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Development of a video-microscopic method to compare the effect of precipitation inhibitors

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PURPOSE

The aim of this study was to develop a video-microscopic method to evaluate the effect of precipitation inhibitors (PI) on supersaturated solutions of the poorly soluble drug tadalafil using a novel small scale setup.

METHODS

A supersaturated tadalafil solution (degree of supersaturation = 29) was induced by spiking 30 µL of a 5 mg/mL DMSO stock into 200 µL fasted state simulated intestinal medium (FaSSIF, biorelevant.com) with predissolved HPMC (0-1 %w/v) as PI. The studies were performed on the oCelloScope System™ (Philips Biocell A/S, Allerød, DK) in a 96-well plate using video-microscopy and the precipitation was followed over time. The induction time was determined as the time point with the first particle in focus and the onwards growth of the particle was measured.

RESULTS

Without PI, the induction time was found to be 5.5 ± 1.1 minutes for tadalafil in FaSSIF (Fig. 1). Addition of 0.05 – 0.5 %w/v HPMC significantly prolonged the induction time (7.7 ± 0.9 to 10.5 ± 2.1 minutes, $p<0.05$). Lower concentrations of HPMC (0.001 – 0.025 %w/v) did not prolong the induction time. The particle growth rate decreased in presence of HPMC (Fig. 1). The maximum inhibitory effect on growth rate was achieved at 0.01 %w/v HPMC. Higher concentrations of polymer (up to 0.5 %w/v) did not further decrease the growth rate. Addition of 0.001 %w/v HPMC did suppress the growth rate, but not to the same extent as higher concentration (0.01-0.5 %w/v). A clear difference was observed in particle size when comparing tadalafil particles with and without PI (Fig. 2).

CONCLUSION

Tadalafil, in presence of HPMC, shows a prolonged induction time and a reduced particle growth rate. Addition of 0.001 %w/v HPMC decreased the growth rate and the maximum inhibitory effect on growth rate was achieved with 0.01 %w/v. However, in order to also significantly prolong the induction time, 0.05 %w/v HPMC was needed. This method is a promising tool for comparing the effectiveness of PI on supersaturation of poorly soluble drugs.

ACKNOWLEDGEMENTS

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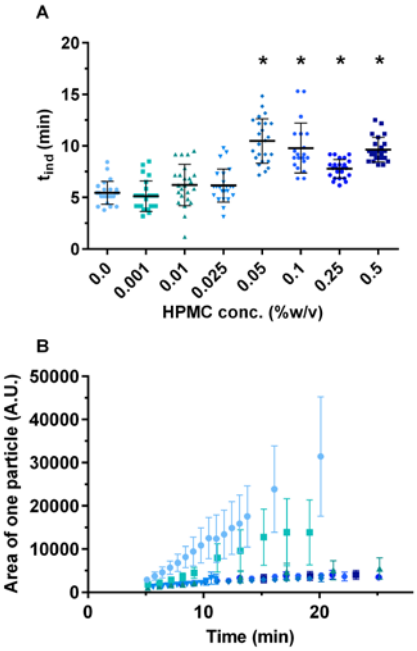

Fig. 1: A) The induction time for tadalafil with different HPMC conc. (mean ± SD, n = 24, * = significantly different from 0.0 %w/v HPMC). B) The area of one well defined particle as a function of time, with different HPMC concentrations (mean ± SD, n = 3-24); ● 0.0%w/v, ■ 0.001 %w/v, ▲ 0.01 %w/v, ▼ 0.025 %w/v◆ 0.05 %w/v, ● 0.1 %w/v, ● 0.25 %w/v and ■ 0.5 %w/v.

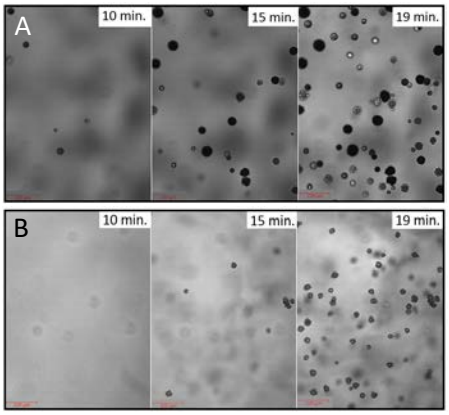

Fig. 2: Pictures taken with the oCelloScope System™ over time. A) Precipitation of tadalafil in FaSSIF. B) Precipitation of tadalafil in FaSSIF with predissolved HPMC (0.5 %w/v).