



Suspensions as a Valuable Alternative to Extemporaneous Compounded Capsules



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INTRODUCTION

Although commercial/licensed medication is preferred, it is not always suitable for all patient groups. This is especially true for pediatric and geriatric patients who frequently need medication in an adjusted dose or form.

For the aging population, there are age-related physiological changes and alterations in pharmacokinetics, such as drug metabolism, distribution, and excretion.¹ In case of pediatrics, they often show a different response to both active ingredients and excipients.²⁻³ The rapid development and maturation of the body composition of children result in a continuum of growth and developmental phases, where body size and weight of an average child increases up to 20-fold from birth to maturity, and dose variation throughout childhood may be 100-fold.⁴⁻⁵ Furthermore, children display a different pharmacokinetic profile compared to adults. Important differences are the developmental changes in absorptive surfaces such as the gastrointestinal tract, skin, and pulmonary tract that can influence the rate and extent of the bioavailability of a drug.³ Due to these widespread variabilities in pediatrics, it is often challenging for the (hospital)

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ABSTRACT

The objective of this study was to determine the variation in content of 74 different active pharmaceutical ingredients and compare it with what is known in the literature for the content uniformity of extemporaneous prepared capsules. Active pharmaceutical ingredients quantification was performed by high-performance liquid chromatography, via a stability-indicating method. Samples for all active pharmaceutical ingredients were taken throughout a 90-day period and the content was determined. In total, 5,190 different samples were analyzed for 74 different active pharmaceutical ingredients at room (15°C to 25°C) and controlled refrigerated temperature (2°C to 8°C). Each of these datasets was analyzed according to the *United States Pharmacopeia's* Content Uniformity monograph, corrected for the sample number. The mean acceptance values were well within specifications. In addition, all suspensions complied with the criteria defined by the *British Pharmacopoeia* monograph for Content Uniformity of Liquid Dispersions for both room and controlled refrigerated temperature. In previous studies, it was found that a routine weight variation check is often not sufficient for quality assurance of extemporaneous prepared capsules. Compounded oral liquids show little variation in content for 74 different active pharmaceutical ingredients; therefore, compounded oral liquids are a suitable alternative when compounding individualized medication for patients.

pharmacists to find suitable commercially available medications for their patients.⁶

Dysphagia or swallowing difficulty is another reason why children and elderly adults require customized medication. Solid dosage forms are frequently unsuitable until the age of six and 25% to 45% of all children suffer from dysphagia.⁷⁻⁹ Additionally, it is estimated that 35% to 68% of the people in elderly homes have some degree of swallowing dysfunction,¹⁰⁻¹¹ and, even in the general population, the prevalence of swallowing difficulties is reported to be between 16.5% and 37.4%.¹²⁻¹³

In these cases, pharmacists often compound extemporaneous prepared capsules for their patients. The drug substance content should be within the pre-determined range as defined by the various pharmacopoeias, including the *United States Pharmacopeia (USP)*, the *European Pharmacopoeia (EP)*, and the *British Pharmacopoeia (BP)*.¹⁴⁻¹⁶ Pharmacists have two tests available to determine if solid preparations meet the pharmacopoeia requirements: weight variation (WV) and uniformity of content (CU). Both tests have been harmonized (by large) between the various pharmacopoeias.¹⁴⁻¹⁶

In this article, the *USP* monograph is being used to determine the CU.¹⁶ Although the *USP* specifically describes that the WV is only valid for higher-dosed capsules, in practice the weight variation test is regularly performed by pharmacists in case of small batch-sized extemporaneous compounded capsules. Various studies have, however, shown that even though compounded capsules might meet the requirements for the weight variation, the uniformity of content may not be within specifications.¹⁷⁻²⁰ The narrow therapeutic window of many medicines implies that small deviations in the content can significantly affect patient safety.

Extemporaneous compounded oral liquids are often a more convenient and better adhered alternative to capsules. Liquids are comparatively swift to prepare and can allow dosage flexibility from a single strength by adjusting the volume, although pharmacists sometimes struggle to obtain physical and chemical stable formulations.²¹⁻²² SyrSpend SF is an oral liquid vehicle range that displays *active suspending technology* to safeguard accurate dosing throughout therapy. The thixotropic behavior prevents active pharmaceutical ingredients (API) settling by increasing the viscosity when left undisturbed. The pseudoplastic behavior facilitates homogenization by lowering the viscosity when shaken. The starch used in SyrSpend SF makes the suspending agent highly compatible, as it has already been shown for a wide range of APIs from different pharmaceutical classes.²³⁻³⁷

In the current study, we have used the stability data that had been obtained during previous performed stability studies of 74 different APIs with SyrSpend SF to determine the content variation for these APIs and compare it with what is known for the CU of extemporaneous prepared capsules.

MATERIALS AND METHODS

All data presented were performed by a single, International Organization for Standardization, good laboratory practice validated lab. The stability of each individual API in SyrSpend SF was assessed by measuring the percent recovery at varying time points throughout a 90-day period. In short, API quantification was performed by high-performance liquid chromatography (HPLC-UV), via a stability-indicating method. Methods and their acceptance criteria were established on the basis of *USP* protocols³⁸ and International Conference on Harmonisation guidelines.³⁹ Samples were subjected to stress conditions (acid, base, ultraviolet, and heating) during the forced-degradation studies. These forced-degradation parameters were applied to validate the HPLC method which was used to assay the samples. Precision and repeatability were determined. For the stability study, pharmaceutical raw materials were used. Samples were assayed by HPLC at pre-determined time points to verify the stability of the API in SyrSpend SF. The samples were shaken manually for 1 minute to simulate patient dosing. Adequate volumetric aliquots for quantification were withdrawn from the middle of the bottles without contacting the inner surface of the bottle. They were appropriately diluted to obtain work solutions in the concentrations described under "Chromatographic Conditions."

Samples were taken at several time points, including 0 (baseline), 7, 14, 30, 60, and 90 days. All suspensions were immediately assayed six times at each time point. The evaluation parameter was the percent recovery (%) with respect to T = 0 using HPLC. Mean and standard deviation were calculated for all data-points combined.²³⁻³⁷

For assessing the CU, the *USP* describes that no less than 30 units need to be selected, of which 10 are being assayed. This applies to both solid and liquid dosage forms. The acceptance value (AV) for the CU is calculated using:

$$\text{Acceptance value} = |M - \bar{X}| + ks$$

M: Reference value,

- If $98.5\% \leq \bar{X} \leq 101.5\%$, the $M = \bar{X}$ ($AV = ks$)
- If $\bar{X} \leq 98.5\%$ then $M = 98.5\%$ ($AV = 98.5 - \bar{X} + ks$)
- If $\bar{X} \geq 101.5\%$ then $M = 101\%$ ($AV = X - 101.5 + ks$)

\bar{X} : Mean of the individual contents (x_1, x_2, \dots, x_n)

x_1, x_2, \dots, x_n : individual contents of the units tested, expressed as a percentage of the dosage strength.

n: Sample size (number of units in a sample)

k: Acceptability constant

s: Standard deviation of the sample

L_1 : Maximum acceptance value = 15.0 (unless otherwise specified)

L_2 : Maximum allowed range for deviation of each dosage unit tested from the calculated value of $M = 25.0$ (unless otherwise specified)

The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L_1 . If the acceptance value is greater than L_1 , another 20 dosage units need to be tested. The requirements are then met if the final acceptance value of the 30 dosage units is less than or equal to L_1 , and no individual dosage unit is less than 75% or more than 125% of the declared dose.

The acceptability constant (k_1) for the first 10 samples is 2.4; the acceptability constant (k_2) for 30 samples is 2.0.¹⁶ As pharmacists struggle to have large sampling from smaller compounded batches, acceptability constant for more limited sampling plans are being described in practical pharmaceutics. It is calculated that in case of 6 samples, k_1 is 3.0 and k_2 is 2.0.⁴⁰

In addition to the CU test of the different pharmacopoeias, the *BP* has a specific monograph on the Content Uniformity of Liquid Dispersions. Homogeneity and resuspendability of a liquid dispersion complies if each dose is between 85% and 115% of the average dose. The preparation fails if more than one dose (out of 10) is outside of these limits or if one individual dose is outside the limits of 75% to 125%.¹⁴

RESULTS

In total, 5,190 different samples were analyzed for 74 different APIs at both room (15°C to 25°C) and controlled refrigerated temperature (2°C to 8°C). One API was studied at controlled refrigerated temperature only, as it was known to be unstable at room temperature. Within the data, each time point for each individual

API represents a dataset of 6 measurements, for both room and controlled refrigerated temperature. Therefore we analyzed these datasets in accordance to the CU monograph, corrected for the sample number of 6 as described by practical pharmaceuticals. Calculations were only performed until the maximum beyond-use date of the sample. The acceptance values were calculated for all 74 different APIs, at all time points and at both temperatures. The mean AV for room temperature and controlled refrigerated temperature are 3.20 and 3.24, respectively. As shown from all the AVs plotted in Figure 1, not a single AV was more than L_1 , indicating that all APIs comply with the content uniformity monograph of the *USP*.

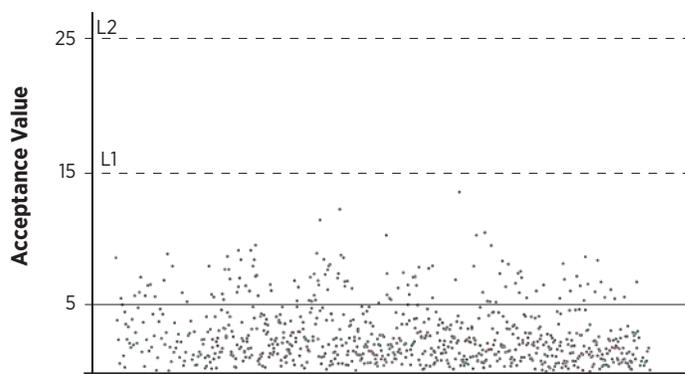
The *BP* describes a method of evaluating the CU of suspensions. When the *BP* CU of Liquid Dispersions is used, all APIs comply with both room temperature and controlled refrigerated temperature. The mean concentration of all samples was 100.02% with a standard deviation of 3.52%. The highest concentration measured in the 5,190 samples was 110.46%, the lowest 89.54%. All individual data-points are displayed in Figure 2.

DISCUSSION

To our best knowledge, this is the first study that has so extensively evaluated the content variation of a liquid administration aid.

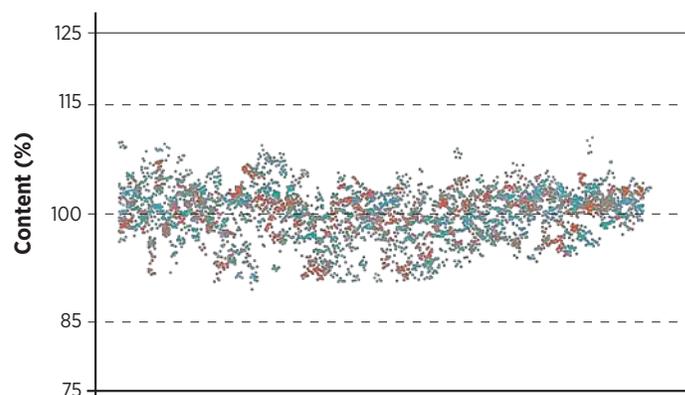
Compounding capsules is applied daily in pharmacy practice. In case of small-batch preparations, weight variation tests are generally being performed to validate the compounding process. Various studies have, however, shown that even though compounded capsules might meet the weight variation requirements, the content may not be within specification. At the Department of Pharmaceutical Technology, Faculty of Pharmacy at the University of Athens in Greece, a recent study was performed by Tzouanaki et al among 10 different pharmacies for both 60 chartulaes (folded powders) of 2 mg of spironolactone and a 2 mg/mL of suspension. The chartulaes of 5 pharmacies were evaluated; of the remaining 5 pharmacies, the suspensions were evaluated. The study revealed that only 1 out of 5 produced batches of chartulaes satisfied the requirements for uniformity of weight. Only one other batch was in conformance to the specifications for the uniformity of content, with a range from 84% to 165% of the declared content, whereas all 5 suspensions satisfied the requirements of the *EP*.⁴⁰ A Brazilian study with 40-mg simvastatin capsules showed that only 14 out of 18 and 11 out of 18 capsules were within specification for the weight variation and content, respectively.¹⁷ Colucci et al evaluated 1-mg micro-dose extemporaneously compounded captopril capsules, commonly used for the initial dose titration in patients with congestive heart failure. In practice, variability in patient's response has been observed with the micro-dose captopril capsules. The 48 extemporaneously prepared micro-dose captopril capsules were within acceptable limits for weight variation described in the *USP*. Content analysis revealed a mean content of $1.27 \text{ mg} \pm 0.31 \text{ mg}$ (range; 0.84 mg to 1.96 mg), indicating that the actual dose administered to the patients could vary by as much as 25%.¹⁸

FIGURE 1. THE INDIVIDUAL CALCULATED ACCEPTANCE VALUES.



DOTTED LINES INDICATE THE L_1 AND L_2 CRITERIA DESCRIBED IN THE *UNITED STATES PHARMACOPEIA*. THE RED DOTS ARE SAMPLES STORED AT ROOM TEMPERATURE, AND THE BLUE DOTS WERE STORED AT CONTROLLED REFRIGERATED TEMPERATURE.

FIGURE 2. THE CONTENT (IN PERCENTAGE) MEASURED IN ALL INDIVIDUAL DATA-POINTS.



DOTTED LINES INDICATE THE 100% TARGET AND THE FIRST RANGE (85% TO 115%) PRESCRIBED IN THE *BRITISH PHARMACOPEIA*. THE RED DOTS ARE SAMPLES STORED AT ROOM TEMPERATURE, AND THE BLUE DOTS WERE STORED AT CONTROLLED REFRIGERATED TEMPERATURE.

In a study with 22 samples, each consisting of 50 capsules of either a low (0.1 mg) or higher (1 mg) sodium chloride dose, all capsules met the *USP* requirements for weight variation. The CU analysis revealed, however, that in the low dose group 64% of the capsules did not meet the criteria. The average content was 89% with a range between 53.1% and 105.5%. In the higher-dose group, 46% of the capsules were out of specification, with an average of 86.1% (78.1% to 95.3%) of the labelled concentration.¹⁹

These studies show that a routine weight variation check is not sufficient for quality assurance of capsules, and confirms that for lower concentrations, a higher percentage of non-conformity is

found. A study performed by D'Hondt indicated the mortar surface as the largest API loss-location during the manual compounding of capsules.⁴¹

A recent study indicates that a V-blender and sieving are needed to optimize homogenous API distribution and prevent segregation to be able to comply to the content uniformity.²⁰ In addition, dyes are being used in practice to evaluate homogeneity of the powder mixture. A recent study by Hoffmann et al, however, indicate that a visual even distribution of the color does not necessarily have to correlate with a quantitative homogeneity of the mixture.⁴²

The study presented was performed with pharmaceutical raw materials. Due to convenience and availability of ingredients, oral liquids are frequently prepared from commercially available solid dosage forms, which may contain dilution, flow, and disintegration, promoting excipients, colorants, flavors, and binding agents next to the API.²¹ The recently accepted study of SyrSpend SF has shown that there is no influence of the excipients of capsules and tablets of 5 different APIs.⁴³

A clear advantage of the use of capsules over oral liquids is that no preservatives are needed. This is especially important in the case of neonates and young children, as the use of preservatives should be limited within that patient group.⁴⁴

CONCLUSION

As was shown by various studies, for many extemporaneously compounded capsules a routine weight variation check does not seem to be sufficient to guarantee the right content. Compounded oral liquids showed little variation in content for 74 different APIs, and when evaluated according to the USP's CU guidelines and the BP's Content Uniformity of Liquid Dispersions guidelines, all were well within the criteria defined. Therefore, this indicates that compounding oral liquids could be a suitable alternative when compounding individualized medication for patients.

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