Poster number 06R0900

Effect of crystallinity on the bioavailability of marketed tacrolimus amorphous solid dispersions

Hitesh S. Purohit[1], Donald J. Osterling[2], Gary J. Jenkins[2], DeAnne F. Stolarik[2], Wenqing Gao[2], Yi Gao[2], Geoff G. Z. Zhang[2], Lynne S. Taylor[1]

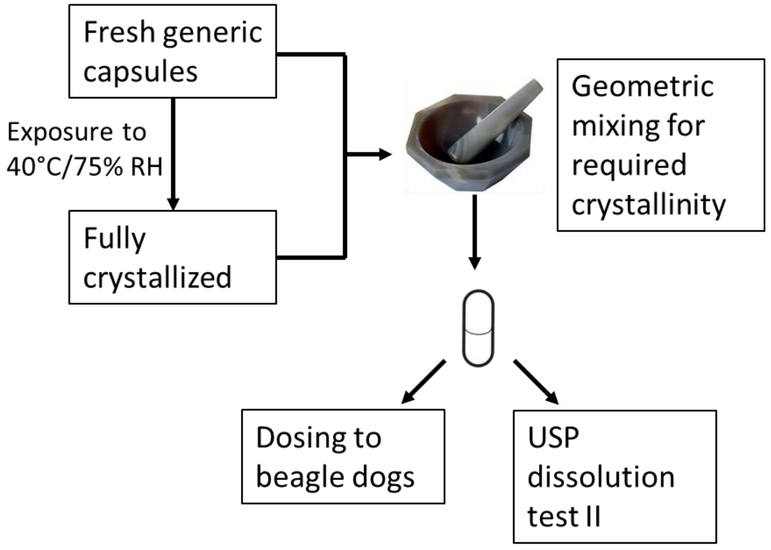
[1]Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN, [2]AbbVie Inc., IL

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
aaps

PURPOSE

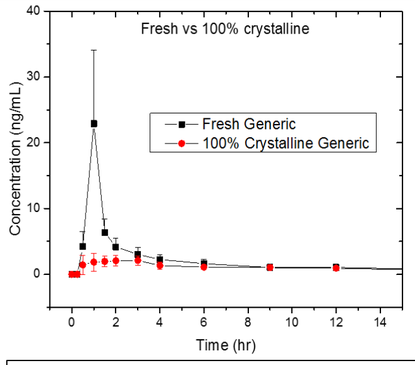
It has been observed that formulating a poorly soluble drug as an amorphous solid dispersion (ASD) can lead to an increase in the bioavailability. The drug in the ASD, being higher in free energy, can crystallize during storage or during the manufacturing process. If crystallization occurs, it can negatively impact the dissolution performance of the ASD thereby resulting into a decrease in the fraction absorbed. A number of studies in the literature have highlighted the implications of ASD crystallization during *in vitro* dissolution; however, studies relating the level of crystallinity to the dissolution and the bioperformance of (partially) crystalline ASDs have been very limited. Therefore, it was the aim of this research to study the impact of recrystallized tacrolimus ASD formulations on bioavailability in beagle dogs. The United States Pharmacopeia (USP) dissolution test II was also performed to assess the discriminatory power of the compendial test.

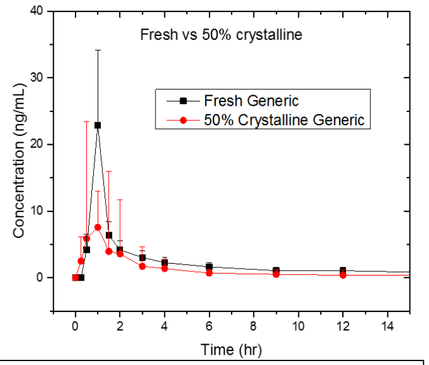
METHODS

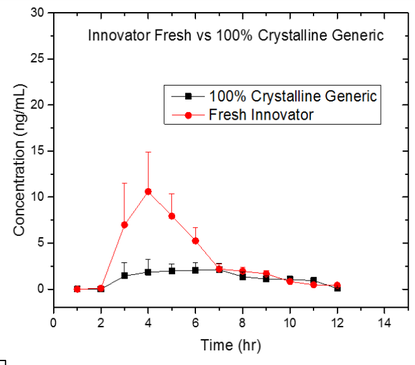


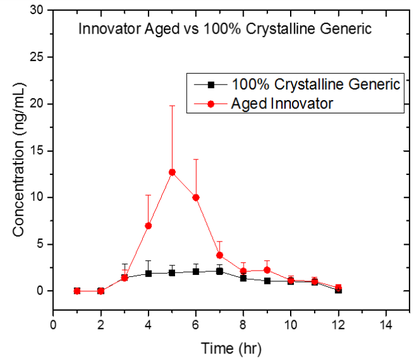
- **Tacrolimus analysis:** The dog plasma was analyzed by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) for tacrolimus. The LOQ was found to be 0.4 ng/mL. Tacrolimus in the dissolution medium was analyzed by HPLC using the method given in USP.
- **Scanning electron microscopy (SEM):** Capsule contents were added to water and filtered. The dried powder was imaged using Nova NanoSEM instrument.

RESULTS



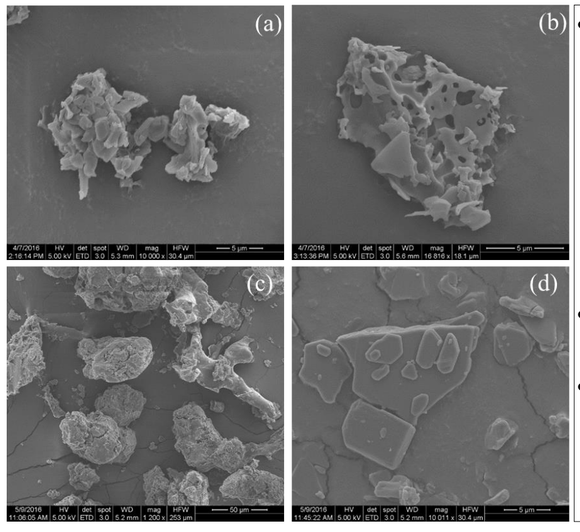




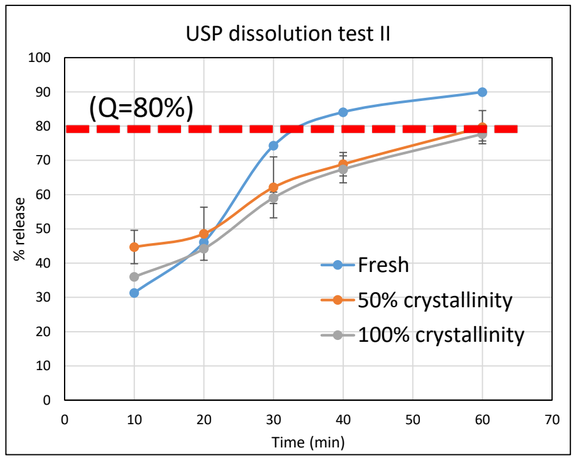


- The figures above show the plasma concentration versus time profiles for different levels of crystallinity.
- A decrease in the area under the curve (AUC) was not as significant as expected for generic capsules containing 50% and 100% crystalline tacrolimus (Table below). Based on data from literature, the AUC of pure crystalline tacrolimus monohydrate was found to be 1/10th of the ASD.
- The AUC for 50% and 100% crystallized generic was the same (90% C.I.) whereas the fresh and crystalline formulations showed different profiles.

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/mL)	F (%)
Generic fresh	25.3 (10.5)	0.83 (0.11)	42.1 (15.9)	1.94 (0.69)
Generic 50% crystalline	9.31 (3.13)	0.96 (0.21)	22.9 (7.2)	1.08 (0.31)
Generic 100% crystalline	3.84 (1.10)	2.8 (1.3)	21.6 (5.94)	1.03 (0.24)
Innovator fresh	16.8 (6.6)	1.3 (0.2)	44.0 (18.4)	2.12 (0.85)
Innovator aged	12.3 (4.3)	1.6 (0.5)	33.7 (10.5)	1.61 (0.46)



- The figure on the left shows SEM images of crystallized generic (a), fresh generic (b), fresh innovator (c) and crystalline tacrolimus (d).
- Crystals can be observed in (a).
- Fresh generic and innovator formulations seem very different.



- The tolerance criteria for USP dissolution test II is 80%.
- The generic formulations containing 0% and 50% crystallinity showed ~85% release in 60 min.
- Even the 100% crystalline generic showed ~80% release.

CONCLUSIONS

1. USP dissolution test II proved to be non-discriminatory for the fresh and crystalline formulations.
2. The recrystallized generic samples showed higher bioavailability than the reported literature value for pure crystalline tacrolimus, albeit with a lower AUC than the fresh generic capsules

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. D.J.O, G.J.J, D.F.S, W.G, Y.G. and G.GZ.Z. are AbbVie employees and may own AbbVie stock.