precipitated from solution with both salts reaching a similar plateau.



It was considered that differences in the particle size distribution of the two salts may be responsible for the observed differences in dissolution rate. It was also proposed that the differences are due to an intrinsic property of the two salts. However, from this data it was not possible to determine the mechanism behind the dissolution process.

Method 2 – SiriusT3

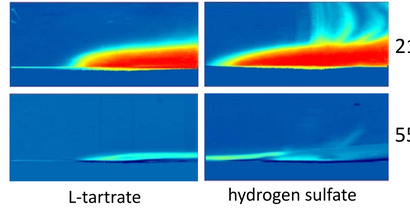
Dissolution of the salts was performed at pH 6.5, as it was considered a more discriminating medium (i.e. in which in the compounds have lower solubility). From the dissolution studies performed on the SiriusT3 it was seen that the dissolution rate of the hydrogen sulfate salt is significantly faster than the tartrate salt.



If the observed differences in dissolution from the Sirius inForm were solely related to particle size we would expect no differences in the dissolution rates determined in this investigation, as it is representative of the intrinsic dissolution rate. Therefore the differences in dissolution are likely to be to due an intrinsic property of the salt as opposed to dissimilarities in the particle size distribution.

Method 3 – Sirius SDI

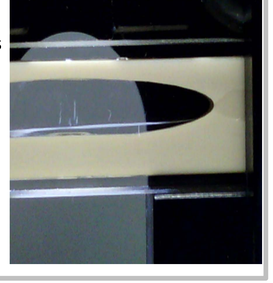
Because differences in the particle size distribution were discounted as a potential reasons for differences in the dissolution rates of the two salts, the surface dissolution behavior was investigated using the Sirius SDI. Analysis of the dissolution behavior at the surface of the two salts showed some significant behavioral differences when analyzed at 214 nm.



The surface dissolution of the L-tartrate salt showed the typical laminar profile associated with the Sirius SDI. However, the dissolution of the hydrogen sulfate salt appeared particularly dramatic with 'wisps' of material being removed throughout the dissolution process.

Analysis at a wavelength where it was anticipated that dissolved drug would not absorb (550nm) was performed. The 'wisps' were also present at this wavelength, indicating that these are associated with undissolved material. The formation of a 'second layer' above the tablet surface was also observed. This was evident in both salts – although more pronounced with the hydrogen sulfate salt.

To understand the nature of these 'wisps' and the absorbance above the surface at 550 nm, the dissolution of the hydrogen sulfate salt was investigated using a webcam. Two observations were made: 1) particulate material appeared to leave the surface, indicating possible disintegration of the compact, 2) the 'second layer' above the tablet surface is also clearly visible. Although the nature of this layer is not clear, it is considered that it could be a concentrated layer of the salt component (hydrogen sulfate). This would result in a very low pH at the surface of the compact, which would account for the rapid dissolution. The pH of a concentrated tartrate salt would not be so low, therefore resulting in slower dissolution.



For more information please contact:
Sirius Analytical, Forest Row Business Park, Station Road, Forest Row, East Sussex, RH18 5DW, UK
T +44 (0)1342 820720 **F** +44 (0)1342 820725 **E** sales@sirius-analytical.com