Poster Number 36W0930

Study of the impact of different salts on the intrinsic dissolution rate of pharmaceutical compounds

Breeze Outhwaite, Rebeca Ruiz, Karl Box

Sirius Analytical, Forest Row, East Sussex, UK

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
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PURPOSE

The selection of an appropriate salt form for a potential drug candidate is an opportunity to modulate its characteristics to improve bioavailability, stability, manufacturability, and patient compliance.

We investigated the effect on the intrinsic dissolution rate (IDR) and the mass released of a free base and four complimentary salts over the course of 2 hour experiments in an aqueous system. This research aimed to understand the effect of the counterions and identify the best salt that reached the highest concentration in solution by the end of the experiment.

METHOD

The dissolution profile of one free base compound and its four associated salts have been determined and the corresponding IDRs calculated, using the Sirius inForm.

Dissolutions experiments were performed on Sirius inForm platform. The dissolution rates and mass released of the free base and four salts; hydrochloride, p-toluenesulfonate, naphthalene-2-sulphonate and maleate were analysed using the UV-metric dissolution technique. The samples were prepared as tablets with 3 mm diameter, using a screw press and applying 100 kg load force to compress approximately 10 mg of powder into a cylindrical depression in the face of a steel tablet disc. Dissolution of compressed tablets of the compound was monitored at 37°C for 2 hours, using an in-situ UV fibre optic probe to determine the amount of drug appearing in the dissolution medium (fig. 1).

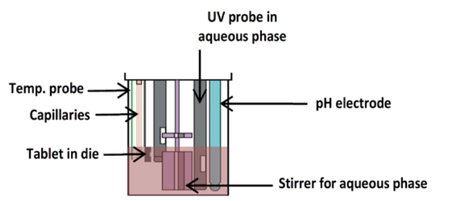

Figure 1: Probe set on the Sirius inForm platform showing UV fibre-optic probes for quantitating drug in aqueous media

The dissolution media contained 0.01 M acetate/ phosphate buffer system. After adjusting the media to pH 5.0, the instrument lowered the tablet disc into the 40 mL aqueous solution, allowing instantaneous data collection. Only one face of the tablet was exposed to the dissolution medium. Stirring of the solution was continuous at a constant rate of 100 rpm. The absorption data was converted to absolute sample weights using the pH-dependent, molar extinction coefficients that had previously been determined using the Sirius InForm (fig. 2). Each compound was performed in duplicate, from which the IDR and mass released were determined.

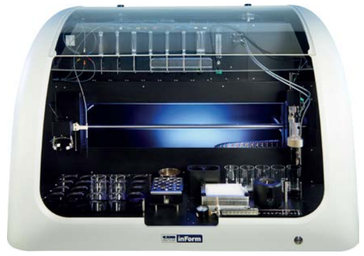

Figure 2: Sirius inForm platform used for IDR analysis

Sirius inForm measures the kinetics of dissolution, absorption, controlled supersaturation and precipitation, and accommodates multiple dosage forms and sample types.

RESULTS

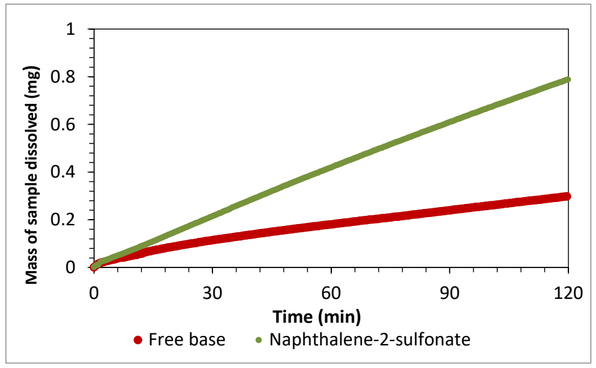

Figure 3: Dissolution profiles of free base and naphthalene-2-sulfonate salts

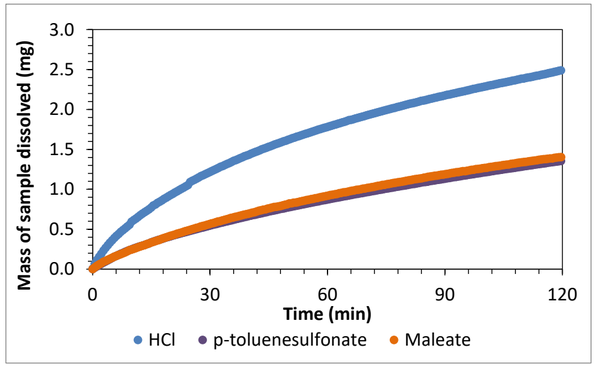

Figure 4: Dissolution profiles of HCl, p-toluenesulfonate, maleate salts

Table 1: Mass dissolved and IDR of free base and four salts

Compound	Mass Dissolved* (mg)	IDR** (µg/min/cm^2)
Free base	0.281 - 0.298	48.8 ± 1.4
Naphthalene-2-sulfonate	0.788 - 0.813	106.5 ± 3.8
p-toluenesulfonate	1.355 - 1.371	249.2 ± 17.5
Maleate	1.403 - 1.514	298.9 ± 20.4
Hydrochloride	2.128 - 3.042	481.4 ± 10.8

The range of mass dissolved at the end of two experiments (2 hours per experiment).
****** These values were determined from the average of the two experiments.***

The results obtained showed that all salts dissolved more sample than the free base after a 2 hour experiment under the same conditions. However, significantly greater quantities dissolved of hydrochloride, p-toluenesulfonate and maleate salts (table 1).

The free base had an average IDR of 49 µg/min/cm^2, releasing an average value of 290 µg of drug over the course of the two experiments (fig.3). The hydrochloride salt showed the largest increase in dissolution in comparison to the free base, with an average IDR of 481 µg/min/cm^2, and an average value of 2.59 mg of sample released (fig. 4). The maleate and p-toluenesulfonate salts displayed similar dissolution rates (fig. 4). The maleate IDR was 299 µg/min/cm^2, with 1.46 mg of sample released, whilst p-toluenesulfonate had an IDR of 249 µg/min/cm^2, with 1.36 mg of sample released. The naphthalene-2-sulphonate salt showed the smallest increase in dissolution with an IDR of 107 µg/min/cm^2 and 801 µg was released (fig. 3).

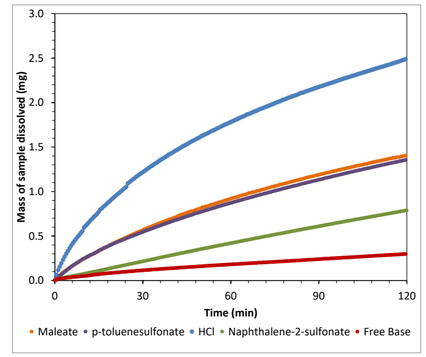

Figure 5: Dissolution profiles of free base, HCl, p-toluenesulfonate, maleate and naphthalene-2-sulfonate salts

CONCLUSION

The intrinsic dissolution rate of a pharmaceutical compound could be improved by the use of counterions in it's formulation. In this study we have shown that the hydrochloride salt had the largest increase in IDR and the highest sample released in comparison to the other salts studied (fig. 5).

Sirius inForm is a versatile instrument capable of providing valuable insights into the dissolution behaviour of different drug forms during salt selection.

REFERENCES

Gravestock, T. B., K. Comer, J. Frake, E. Judge, S. Ruiz, R. , *The "GI dissolution" method: a low volume, in vitro apparatus for assessing the dissolution/ precipitation behaviour of an active pharmaceutical ingredient under biorelevant conditions*. Anal. Methods 2011, 3, 560-567