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Investigating the pH-dependent dissolution behavior of ketoconazole using a microscale medium/pH-shift *in vitro* model

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PURPOSE

The aim of the study was to develop a microscale dissolution method that was able to mimic both gastric and intestinal conditions of "normal" and hypochlorhydric patients. This was then used to develop a formulation that can overcome the poor performance of weak bases in hypochlorhydric patients using ketoconazole as model compound. The objectives were to:

- Produce co-amorphous, neat amorphous and an amorphous solid dispersion of ketoconazole
- Use the microscale dissolution method with medium- and pH-shift to investigate their dissolution performance
- Use the method to test the dissolution of crystalline, co-amorphous and amorphous ketoconazole, and an amorphous solid dispersion of ketoconazole

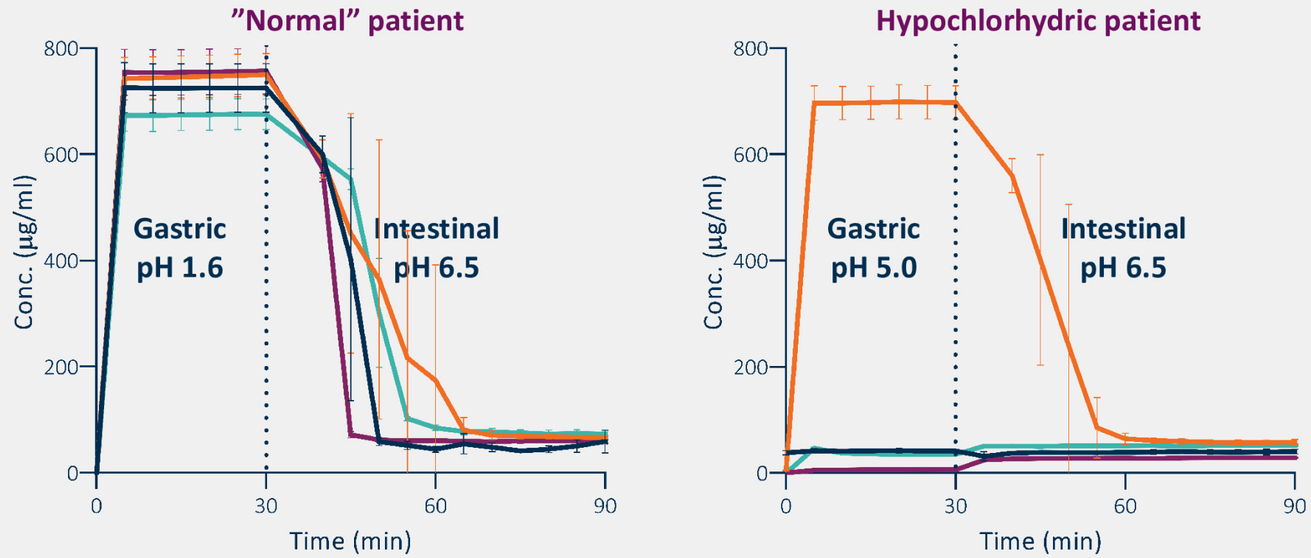

Figure 1: Dissolution / precipitation of the four ketoconazole formulations in the microscale method. The initial 30 minutes were in simulated gastric fluid (FaSSGF) pH 1.6 (left) or 5.0 (right) and the subsequent 60 minutes in a simulated intestinal fluid (FaSSIF) at pH 6.5. The tested materials are: crystalline ketoconazole (**dark blue**) amorphous ketoconazole (**purple**), amorphous solid dispersion of ketoconazole:PVP 25:75 w/w (**turquoise**) and co-amorphous ketoconazole:oxalic acid 1:1 mol (**orange**). Data represent mean ketoconazole concentration ± SD (n = 5).

RESULTS

- All four formulations displayed similar dissolution at "normal" gastric pH 1.6. Following medium- and pH-shift, ketoconazole precipitated in all four formulations to reach equilibrium solubility at 90 min
- Only the co-amorphous formulation displayed similar dissolution at "normal" (1.6) and elevated gastric pH (5.0). This was likely the result of oxalic acid reducing the pH of the gastric media with elevated pH from 5.0 to around 3.6
- Neat amorphous and amorphous solid dispersions did not display superior dissolution performance at elevated gastric pH compared to crystalline ketoconazole

METHODS

- The co-amorphous ketoconazole and oxalic acid was made at a 1:1 molar ratio by ball-milling for 90 minutes at 30 Hz
- Neat amorphous ketoconazole was made by quench-cooling: heating to 150°C (melt) followed by quench-cooling and grinding
- The amorphous solid dispersion of ketoconazole in PVP (25:75 w/w) was made by quench-cooling (see above)
- The simulated gastric and intestinal media used were FaSSGF and FaSSIF, respectively

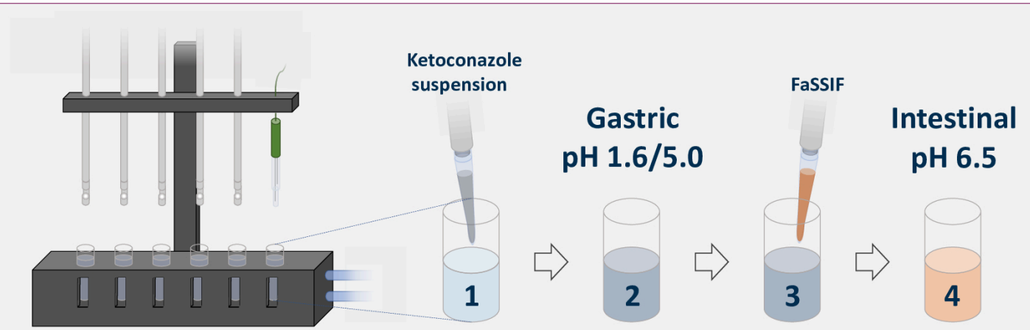

Figure 2: Micro-dissolution apparatus sketch depicting the heating element including 6 dissolution vessels, 5 UV-probes and a pH-probe. During the experiment the probes were lowered into the dissolution media to give inline measurements. Additionally, the four steps of the method are shown: **1)** ketoconazole formulation is pre-dispersed and added to the gastric media (FaSSGF) in the dissolution vessel, **2)** the formulation remains in FaSSGF pH 1.6 or 5.0 for 30 min, **3)** 9x concentrated intestinal media (FaSSIF) containing NaOH to adjust the pH to 6.5 was added to the dissolution vessel and **4)** the formulation remains in FaSSIF pH 6.5 for an additional 60 min.

CONCLUSION

- The microscale dissolution method proved to elucidate differences in "normal" and hypochlorhydric conditions
- The co-amorphous system displayed identical dissolution behavior at normal and elevated pH *in vitro*. This may help to normalize the dissolution behavior and thus, bioavailability of weak bases in hypochlorhydric patients

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