

METHODS FOR DETERMINING CONTENT OF ACTIVE PHARMACEUTICAL INGREDIENT OR CONTENT UNIFORMITY IN TABLETS.

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Abstract

There are many pharmaceutical drug products available in the market in different dosage forms i.e., Tablets, Capsules, Suspensions, Solutions, Injections. Inhalations etc. Each and individual dosage form has its own property of Pharmacological and Pharmacokinetic action on the human body. The primary effect of each dosage form depends on the most important property of the drug product, and it is called Bioavailability. Bioavailability of drugs, in other words, is the amount of drug substance available at the target site to show its respective pharmacological action. Therefore, it is a very important deciding factor of a drug product that individual dosage form contains 100% of the drug substance. There are many quantification tests readily available in different sources like USP, E.Ph, JP, etc. Among different quantification tests, Uniformity of dosage units is one, which will be performed by the quality control department of the manufacturer to assure that the individual dosage form of the batch contains the labeled amount claimed before marketing.

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INTRODUCTION

Percent assay of each dosage form is determined by preparing and analyzing the sample for assay of the content of drug substance present in the individual unit. Whereas weight variation is determining the content of an individual unit of dosage form based on the assay value and considering the weight of a tablet or capsule.

During manufacturing of finished products, composite blend power is compressed into tablets or encapsulated into empty capsule shells of varying shapes, sizes and weights. The process is performed on highly advanced and fast operating compression or encapsulation pharmaceutical equipment. In the process of compression and encapsulation, a powder sample passes through many parts of the equipment starting from Drums (Blend powder is stored), Hopper, Turret, Tablet Compressor, Conveyor Belts, Tablet Deduster and bottles. In this whole process the dosage unit should be intact and there should not be any loss of drug substance due to chipping or cracking, the labeled amounts of drug substance must be present consistently in each and individual dosage unit.

However, all manufacturing equipment will undergo regular maintenance, qualification and calibration tests, and every equipment should meet the equipment specifications. In the end, the QA manufacturing department collects and submits the sample to the QC department for quality control check. The quality control department tests the product for quality by performing various analytical tests such as Description, Water content, Organic Impurities, Assay, Residual Solvents, and Dissolution. Finally, the results are reported and submitted in the form of COA (Certificate of Analysis). Therefore, to assure uniformity of each dosage form of a batch and consistency for the content of drug substance, Uniformity of dosage unit will be performed.

Uniformity of dosage units is evaluated by either of two methods.

- 1.Weight Variation
- 2.Content Uniformity.

Weight Variation (WV)

Weight Variation is another method of determining the content of drug substances in individual dosage units of a batch. A weight variation test is performed based on the percentage or the amount of drug present in one unit. If the formulation of a drug product contains drug substance $\geq 25\text{mg}$ or $\geq 25\%$ of drug substance present in the final weight of the drug product. Once, the composite assay value is determined, the assay value is applied and content uniformity is evaluated with the weight of the individual unit.

% UOD by WV of individual unit $X_i = W_i \times \text{Assay} / \text{Avg. Wt of Tablets}$

X_i = %UOD of individual unit weighed for assay determination. W_i = Weight of individual unit weighed for assay determination.

Content Uniformity

Content Uniformity test is performed by preparing analytical sample solutions for individual dosage units (NLT 10) and determining percent assay value by appropriate analytical methods such as HPLC, UV, RI, etc. Once the analysis is completed acceptance value (AV) will be calculated and reported if all results are with the acceptance criteria. If assay values of any individual unit or the average value do not meet the acceptance criteria, the test will be repeated with additional 20 units. The final acceptance value for $N=30$ units should be within the specification as per USP<905> general chapter.

Table-1: Example for % Content uniformity

Tablet #	% Content Uniformity
1	99.5%
2	100.1%
3	100.0%
4	99.1%
5	99.9%
6	99.7%
7	101.0%
8	100.8%
9	100.2%
10	100.3%
Mean	100.1%
SD	0.56
%RSD	0.6%
AV (Acceptance Value)	1.4

- Values in the table are randomly selected to demonstrate calculation of % content uniformity

Acceptance Value

Acceptance Value is the specification value determined for the number of units UOD is performed. As per the USP general chapter <905>, acceptance value or AV should be not more than 15.0 if UOD is performed for 10 individual units. AV is calculated based on the obtained mean % assay value of units performed. AV value is calculated in 3 different instances and is calculated using the formula below,

Equation - 1

If mean % assay value falls between 98.5 to 101.5, then

$$AV = \text{Std.Dev} \times k$$

Equation - 2

If mean % assay value is < 98.5, then

$$AV = (\text{Mean} - 98.5) + (\text{Std.Dev} \times k)$$

Equation - 3

If mean % assay value is >101.5, then

$$AV = (101.5 - \text{Mean}) + (\text{Std.Dev} \times k)$$

Where,

k= Acceptability Constant

If n=10 then k=2.4; if n=30 then k=2.0

S= Sample Standard Deviation

Out of Specification (OOS)

The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1. If the acceptance value is greater than L1, a test is performed for additional 20 units, and the acceptance value is calculated.

The requirements are met if the final acceptance value of the 30 tablets is less than or equal to L1, and no individual content of any dosage unit is less than $[1 - (0.01) L2] M$ and more than $[1 + (0.01) L2] M$.

Where, L1 = 15.0 and L2=25.0.

Split Tablet Test

In some instances complete dose will not be prescribed by the physician due to several reasons, they could be patient's age, weight, gender, metabolic rate, and other health related issues, availability of drug product or pharmacological action of drug. In such cases physicians will recommend a patient split tablet into almost equal or quarter size and consume as per the instructions. Therefore, as per the FDA draft guidance all pharmaceutical companies must and should perform the half tablet and quarter tablet content uniformity studies while submitting the data to the FDA for approval. On other hand, if there is no scoring required on the tablet of any less potent or full dose drug product, it is not required to show study results for such drug product.



Figure 1: Representation of half and quarter split tablets (Reference 2)

As per the physician prescription, if a patient is recommended to take half or quarter tablet commercial tablet splitters are available in the market varying in different sizes and shapes. These tablet splitters are very much useful and convenient for the elderly patients to split the tablet into half or quarter split.

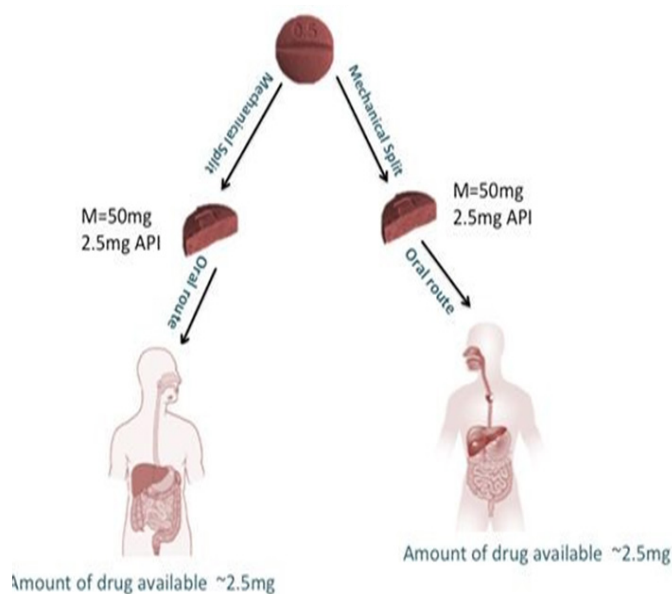


Figure 2: Depiction of the bioavailability of split tablets

REFERENCES

1. Guidance for Industry 1 Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation.
2. <https://uncoveredhc.com/blog/how-to-safely-split-your-pills-at-home/>
3. Nanji J A, Guo N, Riley E T, Faulkner B, Do C, et al. Evaluation of Opioid Use With Split Doses of Oral Opioids in a Postcesarean Delivery Analgesia Order Set. *Obstet Gynecol* . 2019; 134(1): 120-127.
4. Basha SS, Manikanta S, Jahnavi T. UV spectrophotometric

- determination of rupatadine fumarate in bulk and tablet dosage form by using single point standardization method. *Int J Pharm Pharm Sci.* 2019; 11(7): 120-124.
5. Lakshmi Narasimha Rao K. Split –Half tablets: A complete Review for analytical Testing. *Asian J Pharm Clin Res.* 2019; 12(9): 27-38.
 6. Melo V V, Pereira G R, Soares A Q, Silva I C, Taveira S F, et al. Prevalence of tablet splitting in a Brazilian tertiary care hospital. *Pharmacy Practice.* 2020;18(2): 1910.
 7. Pajić N B , Račić A, Gatarčić B. Whole vs. Half-Tablets – a Case of Diazepam. *Scr Med.* 2019; 50(4):153-160.
 8. Jacques ER, Alexandridis P. Tablet scoring: current practice, fundamentals, and knowledge gaps. *Appl Sci.* 2019; 9(15): 3066.
 9. Eserian JK, Lombardo M, Chagas JR, Galduróz JCF. Unmet Quality Needs in Oral Drug Delivery: Contrasts of Drug Content and Uniformity on Distinct Approaches for Achieving Individual Dosing. *AAPS Pharm SciTech.* 2019; 20(8): 332.
 10. Gharaibeh SF, Tahaineh L. Effect of different splitting techniques on the characteristics of divided tablets of five commonly split drug products in Jordan. *Pharmacy Practice.* 2020; 18(2): 1776.
 11. Seong S, Ju-Young S, Daejin K , Inmyung S, Sangouk S , et al. The effect of tablet splitting on the mass loss, uniformity, and stability: by hand or splitter? *Journal of Asian Association of Schools of Pharmacy.* 2019; 8: 7–14.
 12. United States Pharmacopeia and National Formulary. USP39-Nf34. Chapter 711: Dissolution. Rockville, Md: United States Pharmacopeial Convention, Inc.
 13. United States Pharmacopeia and National Formulary. USP39-Nf34. Chapter 905: Uniformity of Dosage Units. Rockville, Md: United States Pharmacopeial Convention, Inc.
 14. United States Pharmacopeia and National Formulary. USP39-Nf34. Chapter 1216: Tablet Friability. Rockville, Md: United States Pharmacopeial Convention, Inc.