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Limitations in the pharmacopeial dissolution testing of marketed tacrolimus amorphous solid dispersions

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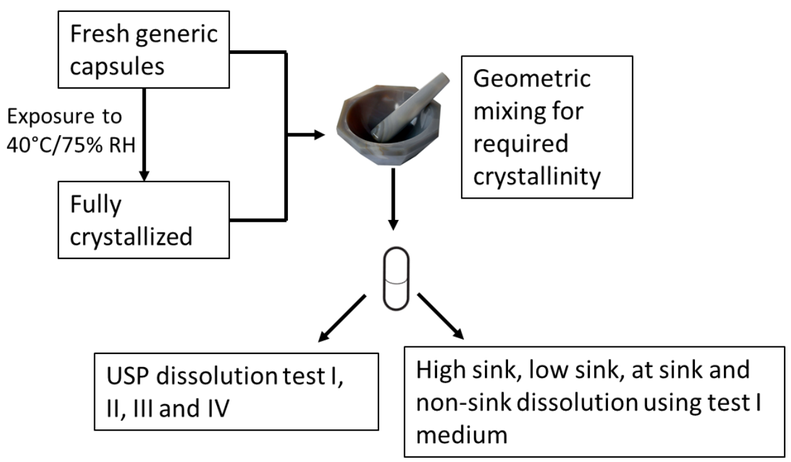
PURPOSE

With the increase in the number of poorly soluble compounds in the drug development pipeline, amorphous solid dispersions (ASDs) are gaining increasing importance as a solubility enhancement strategy. Since the amorphous drug in an ASD has higher free energy, it can undergo crystallization in the solid formulation during manufacture or during storage over the shelf life. From a performance standpoint, crystallization leads to decrease in the free energy and a corresponding decrease in the solubility advantage of the amorphous form. Compendial dissolution testing serves as a quality control tool for the changes in the formulation that can possibly lead to a negative impact on the performance of a formulation. With respect to an ASD, ideally, a dissolution method should be able to discriminate formulations with varying levels of crystallinity so that any amount of crystallization of the drug (manufacturing or storage induced) in an ASD can be detected during dissolution testing. Thus it becomes important to assess the discriminatory power of the conventional dissolution testing methods to determine how sensitive they are with respect to crystallinity detection and discrimination. The purpose of this study was to employ United States Pharmacopeia (USP) dissolution tests for two marketed formulations of tacrolimus, the innovator product and a generic version. The sensitivity towards crystallinity detection of non-conventional low-sink and non-sink dissolution methods was also tested for comparison with the USP methods.

METHODS

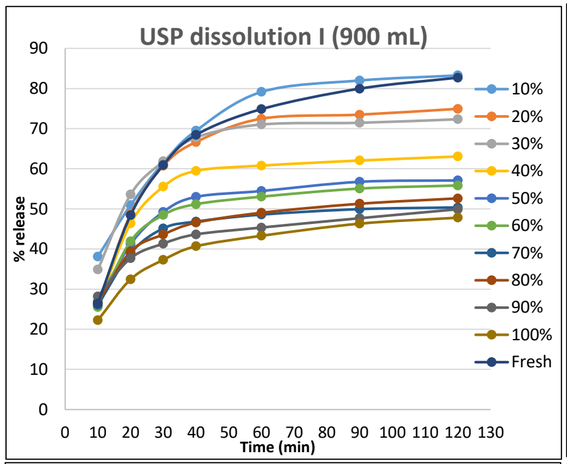


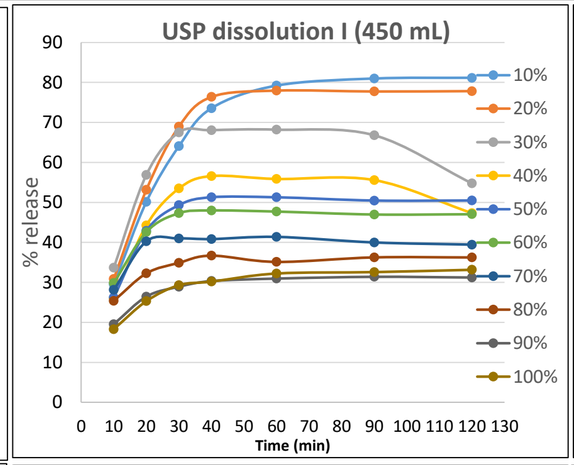
METHODS

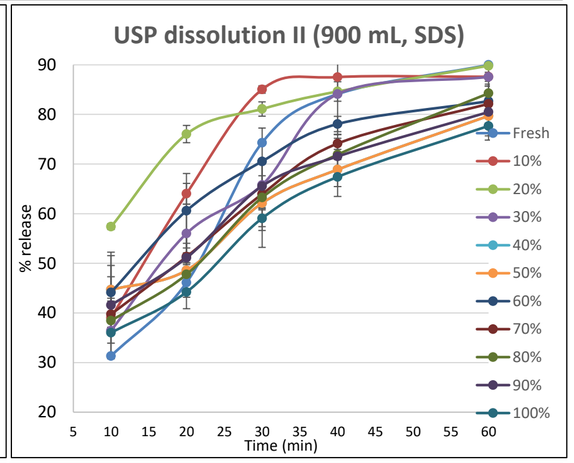
- **Amorphous solubility determination:** A stock solution of the drug was prepared in methanol and infused at a controlled rate using a syringe pump in the dissolution medium (pH 4.5 water containing 50 µg/mL hydroxypropyl cellulose). The extinction at a non-absorbing wavelength of 380 nm was measured as a function of added concentration using a UV dip probe.
- **X-ray diffraction:** Calibration samples were prepared by mixing crystalline tacrolimus with unexposed generic formulation. Crystallization kinetics in the exposed generic and innovator formulations were measured at different time intervals for 4 weeks.

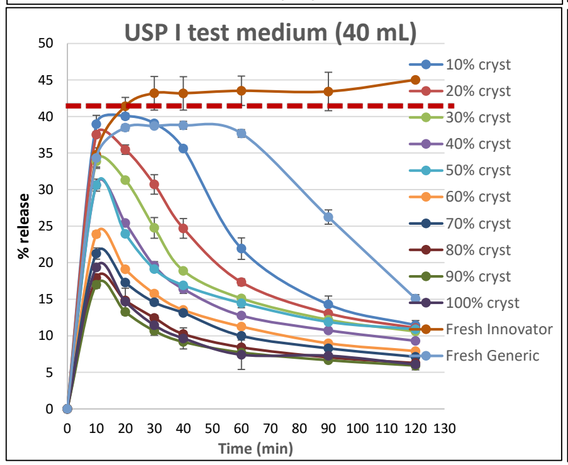
RESULTS

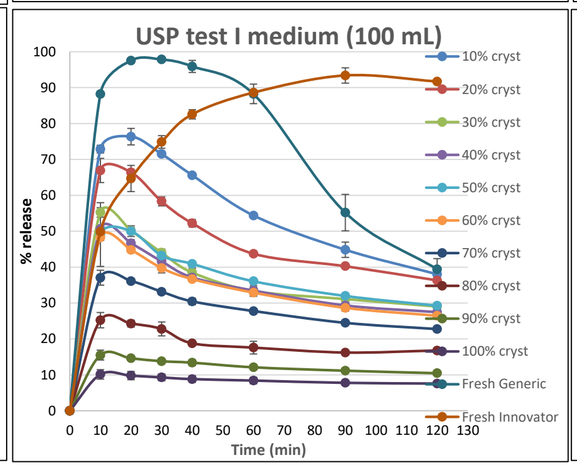
- **Amorphous solubility/LLPS onset:** The amorphous solubility of tacrolimus was found to be ~50 µg/mL.
- **X-ray diffraction:** The generic formulation crystallized completely in 4 weeks under 40°C/75% RH. The innovator formulation was X-ray amorphous under these conditions.











- USP test II is the least discriminatory as samples with 100% crystallinity show 80% release and passed.
- Samples up to 30% crystallinity pass the USP test I.
- Dissolution in 100 mL and 40 mL volume indicates there might be residual crystallinity in the fresh generic formulations.
- 100 mL volume (at sink) gave the most distinction between formulations with different crystallinity levels.

CONCLUSIONS

1. Dissolution in 100 mL (at sink with respect to amorphous solubility) was the most discriminatory.
2. Attention should be given to surfactant amount while developing a discriminatory dissolution method.

DISCLOSURE

H.S.P is a graduate student and LS.T. is a professor at Purdue University. They have no additional conflicts of interest to report. Y.G. and G.GZ.Z. are AbbVie employees and may own AbbVie stock.