How gravimetric sample preparation is helping pharmaceutical manufacturers meet the demands of consumers, regulators, and the market

Mettler-Toledo

Since the groundbreaking Barr Labs case in 1993, the FDA has issued hundreds of observations concerning poor handling of out-of-specification (OOS) investigations, necessitating untold hours of lab effort as well as significant fines. Today, gravimetric sample preparation is giving pharmaceutical companies around the world a cost-effective way to avoid OOS errors, which in turn is helping them to reduce the occurrence of time-wasting investigations, enhance productivity and safety, and save costs.

From the number of warning letters issued periodically by the US Food and Drug Administration (FDA), it is apparent that OOS results are more common in pharmaceutical manufacturing than they should be. These errors not only result in time-consuming internal investigations and fines. Depending on an error's extent and market visibility, it can also make a significant impact on a pharmaceutical company's reputation and profitability, as has been seen most recently with concerns about US-based pharmaceutical giant Johnson & Johnson's contract manufacturing partner during COVID-19 vaccine production.

When errors in pharmaceutical research or production come to light through quality control assessment or external audit, it can be difficult for lab managers to pinpoint the cause of the problem, let alone assure regulators it will not happen again. Pharmaceutical groups find themselves consuming valuable resources conducting or supporting an analytical lab investigation. This often leads to an uncomfortable deviation report, a more expensive corrective and preventive action (CAPA), or even a full-blown root cause analysis. This is especially true of modern complex, multistep analytical processes that are relying on smaller and smaller doses of potent active pharmaceutical ingredients (APIs) for research and formulation activities.

Why do labs have such difficultly getting a handle on the source of OOS results? Part of the answer can be attributed to the still-common practice of manual volumetric sample preparation. Workflows using volumetric flasks have not changed significantly in nearly 100 years. During this same time, however, the substances being handled have become more refined, more potent, and in most cases more hazardous to handle. Meeting this heightened risk safely has sometimes caused handling time to increase, even as competition has necessitated faster processing. This has sometimes had the unfortunate consequence of pitting analytical accuracy, operator safety and processing speed against each other. Previous-generation balances also played a role, as minimum weights typically did not allow direct preparation of required concentrations, with serial volumetric dilutions compounding any errors that occurred.

One solution that is helping to eliminate OOS errors - or, at the very least, ensure that sample and standard preparation is not the cause of errors that are identified by regulators - is gravimetric sample preparation. The systematic change represented by this next-level dosing and weighing technology is so significant that accurate processing of even the most minute quantities is making it possible to achieve precise concentrations while enhancing productivity, limiting solvent usage, and eliminating operator contact with APIs and other potentially hazardous substances altogether.

In short, gravimetric sample preparation is helping labs achieve accuracy in sample preparation workflows that far outpace even the most consistent human operator using volumetric methods with its inherent and well-documented variability. The addition of safety, speed, and cost-effectiveness makes the advantages of gravimetric sample preparation difficult to overstate.

Make multi-component standard preparation easy

A good example of the impressive gains in speed, safety and savings represented by gravimetric processes can be found when using automated powder and liquid dosing in the common lab workflow of preparing multi-component standards.

When manually weighing substances into a volumetric flask during standards creation, the risk of overshoot for each individual component is high, as is the potential cost of any errors. To reduce this risk, an operator will typically weigh a substance onto weighing paper and then transfer it into a flask, rather than weigh it into the flask directly. Does the operator then backweigh the paper to ensure no substance is left behind? If not, doubt is created about process accuracy. If so, extra time is added to the workflow. Neither choice is ideal.

Gravimetric preparation helps to eliminate uncertainty and save time. Both solids and solvents are measured by weight, not volume.

This produces specific, precise concentrations, which help to minimise out-of-specification errors and enable faster processing. Gravimetric dosing can also result in substantial reductions in sample and solvent usage while eliminating bad batches and waste, further reducing costs.

Enhance quality and maximise safety

Another important benefit of automated sample handling is the reduced exposure risk for the analyst. A leading pharmaceutical QA/QC department implemented gravimetric sample preparation specifically for this reason.

The group is responsible for in-process control of highly potent compounds. Their legacy approach, which was manual, involved working in a glovebox in a full body suit for a multi-hour weigh-out. The task was not popular among analysts, and OOS results and re-testing caused operators to spend even more time in protective gear trying to prove detected errors were reproducible.

An automated dosing process built on gravimetric preparation inside the glove box has helped the lab meet their safety requirements and eliminate human error while freeing operators to focus on more challenging and impactful tasks.

Quantify Time Savings: Gravimetric Prep

Just how much time can gravimetric sample preparation save? A simple example of the preparation of a multi-component standard demonstrates the advantages of using an automated powder dosing system equipped with a liquid dosing head.

A five-component mixture was prepared in a single vial per concentration level. The five compounds were all weighed into the same vial at different target weights. Linearity tests were performed by UHPLC measurement at five different concentrations. The correlation coefficient was greater than 0.999 for all analytes and the intercept was close to zero.

Analyte	Standard 1 (mg)	Standard 2 (mg)	Standard 3 (mg)	Standard 4 (mg)	Standard 5 (mg)
Acesulfame K	7.390	9.730	9.930	11.450	13.650
Saccharin	2.695	3.480	3.890	4.305	5.085
Caffeine	2.800	3.700	3.995	4.355	5.220
Vanillin	6.285	8.110	8.995	9.860	11.655
Benzoate	14.050	18.100	19.965	21.910	25.855

Actual concentrations of soft drinks ingredients prepared using the automated liquid dosing system.

The time taken for manual preparation of the five-component standard was 3-4 hours. The preparation of these samples much safer powder dosing heads - including the time to fill them - was less than one. Adding automated liquid dosing for the diluent to create a fully automated workflow further reduced preparation time to less than 10 minutes.

This example illustrates the time savings that can be made by automation: Multi-component standards prepared in one-quarter or less the time while still obtaining high quality data and reducing error risk.

Reduce sample volumes

In addition to enhancing safety and improving productivity, preparing samples gravimetrically presents the opportunity for a substantial reduction of sample volume and significant materials savings. Gravimetric addition of diluent means the amount of solution prepared is not dictated by the sizes of volumetric flask that the operator must handle. Therefore, concentrations need not be prepared at discrete intervals, such as 20, 50 or 100 millilitres.

Instead, just the amount of solution required can be prepared. This factor, combined with the lower minimum weight achievable for automated gravimetric dosing, means that smaller amounts of sample can be used, smaller solution volumes prepared, and less material disposed of or wasted. This results in conservation of often costly materials, as well as a reduction in environmental impact and waste disposal fees.

Get rid of glassware variability

Based on widely accepted surveys of lab practices, many aspects of manual volumetric sample preparation are subject to variability or uncertainty and can lead to imprecise concentrations and OOS results. These include glassware failure, endo- or exothermic reactions caused by environmental/glassware temperature mismatch, glassware contamination, relative percentage errors (especially with smaller flasks), labelling errors, and sample mix-ups. This list does not even account for the cost of periodic flask revalidation, which can be significant in high-volume labs.

Gravimetric sample preparation eliminates these inherent sources of process variability and the costs associated with them, resulting in more accurate, consistent sample concentrations and lower overall processing costs.

Assure accurate results - every time

Technology available to facilitate gravimetric sample preparation varies. However, in general, powders and liquids are both delivered into small, disposable target vials positioned on an analytical or semi-micro balance to achieve a concentration specified by the user.

Spatulas and cross-contamination risk are eliminated by use of an individual dosing head for each powder storage container, enhancing operator safety. However, dosing accuracy is enhanced impressively as well, because if a specific powder is overshot either manually or automatically, the amount of diluent can be increased automatically to keep concentrations consistent. This solves the issue of accuracy without wasting valuable substance or adding rework time to a sample preparation workflow. This repeatable accuracy can all but eliminate the possibility of OOS errors arising from the often-repeated act of sample preparation.

Ensure regulatory compliance

If any lingering questions in the minds of lab operators remain over whether gravimetric sample preparation meets pharmaceutical regulations, USP 1251 should help put them to rest. The United States Pharmacopeia, or USP, has established methods for weighing both solid and solvent into a vial or container on a balance for sample preparation and dilution.

In closing, gravimetric sample preparation produces more accurate, consistent dosing for fewer OOS results. Couple this advantage with enhanced operator safety, smaller sample volumes, and time and monetary savings, and it becomes clear that gravimetric sample preparation is poised to help labs surmount the three primary challenges of modern pharmaceutical manufacturing by helping them create sustainable accuracy, productivity, and safety in their sample preparation workflows.

Safety, Accuracy and Speed: The XPR Automatic Balance

Safety is important when handling active substances, but so are accuracy and speed. Using the XPR Automatic Balance for direct gravimetric dosing reduces your exposure risk while significantly enhancing throughput.

With XPR Automatic, you can dose from an enclosed head into targets including capsules with diameters as small as six millimetres. The balance's ability to actively monitor flow characteristics helps to improve dispensing efficiency, while the addition of automatic weight-based liquid dosing lets you achieve precise concentrations and reduce sample sizes by as much as 30%.

XPR Automatic also supports manual processes and fits easily inside your safety enclosures. Learn more about how this revolutionary balance reduces exposure risk, improves efficiency, and assures weighing accuracy now.

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