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# Innovations in Gravimetric Preparation of Analytical Solutions: Regulatory and Compendial Perspectives

Advances in technology for the preparation of solutions have the potential to improve accuracy in the testing of pharmaceutical samples. New instrumentation permits the automated preparation of analytical solutions using gravimetric procedures, including dispensing and weighing both solids and liquids, resulting in improved accuracy and precision and allowing any desired volume of solution to be prepared. In this regulated environment, where regulatory and compendial requirements define what is or is not allowed, the FDA and USP have made specific allowances for adoption of new technology, when it will have a beneficial effect on product quality.

Quantitative testing of solutions prepared from samples of drug substance or drug product is at the foundation of pharmaceutical analysis. Traditionally, this testing has involved weighing sample materials into a volumetric flask, dis-solving the sample in an appropriate solvent, and filling the flask to a calibration mark on the neck of the flask. Solutions are then sometimes diluted to the desired concentration using transfer pipets.

Although there have been few advances in this approach, which has been in place for over 50 years, instrumentation facilitating gravimetric procedures for solution preparation has been introduced. An example is the Quantos system (*Figure 1*) (**METTLER TOLEDO**, Greifensee, Switzerland), which can automatically weigh out predetermined quantities of solid (reference standards or samples) and liquid (solvents or diluents) materials. If desired, the instrument can calculate


*Figure 1 - Quantos liquid dosing module.*

the mass of solvent needed by entering the target concentration of the analytical solution. The instrument automatically dispenses the correct amount of solvent into a convenient receiver, such as a screw-cap vial. By using gravimetric procedures, solutions may be prepared with much greater precision than when using volumetric flasks, often using smaller quantities of expensive reference standard or sample, and generating less waste which must be disposed of. There is the added advantage that users are no longer limited by the sizes of volumetric flasks available.

## Gravimetric preparation vs volumetric flasks for preparation of solutions

When using Class A volumetric flasks, the tolerances include up to 0.20% limit of error, according to USP.[1] If transfer pipets are used, they can add up to an additional 0.60% limit of error. This does not even include the human error associated with deciding when the flask is filled to the mark, or the influence of temperature changes (since volumetric flasks are calibrated at 20 °C).

In contrast, the USP uncertainty requirement for analytical balances (where the sample is to be accurately weighed) is not more than 0.1%, and most modern electronic analytical balances perform even better than this. Therefore, the reproducibility is expected to be better when using gravimetric preparation of solutions than when using volumetric flasks. The data in Table 1 show that the precision from HPLC determination of nine samples prepared by gravimetric solution preparation is indistinguishable from the injection precision, when one vial is injected 10 times, demonstrating the excellent precision that can be obtained using this technique.

Methods used by the pharmaceutical industry in the U.S. are controlled by the FDA and USP. In general, determination of strength, quality, and purity of a drug is made in accordance with the tests or methods set forth in the official compendium, the USP, or with methods that are contained in new drug applications (NDAs), abbreviated new drug applications (ANDAs), or supplements. Can gravimetric solution preparation procedures be used when the methods specify use of volumetric flasks? Fortunately, both USP and FDA have provided mechanisms by which new technologies can be adopted.

Table 1. Case Study: Gravimetric Standard Preparation

| # | API dosed | Solvent added | Conc. achieved | Area | Area correlated to 0.6mg/g | Solution 1 | Area |
|---|---|---|---|---|---|---|---|
| | mg | g | mg/g | | | Inj. 1 | 2593.067 |
| 1 | 10.105 | 16.7481 | 0.60299 | 2596.883 | 2584.006 | Inj. 2 | 2604.434 |
| 2 | 10.320 | 17.1048 | 0.60298 | 2595.355 | 2582.528 | Inj. 3 | 2604.124 |
| 3 | 10.140 | 16.8063 | 0.60298 | 2597.530 | 2584.693 | Inj. 4 | 2604.894 |
| 4 | 10.125 | 16.7815 | 0.60298 | 2595.556 | 2582.729 | Inj. 5 | 2607.997 |
| 5 | 10.250 | 16.9885 | 0.60299 | 2597.124 | 2584.246 | Inj. 6 | 2605.372 |
| 6 | 10.200 | 16.9058 | 0.60298 | 2596.045 | 2583.215 | Inj. 7 | 2602.295 |
| 7 | 10.130 | 16.7895 | 0.60299 | 2602.422 | 2589.518 | Inj. 8 | 2608.339 |
| 8 | 10.040 | 16.6408 | 0.60297 | 2609.649 | 2596.795 | Inj. 9 | 2593.232 |
| 9 | 10.275 | 17.0297 | 0.60299 | 2604.743 | 2591.827 | Inj.10 | 2601.731 |
| Mean | 10.176 | | 0.603 | 2.599.479 | 2586.617 | Mean | 2602.549 |
| σ | 0.0909 | | 7.071E-06 | 5.0008 | 4.9836 | σ | 5.3764 |
| % RSD | 0.89 | | 0.001 | 0.19 | 0.19 | % RSD | 0.21 |

## Regulatory and compendial basis for revised or alternative procedures

The FDA, in its guidance on changes to an approved NDA or ANDA,[2] indicates that a revised or alternative procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of a drug substance or drug product as the procedure in the approved application is considered a minor change, and can be filed with the Annual Report. USP, in the General Notices,[3] indicates that "alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity," further stating that they should be validated as described in General Chapter <1225> Validation of Compendial Procedures. Since introduction of gravimetric procedures for preparation of analytical solutions would be an improvement in terms of precision, the changes would be acceptable from the viewpoints of both the FDA and USP.

## Implementing changes

In the case of an existing method, where the density of the analytical solutions is known (or can be determined empirically), a straightforward conversion between volume and mass may be made, using the formula: volume = mass/density. If the method calls for a concentration, the solution should be prepared based on the required concentration. With Quantos, the amount of solid to be weighed and the desired concentration can be entered, and the instrument automatically delivers the required amounts of both solid and liquid materials, and provides a printout record of the amounts dispensed. If the method indicates that a certain amount should be added to a volumetric flask, Quantos can be instructed to deliver the amount of solid required, and a corresponding mass of solvent to achieve the desired concentration.

If desired, to conserve solid material or reduce solvent usage, the amounts could be scaled down, maintaining the appropriate concentration (scaleup and scaledown of sample preparation is done fairly routinely in industry with USP methods; many procedures list a concentration rather than a specific amount of solution to be prepared for this reason). If the changes to the procedure are minor, revalidation may not be required. Otherwise, the revised procedure could be considered an alternative method, in the parlance of the USP, and require validation according to General Chapter <1225>. Based on the contents of the FDA Guidance previously referenced, if any filing were necessary, the change would fall into the minor category, and could be submitted in an Annual Report.

## Developing new methods

When new methods are being developed from scratch, the developer has the option of incorporating specific gravity into the procedure, as described above, or to simply use the gravimetric approach and describe the sample preparation in terms of mass of solid and mass of solvent to be used.

## Conclusion

The introduction of new instrumentation for the gravimetric preparation of solutions presents a significant opportunity to improve the quality of results from analytical procedures for pharmaceuticals by reducing the uncertainty associated with the preparation. The generation of more precise results using this technique is likely to result in fewer out-of-specification results, due to the improved methodology. When the results are demonstrated to be "equivalent or better" than the existing methods, the changes are allowed by both USP and FDA.

## References


1. General Chapter <31> Volumetric Apparatus, USP 35-NF 30.
2. Guidance for Industry: Changes to an Approved NDA or ANDA, U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER); Apr 2004, Rev 1.
3. General Notices, 6.30. Alternative and Harmonized Methods and Procedures, USP 35-NF 30.



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