Homogeneity of Dosage Forms

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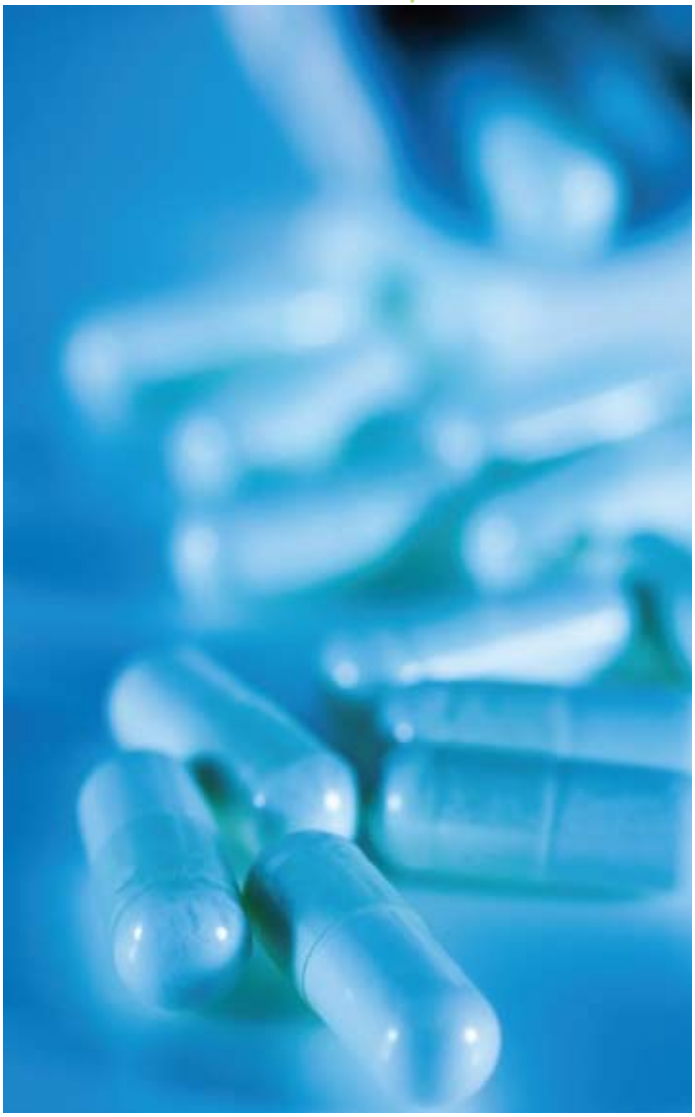
ABSTRACT Content uniformity is the degree of consistency in the amount of the drug substance among dosage units. There are two ways to determine content uniformity according to *United States Pharmacopeial* Chapter <905>; by means of *Content Uniformity* or *Weight Variation* methods. It is essential that compounding pharmacists know the different methods, how they work, and when to use each method to determine the content uniformity of their individual dosages.



Have you ever made a batch of 100 tablets or capsules and thought that every one was identical to the next, or did you think to yourself…close enough? There is a way for you to confirm that they are within the United States Pharmacopeial standards for content uniformity. You just need to know how and when to test your batch. First and foremost, verifying the uniformity of your compounded preparations will help ensure the safety and health of the patient, which is the overall goal of any preparation you are making. This is a process that needs to be clearly defined so that time and money are not wasted as a result of doing quality assurance incorrectly.

Oftentimes, pharmacists will weigh out every type of dosage form to perform their quality check (i.e., Weight Variation (WV) method). If this is you, keep reading! This is appropriate in some situations, but there are many situations where this is not the correct method to establish uniformity. Simply ensuring that each individual dosage unit weighs approximately the same in no way means that the active pharmaceutical ingredient (API) in each unit is equal, as the blended powder may not be uniform. There can be variability in the inactive ingredients versus the active drug in each individual tablet, but the mean average could still show an acceptable weight. For example, if you are making batches of 200 tablets or 200 capsules and want to verify the contents of each individual dose but are not sure where to start, then first you need to determine whether the Content Uniformity (CU) or WV method can be used. Some questions you should be asking yourself are: Is the tablet coated or uncoated? Does the API represent 25 mg or greater and more than 25% of the total weight? Are the capsules hard or soft? These types of questions and this article will help outline the proper way to measure the homogeneity of different compounded dosage forms using CU and WV methods, and when to apply each test.

RESPONSIBILITIES OF COMPOUNDING PHARMACISTS

Every pharmacist is responsible for the preparations they compound, as outlined in the *United States Pharmacopoeia (USP)* Chapter <1075> Good Compounding Practices, which discusses the

TABLE 1. Application of Content Uniformity and Weight Variation Tests for Dosage Forms.[1]

Dosage Form	TYPE	SUBTYPE	DOSE AND RATIO OF DRUG SUBSTANCE	
			≥25 MG AND ≥25%	<25 MG OR <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules			WV	WV
Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

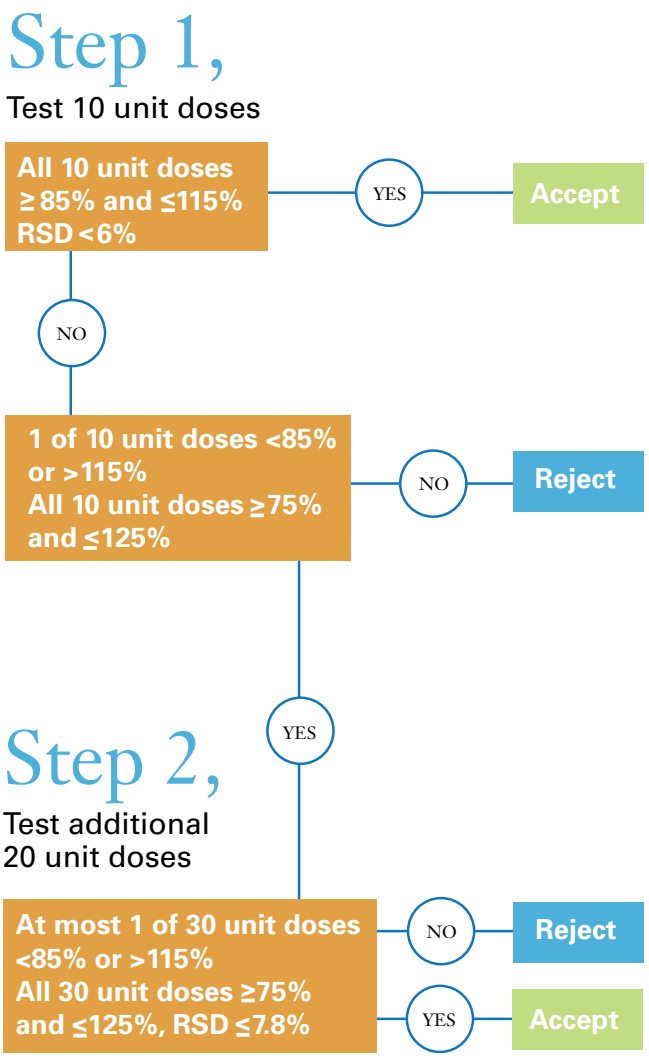
CU = content uniformity
WV = weight variation

controls required by compounding pharmacists to ensure identity, strength, quality, and purity. Each step in compounding is critical to the outcome of the final preparation. Mixing, pH differences, clarity of components, and capsule weight variation can all contribute to differences in content uniformity.[1]

UNIFORMITY OF DOSAGE UNITS

Conventionally, the mean potency of the API is allowed ± 10% deviation from the label claim, and the potency result is derived from testing of a composite mixture of 10 to 20 unit doses. However, in the compounding environment, the potency for a compounded preparation is usually determined from fewer than the required number of unit doses that made up the assay sample, and the test result may not represent the mean potency of a compounded preparation. It is especially critical when the processes involved in compounding have not shown, or the personnel have not demonstrated, the compounding of a homogeneous preparation. Uniformity of a dosage unit is defined by *USP* Chapter <905> as the degree of uniformity in the amount of the drug substance among dosage units.[1] The *USP* has published a set of specific guidelines geared towards the pharmaceutical industry demonstrating two methods—CU and WV—that can be used to evaluate the uniformity of dosage forms.[1]

FIGURE 1. USP Testing Procedure for Tablets.[4]



RSD = relative standard deviation

Content Uniformity

The CU test can be applied in all cases as the gold standard, which uses a specified number of dosages (e.g., 10 unit doses) in an assay procedure outlined in each monograph to determine the API content for each unit dose. The CU test is performed in an analytical laboratory setting where the contents of each individual dosage unit are chemically determined. The method used in content uniformity testing separates the active from the inactive ingredients in each unit dose and evaluates the potency of each active ingredient against the reference standard for the respective drugs.[1] In the CU method, there are two sources of variation: variability of the dosage unit (lack of homogeneity) and the measurement (analytical) error.[2] Analytical variation can be minimized during method validation to reduce any possible systematic errors. Uniformity is then determined by calculating the Acceptance Value (AV). The AV is the limit that the observed mean potency is allowed to deviate from the label claim. The value of AV is derived from the sum of two components; (1) the difference between the observed mean and the reference value, and (2) the width of the tolerance interval.[2] So, accepting or rejecting a batch depends on the width of the tolerance interval and on the shift of the mean from the target value.[2] AVs are not required for suppositories, transdermal systems, and inhalations packaged in premetered dosage units.[1]

CU is the test required for the following dosage forms (see Table 1):[1]

- Transdermal systems (e.g., patches)
- Suppositories
- Coated tablets (other than film-coated) containing 25 mg or more of a drug of a drug substance that comprises 25% or more (by weight) of one tablet
- Suspension or emulsions or gels in single-unit containers or soft capsules that are intended for systemic administration only (not for those drug products that are intended for topical administration)
- Inhalations (other than solutions for inhalation packaged in glass or plastic ampules and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a names inhalation device
- Solids (including sterile solids) that are packaged in single-unit containers and contain active or inactive added substances (see exceptions for the WV method)

Use the following general guidelines in evaluating content uniformity for various dosage forms (see Figure 1):

- *Uncoated, coated, or molded tablets, capsules, oral solutions in unit-dose containers, suspensions or emulsions or gels in single-unit containers (that are intended for systemic administration only), and solids (including sterile solids) in single-unit containers:* If one of the unit doses is not within the required range (± 15% of label claim), then additional dosage units are required to be tested (20 dosage units).[1] Content uniformity is met if all of the 30 dosage units fall within the ± 15% range and none are outside the ± 25% range.[1]
- *Suppositories*: Content uniformity is met if none of the 10 unit doses fall outside the ± 15% range and the relative standard deviation (RSD) is less than or equal to 6%.[1] RSD is the sample standard deviation expressed as a percentage of the mean.[1] Also, uniformity is met if not more than one of the 30 unit doses falls outside the ± 15% range with no individual unit outside the 25% range, and the RSD is not more than 7.8%.[1]
- *Transdermal systems and inhalations packaged in premetered dosage units*: The additional 20 units must be tested if two units are outside the ± 15% range or if the RSD is greater than 6%.[1] For uniformity to be met, not more than 3 dosage units can be

outside the ± 15% and no dosage unit can be outside the 25% range, and the RSD cannot exceed 7.8%.[1]

Monograph testing represents the pharmaceutical industry standard and may be very costly to a compounding pharmacy. Therefore, companies performing the assay may opt to work out an alternative method of quality assurance for evaluating content uniformity of compounded preparations. One strategy that a laboratory might employ is that the pharmacist would send in 10 individual unit doses, and the lab would initially use five units to make a test prep. If the result of the test prep, which represents the batch, falls outside the ± 10% limit for potency, the lab will test additional five units individually to estimate the AV for content uniformity determination. Laboratories involved in CU testing designed this strategy to make CU testing more available and cost-effective.

The following is an example on when to use CU testing:
If you need 10-mg Oxycodone capsules (hard shells), and the total weight of the ingredients is 20 mg, look at Table 1 to determine which test is appropriate.

1. You are using capsules (hard shells), so view this row.
2. Is the dose <25 mg? Yes
3. Use CU method to determine homogeneity of mixture.
4. Send 10 unit doses to lab for content uniformity testing.

Weight Variation

WV testing can be done in the pharmacy but should only be done on the certain unit doses shown in Table 1. There can be variations from batch to batch due to inadequate mixing or segregation, and even differences in particle size.[3] Therefore, it is essential to have a quality-control component to your compounding process. In the WV test, 10 dosage units are individually weighed and compared to the percentage of label claim. An AV is calculated as in the CU method; except the individual contents are replaced with the individual estimated contents based on weight and using assay results of a composite sample derived from 10 unit doses.[1]

WV is the test most often used and misused by pharmacists. Not that the test is done incorrectly, but it is done on all dosage units, when it should only be used in certain dosage forms to correctly identify the differences in weights of the tablets. When used correctly, this test can be used to determine content uniformity. Therefore, there are certain conditions and dosage forms in which quantifying the weight differences can actually determine the percent differences in the API in the individual dosage units. In some situations where CU is required, an alternative method is needed for ensuring content uniformity, the WV method can be used by the pharmacy if the RSD of the concentration per dosage unit (w/w or w/v) of the drug in the final dosage unit is not more than 2%.[1] WV methods should be applied to the following dosage forms (see Table 1):[1]

- Solutions for inhalation that are packaged in glass or plastic ampules and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules
- Solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive
- Solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation
- Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting CU requirements.

The following is an example on when to use WV testing:
If you need 25-mg Oxycodone capsules (hard shells), and the total weight of ingredients is 50 mg, look at table 1 to determine which test is appropriate.

1. You are using capsules (hard shells), so view this row
2. Is dose <25 mg? No
3. Is dose <25% of weight of capsule? Determined by 25 mg divided by total weight of powder in one capsule (50 mg) 25 mg/50 mg = 50%. No
4. The dose is greater than or equal to 25 mg and greater than 25% of total drug substance; therefore, WV testing is appropriate.
5. Use 10 unit doses to determine weight of each individual capsule and compare AV to USP content uniformity criteria.

CONCLUSION

CU and WV methods should be an integral part of compounding to determine the homogeneity of compounded preparations. When applied correctly, content uniformity determination ensures that quality, precision, and safety standards will be met fully. There will always be quality-assurance needs for pharmaceuticals, and these guidelines should help in strengthening the future of compounding.

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