M1253

PURDUE UNIVERSITY

Stability of marketed Tacrolimus amorphous dispersions against crystallization

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Abstract

Purpose:
To determine the stability of commercial tacrolimus amorphous dispersion formulations to crystallization under accelerated storage conditions, the reason for any instability, and the effect on the dissolution profile.
Methods:
The capsule contents of six tacrolimus marketed products were analyzed for dissolution kinetics using non-sink conditions in 40ml pH 4.5 phosphate buffer utilizing a UV dip probe to monitor concentration as a function of time. The capsules were then placed under accelerated stability conditions (40°C/75%RH) with weekly sampling and analysis by X-ray powder diffraction. Quantification of crystalline content was done by preparing calibration samples made by mixing known amount of crystalline drug with fresh capsule contents. At the end of 4 weeks, the dissolution test was repeated on the powders. Reverse engineering of the products was done to determine the proportions of the various formulation constituents. The drug and hydroxypropyl methylcellulose (HPMC) concentration were determined by extracting the two using a methanol and dichloromethane mixture and then determining the drug concentration by UV spectroscopy and the HPMC content colorimetrically by using phenol and concentrated sulfuric acid. Croscarmellose sodium was determined by dissolving the capsule contents in buffer till complete dissolution of the drug and soluble excipients had occurred, followed by filtration and weighing the amount of material that was retained on the filter paper. Vapor sorption analysis was done for the products between 5-95% RH to determine the water sorption behavior.
Results:
The powder from the one of the commercially available capsules showed faster dissolution kinetics compared to the other products, whereby all the products resulted in the same maximum solution concentration within 30 minutes to an hour. After storage at 40°C/75%RH for a month, the dissolution of the product that had the faster dissolution rate when fresh, was drastically lowered compared to the other products; the dissolution rate for these products did not change significantly. X-ray analysis showed that the drug in this powdered sample had crystallized. X-ray analysis of the samples kept on stability showed that other than this product, which started to crystallize within one week, all the other powders were stable for the duration of the experiment. The product that crystallized contained approximately three times more croscarmellose sodium than the other prodcuts. The moisture sorption data also showed three times more water sorption for this product as compared to the other products, presumably due to the higher percentage
of croscarmellose sodium in this formulation.
Conclusion:
The tacrolimus amorphous solid dispersion manufactured by one generic manufacturer showed very low physical stability and crystallized within one week of storage under accelerated stability conditions. The faster crystallization rate is thought to be due to the higher amount of croscarmellose sodium in this product relative to other comparable products, that were physically stable.

Introduction

Amorphous solid dispersions (ASD) are a strategy to improve drug solubility and dissolution in cases where the drug crystal solubility in water is very low due to the increase in free energy of the amorphous solid relative to the crystalline form. This also results in an increased possibility for crystallization during processing and storage and thus polymers are generally added to the formulation to prevent their crystallization during processing and storage. Polymer stabilization occurs due to an increase in glass transition temperature and thus a decrease in the molecular mobility of the drug at room temperature.

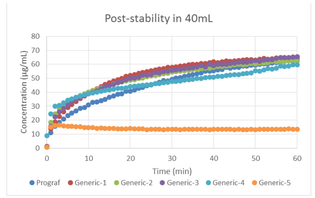
It is extremely important to prevent the crystallization of the drug in an ASD since this will result in a significant decrease in the bioavailability and thus failure of the product. Long term stability of drug products is generally evaluated using accelerated stability conditions to reduce the time frame of experiments and to get a better idea of the stability of the product. Since products are sometimes stored outside of their original packaging and in pill organizer boxes, it is important to study the stability outside of the original bottle. In this study different brands of marketed tacrolimus were evaluated for differences in their solid state stability.

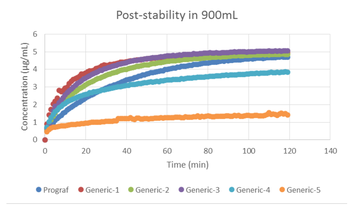
Methods

Drug used: Tacrolimus Monohydrate (Tac MH)
Products studied: Tacrolimus capsule products from the following companies were used Astellas Pharma, Mylan, Panacea Biotech, Dr. Reddys, Intas Pharma and Sandoz.
X-ray powder diffraction (XRPD): This was done using a Rikagu smartlab at angles between 5-20° at a scan speed of 2°/min. Calibration powder samples were prepared by weighing out specific amounts of tacrolimus MH powder and geometrically mixing into the fresh capsule contents.
In-house dispersion: Tacrolimus dispersions were prepared in different ways.
1. Tac MH was rotary evaporated by itself and mixed with HPMC, Croscarmellose sodium (CCS) and lactose in a ratio of (1:1:4:6)
2. Tac MH and HPMC were rotovapped together and mixed with the other excipients and
3. Tac MH and CCS were rotovapped together and mixed with the other excipients
Dissolution: Dissolution studies after keeping on stability were done in 40, 100 and 900ml in a dissolution media of pH 4.5 at 37°C. The drug concentration was determined using a UV dip probe from SI photonics.
Water sorption analysis: Water vapor sorption behavior of the powder samples were determined using a VTI-vapor sorption analyzer by weighing out 10-20mg of the capsule contents and determining the water vapor sorption isotherm at 25°C.
Supersaturation stability: The stability of tacrolimus solution at its amorphous solubility was determined in 100mL using a dip probe to determine the nucleation induction time and the desupersaturation profile in the presence and absence of HPMC.

Results and Discussion

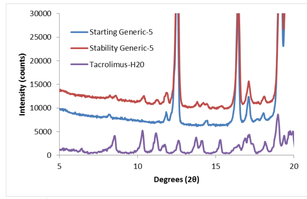
Dissolution of dispersions:

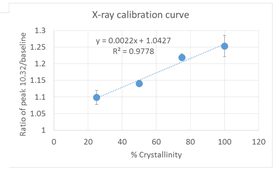


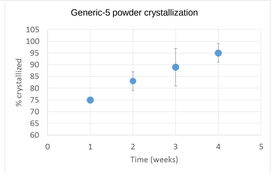


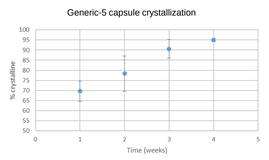
The dissolution of all the products after storing them at accelerated stability for 4 weeks showed that the generic-5 capsules had significantly deceased dissolution rate as well as final solution concentration at both sink and non-sink dissolution conditions.

XRPD analysis:







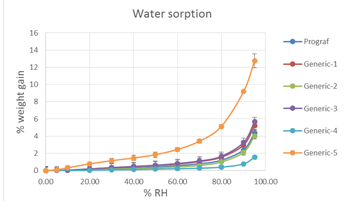


The generic-5 powder showed the clear presence of crystalline monohydrate peaks after storing at accelerated stability conditions. The peak between 10.3-10.4 was the only clear peak without interference by the excipients in the powder. Significant crystallization was observed within 1 week of storage and with nearly 95% of the drug crystallizing in 4 weeks. It did not appear to make a difference if the powder was outside the capsules or inside them.

Water vapor sorption:

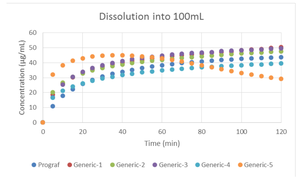
The water vapor sorption profile of the 6 powders showed that the generic-5 powder absorbed a significantly higher amount of moisture as compared to the other products. Generic-4 powder picked up the least amount of moisture due to the fact that most of the powder consisted of lactose monohydrate.

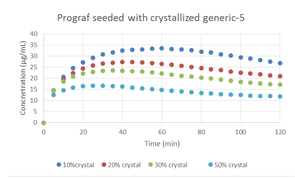
Reverse engineering of the products showed that all the products had a similar ratio of drug and polymer. Generic-4 had the highest amount of lactose. The main difference in generic-5 was the presence of a significantly higher amount of CCS.



Manufacturer	Tacrolimus (mg)	HPMC (mg)	Croscarmellose Na (mg)	Lactose and other excipients (mg)
Prograf	5	5.3(0.6)	5.8	121.4
Generic-1	5	4.8 (0.1)	5.5	84.5
Generic-2	5	5.2(0.8)	8.2	121
Generic-3	5	5.4(0.8)	4.1	126.5
Generic-4	5	4.9(0.4)	6	232
Generic-5	5	5.5(0.1)	21.5	100

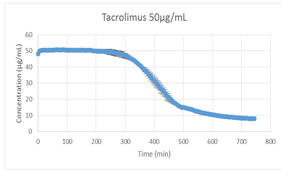
Dissolution into at-sink condition:

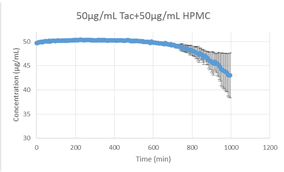




Dissolution into at-sink conditions with respect to the amorphous solubility after complete dissolution showed that the accord powder starting to desupersaturate after 30 minutes. This indicates that there might be some starting crystallinity in the sample since the seeding experiments with Prograf resulted in similar desupersaturation behavior.

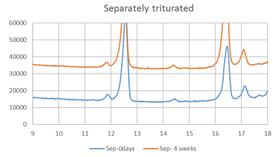
Supersaturation stability



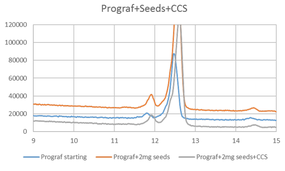


Supersaturation stability of tacrolimus in 100mL showed that in the absence of any polymer the drug spontaneously nucleates in 3-4h. In the presence of 50µg/mL HPMC the nucleation induction time increased to around 10h. The crystal growth rate also appeared to be inhibited in the presence of HPMC.

Potential reasons for crystallization



Powders prepared in the lab by physically mixing amorphous tac with the excipients were stable. Powders also prepared by solvent evaporation of Tac with CCS and then mixing with other ingredients were also stable. External seeding with crystalline tac MH and addition of CCS also did not result in crystallization of the drug.



Conclusions

Only one of the different products studied appeared to crystallize upon storage under accelerated conditions. The rate of crystallization was quite fast for this product since nearly all the drug seemed to crystallize in just one month under these conditions. It was even more surprising to see this behavior since amorphous tacrolimus prepared by solvent evaporation appeared to be stable even in the absence of a stabilizing polymer. Efforts are ongoing to better understand the poor physical stability of this system.

Acknowledgments

The authors thank the U.S. Food and Drug Administration for financial support under grant award 1U01FD005259-01