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LABORATORY SPECIAL

Leaders In-Sight

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Reducing errors and increasing throughput in Content Uniformity & Assay Testing

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What is Content Uniformity and Assay testing?

Content uniformity testing of solid dosage forms is a critical quality control test amongst several other tests (appearance, average mass, dissolution, etc.) that needs to be performed during drug development. As per USP chapter <905>, uniformity of dosage units ensures consistency of dosage units, such that each unit in a batch should have drug substance content within a narrow range around the label claim. Content uniformity tests are performed for drug products with label claim less than 25 mg. Another important quality control test - Assay of the drug product is performed to determine the amount of Active Pharmaceutical Ingredient (API) present in the dosage form. In pharmaceutical analysis, the results of drug product assay testing help in making decisions regarding the quality, efficacy, and stability of the drug product. Prior to commercial release, the content of API in the individual dosage unit and in the bulk samples from a batch needs to be tested and should be within the acceptance requirement set by the regulatory bodies globally.

Content uniformity tests are divided into the two main parts - sample preparation and sample analysis. Sample preparation is most critical step since it has direct impact on the results and there exist a high scope of variability since it involves multistep processes. The workflow of manual sample preparation process includes sample selection, weighing, trituration and transferring, extraction and filtration. Out of all the steps, trituration, transferring, and extraction steps are the most time consuming and the chances of error introduced are highly attributed to these two steps. Other than these process factors, the formulation variables that influence the uniformity of content in the dosage form are the excipient compositions, blend rates, drying time, and tablet compression forces.

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Current challenges of the manual procedure for Content Uniformity testing

Inability in following accurate sample preparation practices, maintenance of appropriate documentation, not tracking and investigating OOS and OOT results have been key points in warning letters issued by the FDA to several companies. The number of dosage units that needs to be examined is considerably large in the content uniformity testing. As per USP chapter <905>, Stage I testing requires that a minimum of 10 individual dosage forms be examined for uniformity although this number can increase to a total of 30 units if Stage II testing is required. Additionally, the manpower, reagents, and time needed to carry out this testing become resource intensive and laborious as the units for testing expands. The commonly faced challenges in the manual sample preparation are listed in the Table no. 1. To summarize, the multi-step manual sample preparation workflow is a time-consuming process, is more prone to introduce errors and inter-lab variations which is attributed to both instrument and analyst intervention.

Importance of automation in sample preparation process for content uniformity and assay testing

The switch to novel, rapid, and resource friendly automated technique for preparation of content uniformity/assay samples automation in sample preparation can overcome the current shortcomings in the manual lengthy and cumbersome processes.

Table No. 1: Challenges in Trituration, Transferring and Extraction Steps in Content Uniformity/Assay testing

Sr. No	Challenges	Outcome
	Trituration	
1.	Hygroscopic API or excipients	Sticking on the wall of the mortar or pestle. Incomplete product recovery.
2.	Unequal forces exerted on the product during extraction is analyst dependent	Introduce variability in results
3.	Serial process of trituration	Time consuming process since one tablet is triturated at one time.
4.	Presence of certain excipients/ingredients (menthol, camphor, phenol, etc.) in the formulation	Liquefaction of contents on trituration.
	Transferring	
1.	Sample loss during transfer	Inaccurate results
2.	Analyst to analyst variation	Irreproducible results
3.	Serial process	Time consuming
	Extraction	
1.	Time consuming – batch testing	Decreased productivity
2.	Non-standardized apparatus used for extraction	High Inter-lab variation
3.	For temperature sensitive drugs, no temperature monitoring during extraction	May result in product degradation

Case Study: In a study performed on automatic sample preparator (Xtractr) for content uniformity/assay testing, the entire process was evaluated and compared with the manually extracted samples by sonication method. In the automated apparatus, up to 10 individual units were tested simultaneously. One dosage unit was added in each tube and was fixed into the