Physicochemical and Microbiological Stability of Compounded Bethanechol Chloride Oral Suspensions in PCCA Base, SuspendIt®

Y.V. Pramar[1], C. Davis[2], K. Ip[2], D. Banov[2]

[1]College of Pharmacy, Xavier University of Louisiana, New Orleans, Louisiana, USA; yvpramar@xula.edu
[2]Professional Compounding Centers of America, Houston, Texas, USA

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BACKGROUND

Bethanechol chloride is a cholinergic agent used to treat acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention. It is available in the United States as tablets for oral administration in four dosage strengths: 5 mg, 10 mg, 25 mg and 50 mg. A review of the therapeutic uses of bethanechol chloride reveals the need for flexibility in dosing. This flexibility is readily achieved using an oral liquid dosage form. However, no commercial liquid dosage form of bethanechol chloride currently exists. An extemporaneously compounded suspension from pure drug powder or commercial tablets would provide a flexible, customizable option to meet unique patient needs with convenient and accurate dosing options.

PURPOSE

To determine the physicochemical and microbiological stability of extemporaneously compounded bethanechol chloride suspensions using two brands of commercially available tablets (Amneal and Upsher-Smith) in the proprietary oral vehicle PCCA Base, SuspendIt, a sugar-free, paraben-free, dye-free and gluten-free thixotropic suspending agent containing a natural sweetener obtained from the monk fruit. It thickens upon standing to minimize settling of any insoluble drug particles, and becomes fluid upon shaking to allow convenient pouring during administration to the patient.

METHOD

Suspensions of bethanechol chloride were prepared from two generic brands of commercial tablets in PCCA SuspendIt at 1-mg/mL and 5-mg/mL concentrations, to represent a range in which the drug is commonly dosed. Samples were stored in plastic amber prescription bottles at room temperature (25^{0}C). Samples were assayed initially, and at pre-determined time intervals (14, 30, 60, 90 and 180 days) over a 6-month period. The chemical characterization employed a stability-indicating Ultra High Performance Liquid Chromatography (UPLC) assay method (Waters Acquity) developed and validated by Eagle Analytical Laboratories (Texas, USA). Physical data such as pH and appearance were noted. Samples were also tested for microbiological stability in compliance with the United States Pharmacopoeia (USP) Chapter <51> Anti-Microbial Effectiveness (AME) testing method.

RESULTS

- Bethanechol chloride tablets formed a homogeneous yellow suspension in PCCA SuspendIt. The pH range (4.83-5.42) for both drug concentrations displayed no significant changes over the test period.
- The UPLC assay method was validated by evaluating the system specificity, linearity and range, accuracy and recovery, precision (repeatability and intermediate), solution stability, robustness, and suitability.
- Drug concentrations were calculated in mg/mL and also as a percentage based on the initial measurements on day 0. The concentrations of the bethanechol chloride suspensions remained within ±10% of the USP specifications (93-106%) throughout the study (Tables 1 & 2).
- The antimicrobial preservative system in SuspendIt successfully protected the oral compounded suspensions from microbial contamination by preventing growth of challenge microorganisms throughout the study for all samples.

Table 1. Bethanechol Chloride Concentration (mg/mL) in PCCA SuspendIt

Time	1-mg/mL		5-mg/mL	
	Amneal	**Upsher-Smith**	**Amneal**	**Upsher-Smith**
Day 0	0.975	1.01	4.75	4.65
Day 14	1.00	1.06	4.78	4.80
Day 30	0.981	1.00	4.83	4.86
Day 60	0.977	1.01	4.84	4.75
Day 90	0.995	1.02	4.81	4.72
Day 180	1.03	0.99	4.78	4.75

Table 2. Percent of Bethanechol Chloride in PCCA SuspendIt Relative to Day-Zero Concentration

Time	1-mg/mL		5-mg/mL	
	Amneal	**Upsher-Smith**	**Amneal**	**Upsher-Smith**
Day 0	97.5	101	95	93
Day 14	100	106	95.6	96
Day 30	98.1	100	96.6	97.2
Day 60	97.7	101	96.8	95
Day 90	99.5	102	96.2	94.4
Day 180	103	99	95.6	95

CONCLUSION

A robust stability indicating UPLC assay method for the determination of bethanechol chloride in PCCA SuspendIt was used to determine the chemical stability of the 1-mg/mL and 5-mg/mL concentrations of Bethanechol Chloride tablets in PCCA SuspendIt at 25^{0}C. This study demonstrated that bethanechol chloride suspensions in PCCA SuspendIt are physically, chemically and microbiologically stable at room temperature at both concentrations studied for up to 180 days, thus providing a viable, compounded alternative for bethanechol chloride in a liquid dosage form with an extended beyond-use-date to meet patient needs.