A rapid in vitro screen method for assessing the potential for precipitation of solubilised drugs in the small intestine

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INTRODUCTION

The solubility of weakly basic drugs in aqueous media, including gastrointestinal (GI) fluids, is largely determined by the pH of the media. The 'Spring and Parachute' analogy is often described as an approach for solubilisation and formulating of such drugs, with excipients used to solubilise the API depicted as the 'spring' and excipients that prevent and prolong the onset of precipitation as the 'parachute' (Xu and Dai, 2013).

The pharmaceutical research and development industry is now tending towards 'biorelevant' pH switch testing methods in order to take into account the pH and composition changes in the fluid throughout the GI tract. These pH switch methods however often involve an immediate change in pH from 2 (Gastric) to 6.8 (Intestinal). In truth however the rate at which the contents of the stomach empty into the intestine should also be considered (Kostewicz et al., 2004).

These test methods also often include sampling at different time points with subsequent offline analysis by HPLC. As the drug in the sample solution is in a metastable state, immediate dilution with a suitable medium after sampling is critical to prevent the drug from precipitating whilst awaiting the analysis, thereby compromising the sensitivity of the method. These analytical processes therefore become time consuming and rate limiting for rapid excipient/ formulation screening.

The aim of this work was to produce a method that simulated the gastric emptying process in the body and allowed fast, online, analysis and screening of formulations to assess the 'spring and parachute' effect.

MATERIALS AND METHODS

Compound X, a BCS Class II drug, is a mesylate salt of a weakly basic compound with a pKa of 4.2 and a dose number of 23 in fasted state simulated intestinal fluid (FaSSIF).

Type III and IV lipid formulations were developed for solubilising Compound X. Different polymeric excipients were incorporated into the formulations in order to delay the drug precipitation as "parachute" effect. A reference formulation, which had shown acceptable drug exposure in humans but required further optimisation, was also prepared and compared with the new formulations developed at Quotient.

The rapid in vitro screen method consisted of two vessels, containing simulated gastric fluid (125mL 0.01H HCl) and simulated intestinal fluid (250mL SIF, pH 6.8), which were constantly stirred and maintained at 37ºC. The two phases were linked via a peristaltic pump with the gastric phase slowly pumped into the intestinal phase at a rate of 4mL/min. Turbidity of the simulated intestinal fluid was determined at t = 0 and every minute thereafter by UV/V is spectrophotometry at 600nm. The onset and the rate of the turbidity increase from the formulations was recorded and compared in order to identify the optimal formulation for the planned clinical study.

A classical pH-switch biorelevant dissolution test on the selected formulations was also conducted, via analysis in 250mL SGF in USP II dissolution apparatus for 30 minutes before immediate pH switch to 500mL pH 6.5 FaSSIF for additional dissolution for 60 minutes. Samples were taken at predetermined time points, filtered through 0.4µm filter and diluted with a suitable medium for HPLC analysis using a diode array detector (DAD) at 220nm.

RESULTS AND DISCUSSION

Results generated from the Quotient rapid in vitro screen method on the solubilised Compound X candidate formulations were plotted as a 'precipitation profile' (Figure 1). As for the initial formulation screen no precipitation inhibitor incorporated in these formulations. Although the data generated was not a direct measurement of the drug per se, i.e. results gained did not directly represent the concentration of Compound X in solution nor the quantity precipitated, the S-shaped 'precipitation curve' could however allow assessment of the onset of precipitation and the subsequent rate of turbidity increase, which would enable quick comparative analysis and screening of the different formulations.

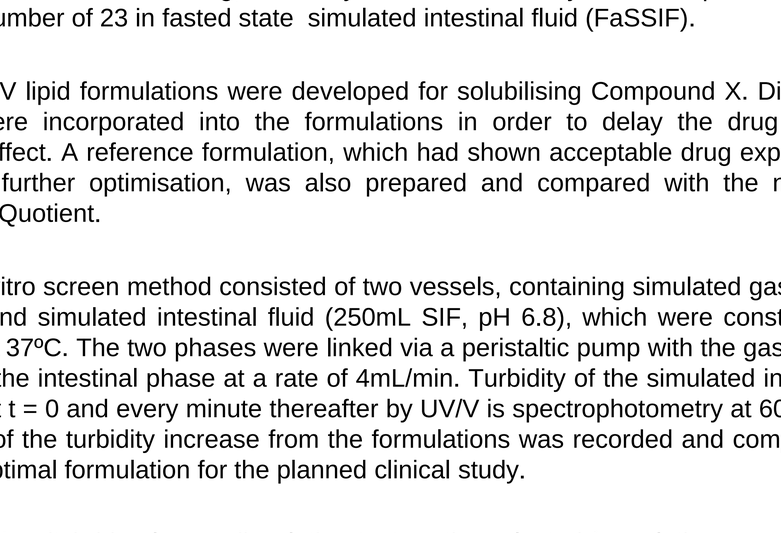

Figure 1. Precipitation profile of Compound X candidate formulations

It was noted that the solubilised drug formulation in the gastric phase should be completely dissolved as incomplete dissolution would lead to an early increase in turbidity over time at a steady rate (Figure 1, Formulation 3).

The effect of precipitation inhibition from different polymeric excipients was investigated and the results are shown in Figure 2. From the excipients tested HPMC E5 was demonstrated as the most effective precipitation inhibitor for Compound X and therefore was selected for further formulation development.

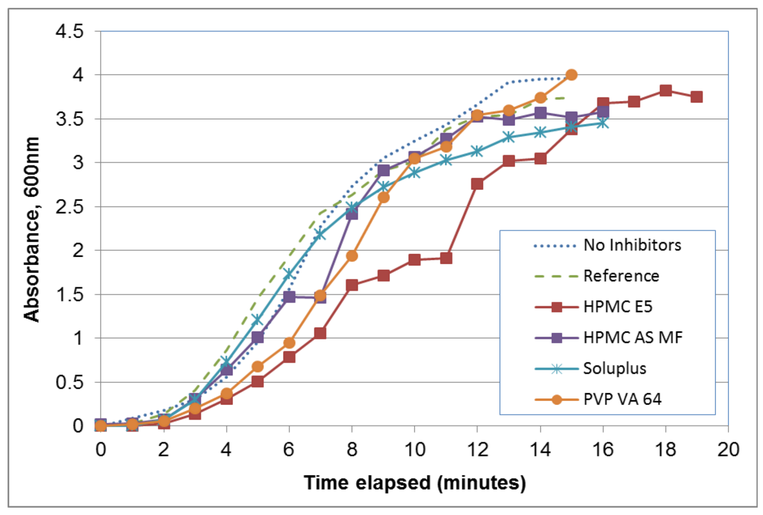

Figure 2. Screening of precipitation inhibitors in a selected formulation

Further testing was conducted on two optimised formulations (Type III and Type IV lipid formulations), together with the reference formulation. For comparative purposes, the formulations were also characterised by using the immediate pH switch in a USP II dissolution apparatus with which samples taken from each time point were filtered, diluted and analysed by HPLC (Figure 3).

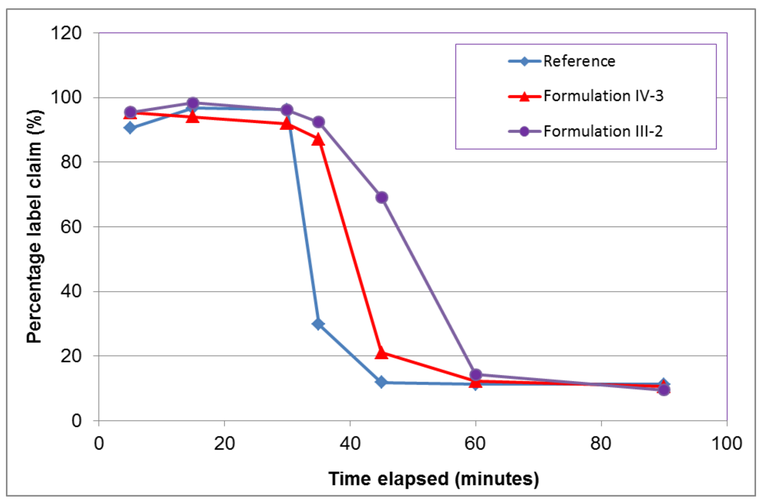

Figure 3. Biorelevant pH switch dissolution analysed by HPLC

Table 1 displays the time point at which the turbidity began to increase from the rapid in vitro screen test. The drug concentrations from the pH-switch biorelevant dissolution test at 35 and 45 min (5 and 15 min respectively after pH switch) were also listed for comparison. It can be seen that Type III formulation performed the best, followed by Type IV lipid formulation and then the reference formulation.

Table 1: Drug precipitation characterised by rapid in vitro screen and pH-switch biorelevant dissolution tests

Formulation	Rapid screen method (Onset of turbidity increase)	pH-switch biorelevant dissolution (% as dissolved drug after pH switch)	
		5min	15min
Type III formulation 2	3 min	92.4%	69.4%
Type IV formulation 3	3 min	87.1%	21.0%
Reference formulation	2 min	29.8%	11.9%

CONCLUSION

The Quotient rapid in vitro screen test allowed for fast semi-quantitative characterisation of candidate formulations in which the drug can be fully solubilised or dissolved in the gastric medium. By comparing the onset of precipitation and the rate of turbidity increase, the "parachute" effect from the formulation i.e. solubilisation and precipitation inhibition on the drug to remain supersaturated in intestinal media can be rapidly assessed. Results generated were comparable to data generated using a USP II pH switch dissolution test, confirming the validity of the rapid screening tool compared to classical biorelevant characterisation methodologies.

ACKNOWLEDGMENT

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