Physicochemical and Microbiological Stability of Tacrolimus Oral Extemporaneous Suspensions

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BACKGROUND:

Tacrolimus is an immunosuppressant commonly prescribed in both adults and children for the prevention of organ rejection in transplant patients. In the United States (US), tacrolimus for oral use is commercially available as capsules and granules (tacrolimus for oral suspension). The tacrolimus granules represent an important therapeutic alternative for children who cannot swallow the capsules. However, tacrolimus has a narrow therapeutic index and therefore it is important to adjust the dosage strength to meet the individual patient needs, particularly considering the pediatric population. There is a lack of an age-appropriate formulation for tacrolimus which allows dosing flexibility.

PURPOSE:

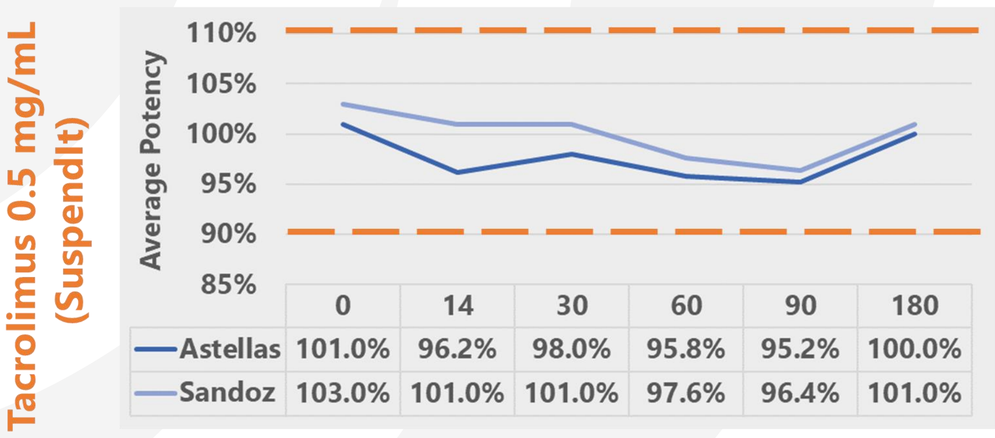
To develop a tacrolimus oral extemporaneous suspension with an extended beyond-use-date (BUD) for use particularly in pediatric patients.

METHOD:

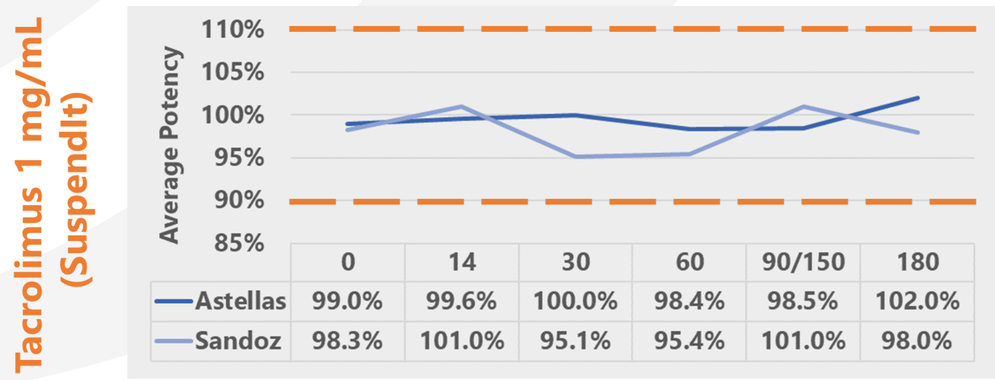
Oral extemporaneous suspensions for tacrolimus 0.5 and 1 mg/mL were prepared by adding the contents of tacrolimus 5 mg commercial capsules (Astellas and Sandoz) to an oral suspending vehicle (SuspendIt). A batch of 500 mL was prepared for each strength and for each commercial source of tacrolimus, which resulted in four different batches. Each of the oral extemporaneous suspensions were evenly distributed into six prescription oval amber plastic bottles and stored at room temperature for 6 months. At pre-determined time points [0 (baseline), 14, 30, 60, 90 (Astellas) / 150 (Sandoz) and 180 days], a study sample of each strength and each commercial source was withdrawn from the storage condition, shaken vigorously and tested for physicochemical and microbiological stability. The physical characterization consisted of observing all samples for appearance/color and testing for pH. The chemical characterization consisted of assay testing employing a stability-indicating High Performance Liquid Chromatography (HPLC) method (Waters Acquity) developed and validated by Eagle Analytical Laboratories (Texas, US). The microbiological stability followed the United States Pharmacopoeia (USP) Chapter <51> Anti-Microbial Effectiveness (AME) testing method.

RESULTS:

- The tacrolimus oral suspensions exhibited a homogeneous white color and the pH did not change significantly throughout the study, as follows: 4.79-5.28 (tacrolimus 0.5 mg/mL oral suspension, Astellas capsules); 4.91-5.40 (tacrolimus 0.5 mg/mL oral suspension, Sandoz capsules); 5.00-5.43 (tacrolimus 1 mg/mL oral suspension, Astellas capsules); and 5.05-5.19 (tacrolimus 1 mg/mL oral suspension, Sandoz capsules).
- The chromatographic assay method demonstrated to be linear, precise, accurate, robust and suitable, as well as stability-indicating.
- The percent potency was calculated taking into account the baseline measurements on day 0. The potency of the oral suspensions remained within ±10% of the specifications throughout the study, for the two commercial sources of tacrolimus, namely: Astellas (95.2%-101.0% and 98.4%-105.0% for tacrolimus 0.5 and 1 mg/mL); Sandoz (96.4%-103.0% and 95.1%-101.0% for tacrolimus 0.5 and 1 mg/mL).
- The preservative system in SuspendIt successfully protected the extemporaneous suspensions from microbial contamination since there was no growth of challenge microorganisms throughout the study for all samples.



	0	14	30	60	90	180
Astellas	101.0%	96.2%	98.0%	95.8%	95.2%	100.0%
Sandoz	103.0%	101.0%	101.0%	97.6%	96.4%	101.0%



	0	14	30	60	90/150	180
Astellas	99.0%	99.6%	100.0%	98.4%	98.5%	102.0%
Sandoz	98.3%	101.0%	95.1%	95.4%	101.0%	98.0%

CONCLUSION:

Oral extemporaneous suspensions may be rapidly prepared, allow dosing flexibility and are easy to administer. However, hospital pharmacists need validated stability studies to prepare oral liquids with high quality and safety. A palatable, sugar-free formula was developed for tacrolimus 0.5-1 mg/mL in SuspendIt to facilitate the extemporaneous preparation in the hospital setting. The corresponding BUD was determined using a valid, stability-indicating analytical method and it was concluded that the two versions of tacrolimus 5 mg commercial capsules (Astellas and Sandoz) are physically, chemically and microbiologically stable in SuspendIt at room temperature for up to 180 days.