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

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SUMMARY

The intrinsic dissolution rate (IDR) of a free base and its four salts were investigated with the aim of selecting the salt with the best dissolution performance. IDRs were measured using the Sirius inForm platform with quantitation by in-situ UV spectroscopy. Results showed that the hydrochloride salt had the highest dissolution rate followed by the maleate and p- toluenesulphonate salts, whilst the naphthalene-2-sulphonate and free base had the lowest IDR values. The Sirius inForm provides valuable insights into the dissolution behaviour of different drug forms during salt selection.

INTRODUCTION

The selection of an appropriate salt form for a potential drug candidate is an opportunity to modify 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 its four complementary salts over the course of two- hour experiments in an aqueous system. This research aimed to understand the effect of the counterions and identify the salt that reached the highest concentration in solution by the end of the experiment.

MATERIALS AND METHODS

Dissolution experiments were performed on the Sirius inForm platform. The dissolution rates and mass released of the free base and four salts; hydrochloride, p-toluenesulphonate, naphthalene-2- sulphonate and maleate were determined using the UV-metric dissolution technique (Box et al 2011).

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 monitor the amount of drug appearing in the dissolution medium.

The dissolution media contained 0.01 M acetate/phosphate buffer system. After adjusting the media to pH 5, 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.

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Stirring of the solution was continuous at a constant rate of 100 rpm. The absorption data was converted to absolute sample weights using pH-dependent, molar extinction coefficients previously determined on the inForm. Dissolutions of each compound were performed in triplicate, from which the IDR and mass released were determined.

RESULTS AND DISCUSSION

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

Table 1. *Mass dissolved and IDR of free base and salts.*

Compound	Mass Dissolved	IDR (µg/min/cm²)
Free base	0.281 – 0.298	48.8 ± 1.4
Naphthalene-2-sulphonate	0.788 – 0.813	106.5 ± 3.8
p-toluene-sulphonate	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 free base had an average IDR of 49 µg/min/cm², releasing an average value of 290 µg of drug over the course of the three experiments (Figure 1). The naphthalene-2-sulphonate salt showed the smallest increase in dissolution, compared to the free base, with an IDR of 107 µg/min/cm² and 801 µg released.

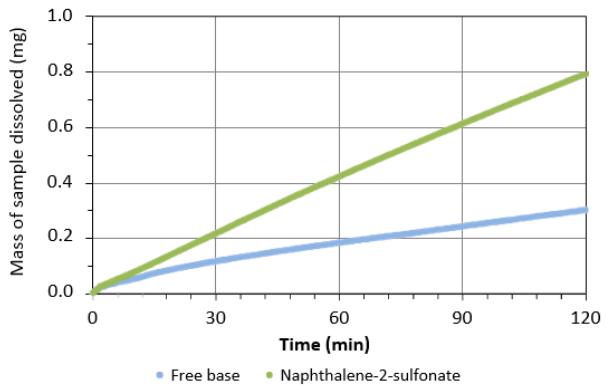

Fig. 1. *Dissolution profiles of the free base and naphthalene-2-sulphonate salt.*

The hydrochloride salt showed the largest increase in dissolution in comparison to the free base, with an average IDR of 481 µg/min/cm², and an average value of 2.59 mg of sample released (Figure 2). The maleate and p-toluenesulphonate salts displayed similar dissolution rates. The maleate IDR was 299 µg/min/cm², with 1.46 mg of sample released, whilst p-toluenesulphonate had an IDR of 249 µg/min/cm², with 1.36 mg of sample released.

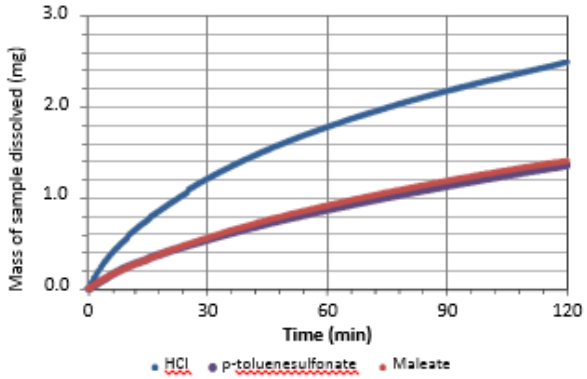

Fig. 2. *Dissolution profiles of the maleate, p-toluene-sulphonate and hydrochloride salts.*

CONCLUSIONS

The intrinsic dissolution rate of a pharmaceutical compound could be improved by the use of counterions in its 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.

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

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