



## **A Review on Tablet Scoring: Background, History and Current Regulatory Considerations**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Tablet splitting or breaking of tablets into multiple strengths has been a common practice across the world. Splitting of tablet offers various advantages such as dose flexibility and ease of swallowing in different population including geriatric and pediatric patients (wide patient acceptance) and cost saving on medications (economic advantage) The tablet products that are meant to be split and approved by the Food and Drug Administration (FDA) will have a scored line indicating the split location to ensure patient can adjust the dose by splitting and such splitting information will be included in the patient package insert. Having a consistent scored reduces difficulty in dose related problems especially when using products made by different manufacturers such as Generic compared to Reference Listed Drugs (RLD). Physical characteristics such as shape, size and tablet score may affect tablet splitability. Currently, various regulatory bodies (FDA, USP, and EP) provide consistent and useful information to the pharmaceutical industry. In this review, authors have compiled information from currently available resources on tablet scoring.

**Keywords:** *Tablet scoring; tablet splitter; scored tablets; split tablets; reference listed drug; dissolution; disintegration; stability.*

## 1. BACKGROUND

Many pharmaceutical products are available as scored tablets. The scored tablet includes a groove also known as the score line on the surface of the tablet to facilitate easy dividing of tablet or splitting of tablet into two or more equal portions [1]. The splitting can be typically achieved by manually using hand or mechanically using tablet splitter. Such score lines can be included on upper and/or lower surfaces of tablet depending upon different tablet designs. One of the main advantages scored tablets offer is the flexibility in dose across different population including pediatric and geriatric patients. The other advantages include reducing the size of the tablet for ease of swallowing and reduced medication costs by splitting tablets to achieve multiple strengths. The accuracy of splitting tablets can be influenced by physical characteristics of tablets such as tablet size, shape, hardness and splitting technique. Recently researchers published different approaches to manufacture scored tablets to improve quality of tablet splitting such as use of compression molding technology and multilayered tablets containing one or more active ingredients in the tablets with inclusion of score line to allow not only dividing of tablet but to provide clinical benefits for flexibility in dosing for more than one active ingredient [2-3]. Such advancement in research is extended to develop tablet splitters/pill cutters that are safer and more effective in cutting tablets into desired portions without excessive tablet crumbling and exposure to cutting edges/blades [4]. There are many products currently on market with scored tablets to allow tablet splitting. Tablet splitting is mainly used for immediate release products such as Morphine Sulfate IR (pain relievers) and Guaifenesin and Phenylephrine HCl IR (nasal decongestant). Tablet splitting is also available in modified release products such as Gliclazide MR 60 mg (hypoglycemic) and Isosorbide mononitrate Sustained Release Tablet 60 mg (used in treatment of angina). However, tablet splitting is not recommended in certain modified release products where coating feature may be impaired due to splitting which results into drug overdose contributed by uncontrolled release pattern [5-7] such as extended release and time release products e.g., birth control pills. The tablet products that are meant to be split and approved by the Food and Drug Administration

(FDA) will have a scored line indicating the split location and such splitting information will be included in the patient package insert. Such consistent scored line ensures that the patients can adjust the dose by splitting the tablet in the same manner without facing dose related problems especially when using products made by different manufacturers such as Generic compared to Reference Listed Drugs (RLD) [8].

## 2. HISTORY AND CURRENT SCENARIO FOR TABLET SPLITTING

During 2009 and 2010, drug safety oversight board of Center for Drug Evaluation and Research (CDER/FDA) evaluated the practice of tablet splitting and increased demand of split tablets due to dose flexibility and cost-saving. However, there were no regulatory requirements to specifically address the scoring of the tablets [9]. The commercially available dosage forms and dose strength may pose some challenges when administering to young children such as commercially available dose strength may need to be adjusted to dose in young children by breaking or splitting to lower dose strength and crushing tablets. Specific instructions to overcome such challenges may not be clearly available therefore parents and health care professionals may consider administering the dose by breaking or crushing tablets and mixing with food or drink to achieve the adequate taste. In such instances, there were possibilities of lower efficacy and higher risk of adverse drug reaction contributed by inaccurate dosing, stability and bioavailability of formulation [10-12]. A review of the studies performed revealed that the accuracy standards between different techniques used to split tablets differed amongst researchers, showing 59% of the researched studies reported the proportion of tablet parts that were within  $\pm 15\%$  of the intended weight and 24% studies reported the percentage deviation from the intended weight [13,14]. A study was conducted describing the basis of manipulation of dosage form required to provide accurate doses for children and WHOP harmonized dose schedule for HIV drugs requires half tablet doses, these include splitting of tablets to obtain accurate doses [10].

The European Pharmacopoeia (EP or Ph. Eur.) had introduced a new test on the accuracy of subdivision of scored tablets in 2002 [15,16].

Consequently, this test became a mandatory test in many European countries in order to achieve uniform halves after tablet splitting and manufacturers following the Ph. Eur. standards must considerably performing tablets as defective products [17,18]. The United States Pharmacopeia (USP) and the British Pharmacopoeia (BP) contained a quality control test regarding the weight uniformity of dosage units. However, at the time they did not have tests for the weight uniformity of the resultant split halves or the performance of score lines of tablets. Pharmaceutical scientists used to test for weight variation and content uniformity standards of whole dosage forms by USP to evaluate accuracy of tablet splits; this may result into inconsistent approach [14]. Several authors implied to establish for the subdivided portions of scored tablets to US regulatory and compendial agencies [19].

The EP provided appropriate provisions to this topic while the United States Pharmacopeia (USP) published a Stimuli article in 2009 [20]. FDA introduced draft guidance on tablet scoring in 2011 to advise manufacturers in order to provide data needed to support applications for scored doses [21]. In this draft guidance, the Agency outlined the concerns and criteria to be met for tablet splitting, split portions, and stability when stored in a pharmacy bottle with a cap but not seal and outlined concerns related to presence of scoring in products where risk of unintended drug exposure such as chemotherapeutic agents and hormones and modified release products. The draft guidance in public domain, allowed public comments and suggestions [22,23]. A final tablet splitting guidance was published by FDA in 2013 "Tablet Scoring: Nomenclature, Labeling and Data for Evaluation" [24]. Recently in 2016, researchers from FDA noted that the tablet splitting can significantly affect dose variability for products of amlodipine and gabapentin [25,26].

The FDA guidance provided a consistent approach and important criteria for scored tablets [22] such as:

- Active amount after splitting the tablet should not be below the minimum therapeutic dose.
- Evaluate Modified release products for which the control of drug release can be compromised by tablet splitting (e.g., exterior film coat) should not have a scoring feature.

- The split tablet should be stable for a period of 90 days at controlled room temperature condition when stored in pharmacy containers.
- The split tablet portions should meet the same requirements as for the finished-product.
- Any recommended dissolution test data must be generated on a minimum of 12 individual split tablet portions.
- To ensure comparability between ANDA and RLD.
- Split portion data as part of NDA and ANDA review.
- Present at least one batch testing for each scored strength on the split tablets.

## 2.1 Details about the FDA Guidance

This guidance is applicable to sponsors of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) that described the acceptance criteria for evaluation and labeling of scored tablets. This indicates the specifics for including scoring feature in the tablets. Tablet splitting is facilitated by scoring feature therefore new products not meeting the criteria for scoring should not have a scoring feature or any reference to scoring in the labeling.

The guidance provides general criteria for scored tablets such as:

- i. Therapeutics dose of split amounts:** The dosage amount of active in split portions should not be below the minimum therapeutic dose as indicated on the approved labeling.
- ii. Handling of Split tablets:** The split portions should be safe to handle and not impose risk of unintended drug exposure.
- iii. Careful consideration for Modified release products:** which the control of drug release can be compromised by tablet splitting should not have a scoring feature.
- iv. Stability of Split Tablets:** to demonstrate adequate stability at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ; 60 %RH  $\pm$  5% RH; 90days; stored in pharmacy dispensing containers (no seal/no desiccant).
- v. Finished Product Criteria:** split portions to meet same finished product criteria as for whole tablets. Any recommended dissolution test data must be generated on a minimum of 12 individual split portions.

- Evaluation for splitting to be presented for split by hand (non-mechanical) and by splitter (mechanical).
- vi. **Comparability of ANDA and RLD:** same scoring configuration.
  - vii. **Evaluation of splitability upon Scale-up and Post-approval changes:** To present an evaluation of the tablet splitability for any product changes at Level 2 and Level 3 as defined in the Scale-up and Post-Approval Changes (SUPAC) guidance.

There are general criteria for pharmaceutical dosage forms such as immediate and modified release solid oral dosage forms to be included in the Pharmaceutical Development sections of NDAs and ANDAs and during primary/exhibit stability batches and scale-up.

#### **2.1.1 Additional specific consideration for immediate release solid oral dosage forms**

- i. **Testing for Uniformity of Content on split portions:** To present the uniformity of content in split portions as per USP General Chapter <905> Uniformity of Dosage Units for weight variation or content uniformity testing.
- ii. **Testing of mass loss (NMT 3%) and Friability at proposed hardness ranges:** Test 15 tablets to ensure a loss of mass of less than 3.0 percent between the individual portions and whole tablets. Verify the split portions meet the USP Friability requirement. Perform test at both proposed upper and lower limits of hardness.
- iii. **Testing of Dissolution data on split portions:** Dissolution data on split tablet portions to meet finished-product release requirements.

#### **2.1.2 Additional specific consideration for modified release solid oral dosage forms**

In addition to general criteria described above for scored tablets, the following criteria are described for modified release solid oral dosage form for matrix technology or compressed film coated tablets.

##### *2.1.2.1 Modified release solid oral tablets (using matrix technology)*

- i. **Testing of Dissolution data on split portions:** Dissolution data on split portions at both ends of hardness range.

- ii. **F2 Comparison of Dissolution split portion and whole tablets:** Dissolution for whole vs split tablets using similarity factor (f2).

##### *2.1.2.2 Modified release solid oral tablets (using compressed film coated components)*

- i. **F2 Comparison of Dissolution split portion and whole tablets:** For Compressed film coated tablets, ensuring the integrity of beads during compression, present the similarity factor (f2) dissolution profile comparison for pre and post compressed tablets.

#### **2.1.3 Labeling information for New products and currently marketed products**

In addition to testing characteristics for scored tablets, labeling should include the information about functional scoring in the dosage form. New products that meet the specified criteria can be labeled to having functional scoring and such information to be included in prescribing information. Labeling information for currently marketed products is to be updated for products with functional scoring and to provide assessment with data for evaluation.

#### **2.2 Details about the USP Requirements**

USP has also proposed a new chapter <705> "Quality Attributes of Tablets Labeled as Having a Functional Score". The general chapter as gave a set of specific procedures and criteria to evaluate the quality of the scored tablets and the performance of the subdivided portions [27]. This proposed chapter covered quality attributes of score tablets and their subdivisions for weight variation, Dissolution for immediate and extended release products and Disintegration (only when used as a surrogate for dissolution testing). The general requirements are as follows:

##### **2.2.1 Testing for weight variation on split portion using non-mechanical splitting**

Using a sample of 30 intact tablets, for each intact tablet, determine the expected weight of the split portions by dividing the whole tablet weight by the designated number of split portions as per labeling. USP mentions the splitting of each tablet by hand (without mechanical assistance) An acceptable tablet breaks into the designed number of portions, and each split

portion has NLT 75% and NMT 125% of the expected weight of the split tablet portion. Acceptance Criteria: NLT 28 of the 30 tablets are acceptable.

### **2.2.2 Testing for disintegration on split portions per USP <701>**

To perform disintegration testing, use the split tablet portions derived from acceptable tablets after testing for weight variation. Disintegration testing is only necessary when it is considered as a surrogate for dissolution testing as specified in the monograph.

### **2.2.3 Testing for dissolution on split portions per USP <711>**

To perform dissolution testing, use the split tablet portions derived from acceptable tablets after testing for weight variation. Perform the testing as per the type of dosage form i.e. immediate release or modified release dosage form:

- a. **Immediate Release Tablets:** Perform dissolution for immediate-release tablets at S2 stage using 12 split tablet portions according to the specified Medium, Apparatus, Times, and Analysis per USP<711>. Acceptance criteria: Average of the 12 results is NLT Q, and no result is less than Q – 15%.
- b. **Modified Release Dosage Tablets:** Dissolution testing on split portions for extended-release tablets by either of the two approaches described below and as per <711> for extended release dosage forms.
  - i. **Approach 1:** Generate dissolution profile from 12 split tablet portions and 12 intact tablets as per the medium, apparatus, time points and analysis given in the monograph. At a minimum, use three time points with no more than one time point where the results exceed 85% dissolved.

**Acceptance Criteria:** The calculated f 2 is NLT 50 (acceptable range: 50–100).

- ii. **Approach 2:** Perform dissolution testing on 12 split portion as per medium, apparatus, and analysis given in the monograph. (Consider a split-tablet portion as the dosage unit).

**Acceptance Criteria:** The percentages of the labeled amount released at the times specified conform to the L2 level acceptance criteria in USP <711>.

## **3. CONCLUSION**

The authors have provided detailed discussion on information available via regulatory guidances and literature. These current regulatory documents (FDA, USP, and EP) provide consistent and useful information to the pharmaceutical industry. ANDA applicants should be aware that recent guidance for Refuse to Receive (RTR) indicates lack of consistent scoring configuration (splittability) as ground for RTR. As per the guidance, the Agency may refuse to receive ANDA if there are inconsistencies in the scoring configuration between the RLD and the proposed generic product and those inconsistencies have not been reviewed and approved by FDA before submission of the ANDA [28]. As per the guidance on ANDA stability, it is recommended to provide one batch stability data for split portions during submission [29]. USP provides split portions made using non-mechanical tool (by hand) for tablet splitting. USP indicates that the testing for scored tablets should be performed soon after splitting unless stability of the samples was demonstrated, and the storage conditions and period should be defined in the test procedure. The FDA guidance recommends demonstrating stability of split portion for up to 90 days at controlled room temperature condition. FDA guidance and USP mention specific considerations about modified release dosage forms. Authors have attempted to gather information from available resources to shed light on the tablet scoring.

## **CONSENT**

It is not applicable.

## **ETHICAL APPROVAL**

It is not applicable.

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## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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