

Abstract: Suspensions are pharmaceutical dosage forms consisting of insoluble APIs dispersed in a vehicle. An ideal suspension should be uniform in content so that each dose is equivalent in the amount of APIs. The purpose of this study was to evaluate the content uniformity of eight suspensions, each containing one API dispersed in SuspendIt, a proprietary suspending vehicle with a synergistic polymer complex (patent pending), which gives suspensions the ability to thin with agitation and thicken upon standing. This study has demonstrated that all eight SuspendIt formulations were uniform in content. By following the SOPs set forth in the PCCA formulas, compounding pharmacists are thus likely to meet the requirements of content uniformity and, as a result, dispense unit dose oral syringes in accordance to the label claim.

Introduction:

Suspensions are pharmaceutical dosage forms consisting of insoluble active pharmaceutical ingredients (APIs) dispersed in a liquid medium (suspending vehicle). The type of suspension varies depending on the route of administration (e.g., oral, topical or injectable suspensions). Oral suspensions, being the most common, are advantageous in their ability to allow for easy swallowing of medication by pediatric and geriatric patients, in comparison to solid dosage forms. However, due to the heterogeneous nature of suspensions, the insoluble APIs have a tendency to settle at the bottom of containers upon standing. For this reason, if patients forget to shake the suspensions or do not shake adequately prior to each dose administration, the content uniformity and dosing accuracy of the medications may be compromised [1]. Content uniformity is defined as the consistency in the amount of APIs among dosage units. An ideal suspension should be uniform in content so that each dose is equivalent in the amount of APIs [2]. Content uniformity within a suspension is highly dependent on the characteristics of the suspending vehicle. If a suspending vehicle is too viscous, the APIs will not be easily dispersed. In contrast, if the suspending vehicle is too thin, the APIs will settle at the bottom of the container [1]. The purpose of this study was to evaluate the content uniformity of eight suspensions, each containing one API dispersed in SuspendIt.

SuspendIt is a proprietary suspending vehicle with a synergistic polymer complex (patent pending), which gives suspensions the ability to thin with agitation and thicken upon standing. This characteristic is very important in suspensions as the polymer complex can enhance redispersion and minimize sedimentation of APIs [3].

Methodology:

The evaluation of the content uniformity of the eight SuspendIt formulations was divided in three stages: elaboration of the suspensions; preparation of the unit dose oral syringes; and High-Performance Liquid Chromatography (HPLC) assay.

(1) Elaboration of the suspensions: The 8 suspensions were elaborated (compounded) in accordance with the Standard Operating Procedures

(SOPs) indicated in the respective PCCA Formulas (Table 1). Each suspension included one API dispersed in SuspendIt (APIs and dosage strengths are displayed in Table 1) in a total volume of 150 mL.

(2) Preparation of the unit dose oral syringes: For each SuspendIt formulation, the total volume of 150 mL was divided in 30 unit dose oral syringes of 5 mL each; suspensions were shaken prior to the drawing of each unit dose. An example of oral syringes is displayed in Figure 1. In accordance with the United States Pharmacopeia (USP) General Chapter <905> "Uniformity of Dosage Units" [2], a random sample of 10 unit dose oral syringes was selected and tested individually for each SuspendIt formulation, using an appropriate analytical method for chemical characterization.



Figure 1. Unit dose oral syringes.

(3) HPLC assay: The content of uniformity of the eight SuspendIt formulations was measured by reverse phase HPLC. The chromatographic system (Waters 2695, Alliance) used a reversed phase C18 column (Xbridge C18, 4.6 x 150 mm, 5 μm, Waters), which was maintained at 40°C. The mobile phase was composed of acetonitrile, or methanol, and water acidified with formic acid 0.1%, in selected ratios depending on the API analysis. The injection volume was 10 μL and the flow rate was maintained at 0.8 to 1 mL/min. Each sample was injected twice. The chromatographic system was equipped with a Photodiode Array (PDA) detector (Waters 2998, Alliance) and detection was carried out at variable wavelength according to the maximum absorption of each API. The data acquisition software was Empower 3 feature release 2.

Table 1. PCCA formula number and chemical characterization of eight SuspendIt formulations.

SuspendIt Formulation	PCCA Formula	Mean Potency (%)	Acceptance Value (%)
Omeprazole 2 mg/mL	11262	91.51	14.90
Captopril 5 mg/mL	11201	102.63	5.15
Enalapril Maleate 0.5 mg/mL	11200	106.23	7.46
Hydrochlorothiazide 10 mg/mL	11202	106.18	8.59
Metronidazole 50 mg/mL	11203	108.53	9.69
Nystatin 100,000 Units/mL	11204	100.06	3.25
Rifampin 10 mg/mL	11206	103.08	3.66
Vancomycin HCl 50 mg/mL	11209	92.72	9.21

Results and Discussion:

The content uniformity is determined by calculating the Acceptance Value (AV), which is the limit that the observed mean potency is allowed to deviate from the label claim [1]. In accordance to the USP General Chapter <905> “Uniformity of Dosage Units,” the requirements for dosage uniformity are met if the AV of the 10 unit doses is $\leq 15\%$. If the AV is $>15\%$, 20 additional unit doses must be tested and the AV recalculated [2]. The AV for all eight SuspendIt formulations was $<15\%$ (Table 1) and, therefore, the requirements for dosage uniformity were met and there was no need for additional testing. The test for content uniformity demonstrated the consistency of unit doses for all eight SuspendIt formulations. In practice, if 5 mL of omeprazole 2 mg/mL in SuspendIt were to be administered to a patient, since each unit dose has an API content within a narrow range around the label claim, the patient would consistently receive approximately 10 mg of omeprazole.

Conclusions:

It is the pharmacists’ responsibility to ensure that compounded medicines are dispensed in accordance to the label claim [5]. For unit dose preparations, the content of uniformity must be ensured so that all individual units meet the label claim. The content of uniformity is particularly important when dispensing unit dose oral suspensions as, depending on the characteristics of the suspending vehicle, APIs may not be evenly dispersed or may settle at the bottom of the container, resulting in oral syringes of variable concentrations [4]. The Food and Drug Administration (FDA) requires that SOPs are followed in the preparation of oral suspensions to ensure the quality

and safety of compounded medicines. Therefore, the FDA may warrant testing of oral suspensions to ensure that segregation has not occurred and that the content of each unit dose is uniform [6]. This study has demonstrated that all eight SuspendIt formulations were uniform in content. By following the SOPs set forth in the PCCA formulas (Table 1), compounding pharmacists are thus likely to meet the requirements of content uniformity and, as a result, dispense unit dose oral syringes in accordance to the label claim.

References:

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