Early Phase Selection of a Controlled Release Amorphous Dispersion Formulation

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Introduction

Currently it is estimated that over 50% of compounds in discovery and early development have poor water solubility and will require an enabling formulation technology to achieve efficacious exposure levels

(1) The spray drying process has been demonstrated as an effective, if not preferred, operation to produce amorphous solid dispersions to increase aqueous solubility and oral exposure

(2) Recently, several active programs have required the combined use of amorphous solid dispersion formulation and a controlled release profile of that supersaturated solubility. To screen and select formulations in early phase work, an in vitro test methodology was developed to evaluate[1] (i) the stability of the high-energy amorphous form in the controlled release dosage form matrix, and (ii) the extent of supersaturation maintained after release from the dosage form into the lumen.

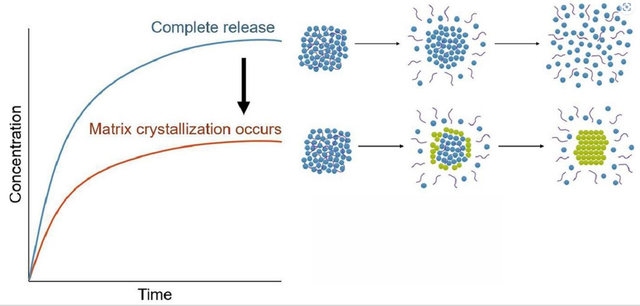


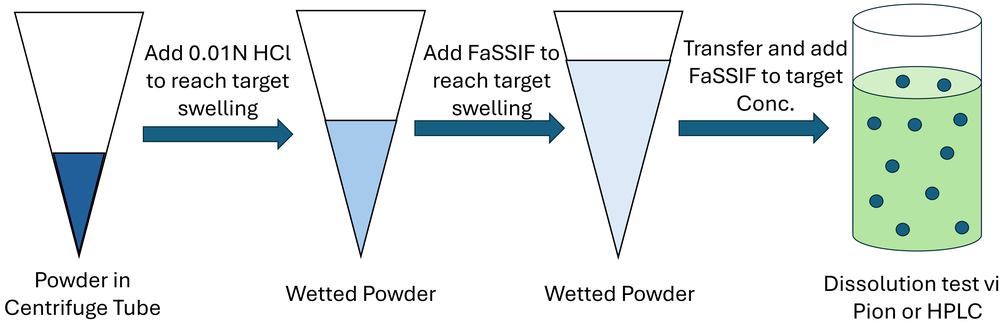
Fig. 1. An illustration depicting the impact of an ASD crystallizing in a matrix tablet and its impact on the release profile. [1]

Methods

- Celecoxib (CBX) was used as a model compound to demonstrate the methodology
- Amorphous dispersions were prepared by spray drying using a 40 kg/hr spray dryer. SDDs were manufacture at active loadings from 25% - 75% active loading using HPMCAS-H and Eudragit L100 as polymers
- Crystallinity of the suspended SDDs was evaluated via polarized light microscopy (PLM)
- Non-sink dissolution testing was performed in simulated intestinal fluid (FaSSIF) using a Pion Rainbow R2D MicroDISS
- Media volumes used for testing were based on measured water uptake of Ibuprofen minitablets measure in Lopes et. al.[2]

Testing Methodology

1. Add the Celecoxib SDD prototypes to the centrifuge tubes at the intended dose.
2. 0.01N HCl added to the centrifuge tubes at 150% (w/w) of the intended tablet weight. Mix the sample continuously using an inversion mixer.
3. After 30 minutes, FaSSIF media added to bring the media to 300% (w/w) of the intended tablet weight.
4. After 1-hour, additional FaSSIF media added to bring the media to 600% (w/w) of the intended tablet weight.
5. Sample and evaluate the physical stability of the SDD via PLM periodically throughout testing.
6. After target release time is achieved, evaluate the final suspension for performance via non-sink dissolution



Results

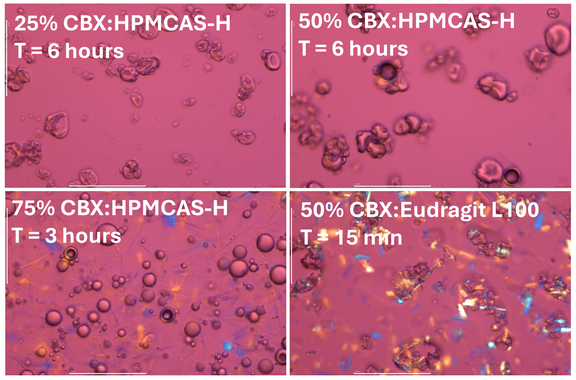


Fig. 2. PLM images from the wetting test. The 25% and 50% CXB:HPMCAS-H did not crystallize. The 75% CXB:HPMCAS-H SDD crystallized at ~1 hour into testing. The 50% CXB:Eudragit L100 SDD crystallized immediately

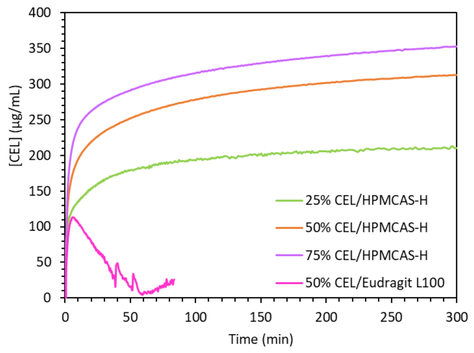


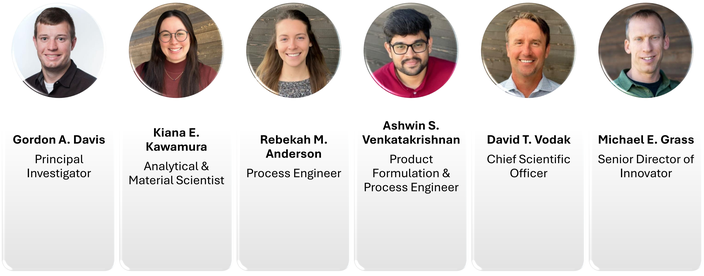
Fig. 3. Non-sink dissolution results after the 6 hour wetting test. The HPMCAS-H SDD sustained supersaturated concentration while the crystallized 50% CXB:Eudragit L100 SDD immediately precipitated.

Conclusion

Controlled release formulations that also provide enhanced solubility were evaluated using a novel modified non-sink dissolution methodology. That test was used to screen multiple formulations for pre-release stability in the 'wet' dosage form followed by non-sink dissolution to assess the ability of the SDD to supersaturate biorelevant media.

- **25% CBX:HPMCAS-H**: stabilized the CBX in the amorphous state for up to 6 hours in biorelevant media and maintained supersaturation during dissolution testing.
- **50% CBX:HPMCAS-H:** stabilized the CBX in the amorphous state for up to 6 hours in biorelevant media and maintained supersaturation during dissolution testing. This SDD prototype balances active loading with physical stability and performance in a controlled release drug product.
- **75% CBX:HPMCAS-H:** stabilized CBX in the amorphous state for ~1 hour before crystallization was observed by PLM. Despite the presence of crystals in the SDD, the formulation maintained super saturated concentration during dissolution testing. The impact of the crystallization after 1 hour *in-vivo* is unknown.
- **50% Eudragit L100 SDD:** Precipitation of CBX was observed during the first timepoint. CBX concentrations fell to the crystalline solubility during dissolution testing. Poor performance anticipated in a controlled release drug product.

References and Acknowledgements



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[1] Dana E. Moseson, Tze Ning Hiew, Yongchao Su, Lynne S. Taylor, Formulation and Processing Strategies which Underpin Susceptibility to Matrix Crystallization in Amorphous Solid Dispersions, Journal of Pharmaceutical Sciences, Volume 112, Issue 1, 2023, Pages 108-122, ISSN 0022-3549, https://doi.org/10.1016/j.xphs.2022.03.020.

[2] Lopes, C.M.; Sousa Lobo, J.M.; Costa, P. "Directly Compressed Mini Matrix Tablets Containing Ibuprofen: Preparation and Evaluation of Sustained Release." Drug Development and Industrial Pharmacy, 2006, 32, 95-106. DOI: 10.1080/03639040500388482.