Studies of Variability in Dissolution Testing with USP Apparatus 2

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ABSTRACT: In this study, gauge repeatability and reproducibility (gauge R&R) was used to analyze variability for USP apparatus 2 dissolution measurement systems. Experiments were designed to assess the variability due to apparatus, operator, and sample tablet. Since dissolution testing is a destructive test, a nested model was used for data analysis. Additionally, perturbation tests with both disintegrating and nondisintegrating tablets were performed to study the variability due to sample position within the dissolution vessel. For the gauge R&R study, two well-trained chemists used two mechanically calibrated USP apparatus 2 units. Six tests were performed by each operator on each apparatus. Evaluation of dissolution test results at 30 min using an internal DPA calibrator tablet NCDA#2 (10 mg prednisone) indicates that the main contribution to the total variance, approximately 70%, is due to the sample tablets, approximately 25% is from the apparatus and approximately 5% is due to the operators. There is no significant difference between operators and apparatuses as shown by the gauge R&R studies. In addition, dissolution results can be strongly affected by the position of the tablet within the vessel. Similarity (f_1) and dissimilarity (f_2) factors were calculated to statistically evaluate differences between perturbed and normal dissolution tests. J Pharm Sci 96:1794–1801, 2007

Keywords: dissolution test; gauge R&R; variability; f_1 and f_2 factors

INTRODUCTION

In-vitro dissolution testing methodology has undergone many improvements over the past 20 years. These improvements have come about through a better understanding of the underlying principles of dissolution testing, and this has led to an appreciation of new problems with the technology.[1–5] The lack of repeatability and reproducibility are of particular concern to the pharmaceutical industry. The large variability observed in dissolution results may arise from uneven distribution of hydrodynamic forces within the dissolution vessel. Some studies showed that this variability is large enough to cause dissolution test failures.[6–9] Although computer modeling and dye studies show nonuniformity of the flow patterns in the dissolution vessel, the quantitative contribution of the various sources of variability, such as apparatus, operators, and tablets, has not been addressed.

Gauge repeatability and reproducibility (gauge R&R) studies have been widely used for assessing the precision of a measurement system.[10–13] The variation observed when a single operator measures the same part consistently is called repeatability or pure error. The variation observed when one operator duplicates the measurement of

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another operator on the same part is called reproducibility.[11] These definitions correspond to those in common use for gauge R&R studies but differ from those currently used by ISO and ICH. A dissolution apparatus is a complicated measurement system, which includes six individual vessels and six stirring elements. In this study, gauge R&R analysis has been performed on a dissolution test measurement system (USP apparatus 2) to examine variability due to apparatus, operator, and tablet.

Mechanical calibration is the most critical step for minimizing variation in dissolution testing when using USP apparatus 2.[1–5] However, an additional source of error can arise from the inability to reproducibly position a tablet in the dissolution vessel. This is entirely independent of any calibration that may have been performed on the apparatus.

Perturbation experiments were carried out to study sources of variability in dissolution testing. Based on previous studies, variation of tablet position in the dissolution vessel leads to substantial variability in dissolution results.[6–9] Because of the uneven hydrodynamic flow distribution in the vessel, changes in the position of the tablet expose it to different hydrodynamic forces which causes the rate of dissolution to change. To better control the hydrodynamics around sample tablets, a positioning guide was developed and used in this study. Using this tool, dissolution results with NCDA#2 and salicylic acid tablets in the center area and 10 mm off-centered position were obtained. To statistically evaluate differences between perturbed and normal dissolution tests, f_1 and f_2 factors were calculated.[14] The FDA has established that f_2 values between 50 and 100 and f_1 values between 0 and 15 indicate similarity of two dissolution profiles.[15,16]

EXPERIMENTAL

Design of Experiment for Gauge R&R Study

Two mechanically calibrated USP Apparatus 2 units were used in this study. Based on a previous study,[12] use of poorly trained or inexperienced operators can compromise the validity of a gauge R&R study. Thus two trained operators carried out dissolution tests with the NCDA#2, 10 mg prednisone tablets. Six replicate dissolution runs, each consisting of a set of six tablets, were made by each operator on each apparatus for a total of $N = 2 \times 2 \times 6 = 24$ replicates or 144 tablets.

Data Analysis

JMP (version 5.1) statistical analysis software was used to analyze the variability contributions of designed factors.[17] Software-generated variability charts were employed to compute variance components such as operators, instruments, or tablets that are systematically different in mean or variance. This analysis allows comparison of the mean, range, and standard deviation of the data for each variable. Although several models employing crossed and nested factors are available, in dissolution tests, each operator can use each apparatus multiple times but each sample can be analyzed only once dictating the use of a three-factor Crossed then Nested study design. The three-factor Crossed then Nested model design for a dissolution test is shown in Figure 1.

Dissolution Instruments and Conditions

- USP Apparatus 2 (paddle), Distek dissolution apparatus (Model 2100A, Serial # D12547291 (A) and Serial # D12547292 (B), North Brunswick, NJ 08902).
- NCDA#2, 10 mg prednisone tablets.
- 300 mg salicylic acid tablets, USP Lot O.
- DPA method degassed[18] 500 mL D. I. water (for NCDA#2 in each vessel) and 900 mL pH7.4 buffer (for salicylic acid in each vessel) at 37°C, with 50 rpm paddle speed.
- All samples were filtered through Distek 10 micron ultra high molecular weight polyethylene filter tips.
- On-line Hewlett-Packard model 8452A UV/vis spectrophotometer, 242 nm with a 0.5 cm cell for NCDA#2 and 296 nm with a 0.2 cm cell for salicylic acid.

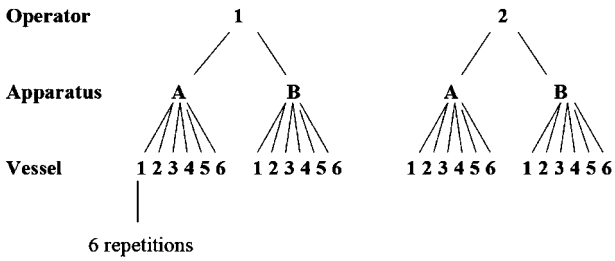

Figure 1. Three-factor Crossed then Nested Model design of dissolution tests.