VOL. 17 NO. 5 PAGES 76 www.expresspharma.in

EXPRESS PHARMA

INDIA'S FOREMOST PHARMA & BIOTECH MAGAZINE APRIL 2022, ₹ 40

MARKET

Can an 'edge' of innovation empower pharma industry to scale global success?

INTERVIEW

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then test developers and sellers will be keen to service this market. The need to reinvent the way antibiotics and diagnostics are deployed is urgent if you consider trends resistance and antibiotic use in many countries, including India.

Finding a viable solution to our reliance on reserve antibiotics

In our recent paper published in *The Lancet*, we explored the growing reliance of health systems in South Africa and India on 'reserve' antibiotics, as resistance increased to both 'access' and 'watch' drug cohorts in the last decade.

Overall, the rising consumption of antibiotics such as meropenem and tigecycline, along with increasing levels of resistance to carbapenems, colistin, tigecycline and vancomycin, as mentioned in the paper, highlights the worrying trend of escalating resistance to last resort antibiotics. Increased use of these products will raise the selection pressure for resistance, thereby further depleting treatment options in countries where infectious diseases remain among the leading causes of mortality.

Access to and registration of new antibiotics, ideally with new mechanisms of action, is, therefore, imperative. So too is a strong and rewarding market for diagnostic tests that aid the effective stewardship of the drugs we have.

We have, therefore, proposed a novel approach to create a predictable Low- and Middle-Income Country (LMIC) market that ensures access to products that address growing resistance and treatment failure. In *The Lancet*, we described how Antimicrobial Subscription and Pooled Procurement (ASPP) could be implemented as a multi-national or regional mechanism in which countries (or states within a country) leverage their combined purchasing power for a portfolio of newer and future antimicrobials and diagnostic products. In India, in particular, we believe this could work at either a state or national level.

ASPP would be operationalised through multi-year subscription contracts for a portfolio of antimicrobials and diagnostic products that are negotiated for participating states. Diagnostic products would include point-of-care tests, routine laboratory reagents and equipment for pathogen identification and susceptibility testing. Including diagnostics in the portfolio would help to ensure that antimicrobials are prescribed on the basis of diagnostic stewardship.

The portfolio approach sends a clear signal to manufacturers that products will be procured when quality, safety, efficacy and pricing criteria set by procurers are met, and that a market exists in countries that are being too often overlooked.

Tackling AMR head on

The impact of AMR is being felt harder in LMICs such as India. It's likely for this reason that it is also at the vanguard of fighting AMR's rise, thanks to concerted efforts and dedicated funding from the likes of BIRAC. India's world-class network of innovators and diagnostic test developers are creating a new generation of tests that can identify bacterial infections and the correct antibiotics to prescribe, not least those pursuing the £8m Longitude Prize.

ASPP could provide a solution to the market question to secure the stable and affordable supply of antibiotics and diagnostic tests to ensure consistent access. Administering the right antibiotic in the first instance is an important part of the strategy to address AMR, and ASPP will support it by making sure products are there when they are needed.

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 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.

Archana Pokkalath

Aditya Marfatia

Content uniformity tests are divided into the 2 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.

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.

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 (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

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. In a study performed on automatic sample preparator for content uniformity/assay testing– Xtractr, the entire process was evaluated and compared with the manually extracted samples by sonication method. In the Xtractr apparatus, up to 10 individual units was tested simultaneously. One dosage unit was added in each tube called Xtainer and was fixed into the Xtractr apparatus. The high shear mixing action of the SS blades crushed the tablets and allowed entire extraction to be completed within minutes.

The samples extraction using the Xtractr apparatus was proven to be significantly

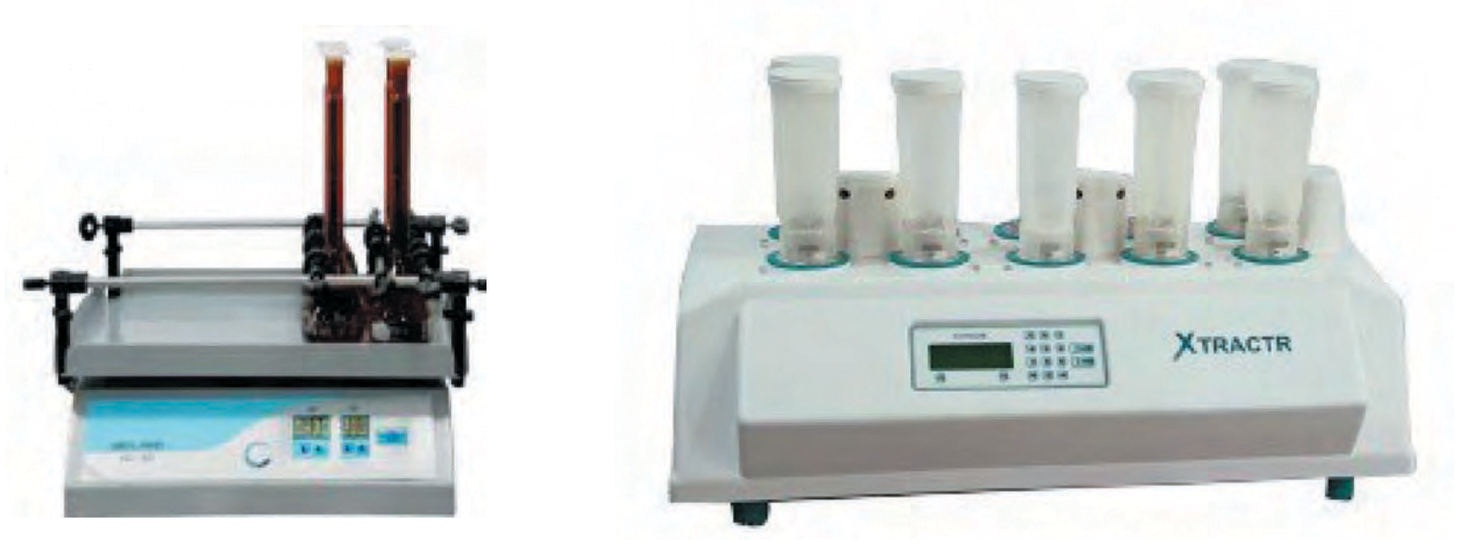


Figure 1: Setup for manual extraction (left) and Xtractr (right)

shorter than that required by the manual process, i.e., 5 mins at 2000 RPM vs 1 hr with Xtractr and manual process, respectively. On extrapolating this data to the 10 & 30 samples in Stage I & Stage II levels of content uniformity testing, respectively, significant time can be saved in automatic preparation compared to the manual process. As depicted in the Fig 2 (b), the samples that were prepared using Xtractr aided in reducing RSD (0.903 %) within assay results compared to the samples prepared by the manual process (1.155%). This can be attributed to the minimal analyst intervention occurring when the Xtractr apparatus is used. The automated sample preparation typically requires little user interface for operation and involves lesser chances of error. Additionally, the samples extraction via the automated sample preparator led to 100% drug recovery. By increasing the throughput with simultaneous sample preparation of multiple dosage units, the automated sample preparation in content uniformity and assay testing can be an effective alternative to traditional sample preparation methods.

Key Features of Xtractr:

◆ The automatic sample preparator can prepare 10 samples at one time compared to serial lengthy manual preparation process.

◆ Quick sample extraction from high-shear mixing action of the built-in stainless steel blades helps in analyst save a significant amount of time in testing.

◆ TemSen technology - Contactless temperature monitoring and control by automatic motor on/off within the set temperature range throughout the test. Ideal for temperature control in temperature sensitive APIs and excipients (eutectic mixture, polymers) used in the formulation.

◆ Available with wide volume ranges of sample holder tubes called Xtainers in both clear and amber color (light sensitive products).

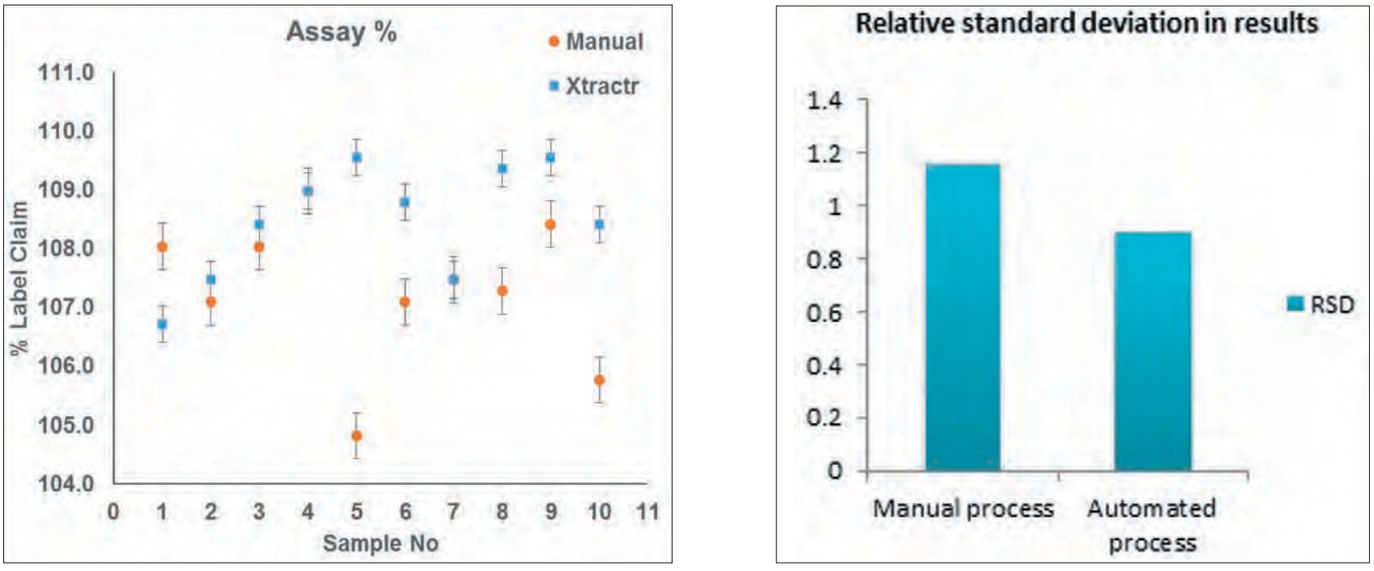
◆ The tester routinely prompts audio-visual alerts about the instrument status (D'light technology)

◆ The generated data from the apparatus can be printed via serial printer and documented as part of data management for routine audits.

References:

1. <905> Uniformity of dosage units – USP

2. G. Romberger et al, "Content Uniformity Testing Through Utilization of Automated Dissolution Technologies", American Pharmaceutical Review (November 2014)



a) b)

Figure 2: a) Individual values plotted for the assay results in content uniformity testing from manual process and using Xtractr apparatus. b) The comparison in RSD in assay results from manual and automatic sample preparation techniques