Physicochemical and Microbiological Stability of Ursodiol Oral Compounded Suspensions

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ashp SUMMER MEETINGS & EXHIBITION 2022

Purpose

Ursodiol (ursodeoxycholic acid) is a naturally-occurring bile acid that is frequently prescribed in children with biliary atresia and cystic fibrosis. In the United States (US), ursodiol is commercially available as solid dosage forms (250, 300 and 500 mg) which represents a problem for children who cannot swallow capsules or tablets, and also for the caregivers who have to adjust the dosage strength to meet the individual patient needs. There is a lack of an age-appropriate formulation for ursodiol and the extemporaneous preparation of an oral suspension with an extended beyond-use-date (BUD) may represent a good therapeutic alternative for the pediatric population.

Methods

Oral compounded suspensions for ursodiol 20 mg/mL and 60 mg/mL were prepared by adding the contents of ursodiol 300 mg commercial capsules (Actavis®, KVK Tech® and Mylan®) to an oral suspending vehicle (PCCA SuspendIt®). A batch of 495 mL was prepared for each strength and for each commercial source of ursodiol, which resulted in a total of six different batches. The oral compounded suspensions were evenly distributed into six prescription oval amber plastic bottles and stored at room temperature for the study period of 6 months. At pre-determined time points [0 (baseline), 14, 30, 59, 90 and 181 days], a study sample of each strength and each commercial source was withdrawn from the storage condition, shaken vigorously and tested for physicochemical and microbiological stability.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 Ultra-High Performance Liquid Chromatography (UHPLC) 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.

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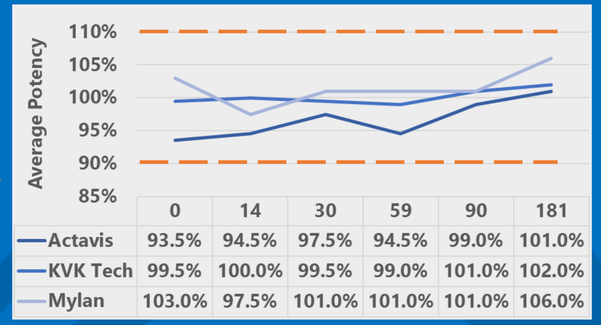
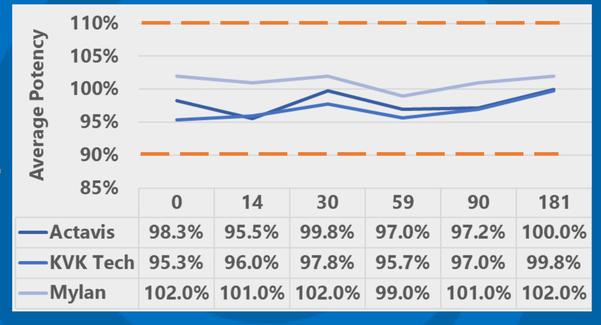
Ursodiol 20 mg/mL (SuspendIt)



	0	14	30	59	90	181
Actavis	93.5%	94.5%	97.5%	94.5%	99.0%	101.0%
KVK Tech	99.5%	100.0%	99.5%	99.0%	101.0%	102.0%
Mylan	103.0%	97.5%	101.0%	101.0%	101.0%	106.0%

Ursodiol 60 mg/mL (SuspendIt)



	0	14	30	59	90	181
Actavis	98.3%	95.5%	99.8%	97.0%	97.2%	100.0%
KVK Tech	95.3%	96.0%	97.8%	95.7%	97.0%	99.8%
Mylan	102.0%	101.0%	102.0%	99.0%	101.0%	102.0%

Results

Considering the physical characterization, the ursodiol oral suspensions exhibited a homogeneous white color and the pH did not change significantly throughout the study, as follows: 5.00-5.26 (Actavis ursodiol capsules); 5.00-5.24 (KVK Tech ursodiol capsules); and 5.10-5.50 (Mylan ursodiol capsules).

Considering the chemical characterization, 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 three commercial sources of ursodiol, namely: Actavis (93.5% - 101.0% for ursodiol 20 mg/mL and 95.5% - 100.0% for ursodiol 60 mg/mL); KVK Tech (99.0% - 102.0% for ursodiol 20 mg/mL and 95.3% - 99.8% for ursodiol 60 mg/mL); and Mylan (97.5% - 106.0% for ursodiol 20 mg/mL and 99.0% - 102.0% for ursodiol 60 mg/mL).

Considering the microbiological characterization, the preservative system in PCCA SuspendIt successfully protected the compounded suspensions from microbial contamination since there was no growth of challenge microorganisms throughout the study for all samples.

Conclusion

Oral compounded 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 ursodiol 20-60 mg/mL in a suspending vehicle to facilitate the extemporaneous preparation in the hospital setting.

The BUD was determined using a valid, stability-indicating analytical method and it was concluded that the three versions of ursodiol 300 mg commercial capsules (Actavis, KVK Tech and Mylan) are physically, chemically and microbiologically stable in PCCA SuspendIt at room temperature for up to 180 days.