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Brief/Technical Note

Dissolution Variability: Comparison of Commercial Dosage Forms with US Pharmacopeia Lot P Prednisone Reference Standard Tablets—A Technical Note

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INTRODUCTION

Dissolution testing of solid oral dosage forms plays a critical role in product development by providing a link (1) between drug release and bioavailability (BA) and bioequivalence (BE) and (2) between drug release and formulation and manufacturing process variables (1–4). The importance of dissolution in quality assurance and regulatory science is well known (5–7). *In vivo–in vitro* correlations and relationships (IVIVC/R) can be established when in vivo absorption is solubility- or dissolution rate-limited. A correlated dissolution test allows waiver of clinical studies for the documentation of BA, BE, and, scale-up and post-approval changes (SUPAC; 5,7).

USP dissolution apparatus 1 and 2 are widely used for testing solid oral dosage forms (8). As with any analytical equipment, and perhaps particularly with dissolution assemblies, installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) are important. For a dissolution assembly, mechanical calibration provides OQ. For the assembly, analysis, and analytical procedure, the USP dissolution procedure as described in General Chapter *Dissolution* <711> and other General Chapters, together with USP Prednisone Reference Standard (RS) and other Reference Standard Tablets provides PQ (9). Beyond these cGMP approaches, USP's physical tablets support proficiency testing, thus leading to USP's new term Performance Verification Test (PVT) for the term *apparatus suitability* in <711> (10,11). USP has extensively studied the quality attributes of USP Lot P Prednisone RS Tablets and their sensitivity to selected variables of the dissolution test procedure using apparatus 1 and 2 (12–14).

Some have argued that dissolution testing is specific to a particular product and thus have recommended the use of in-house standards for PQ of dissolution equipment (15,16). Some members of the scientific community are also of the opinion that USP RS Tablets contribute much of the variability observed in dissolution testing (17). The purpose of the study reported here was to determine the dissolution variability associated with selected commercial dosage forms in comparison to USP Lot P Prednisone RS Tablets. The secondary purpose was to gain data that would inform the process of choosing an RS for dissolution PQ. A product that displayed low variability (repeatability) and sensitivity to selected variables during dissolution testing would be an ideal dissolution RS. This study did not attempt to evaluate the quality of the commercial medicines for their intended therapeutic use.

MATERIALS AND METHODS

Study Materials

The selection criteria for the immediate-release products tested in this study were: availability of a USP monograph and RS; active ingredient sufficiently nontoxic that the material could be handled under normal laboratory conditions; availability of a UV method of analysis; and prevalence of the dosage form's use. Based on these criteria the authors selected four products for initial study: USP Prednisone RS tablets, Reference Standard Lot P0E203 (United States Pharmacopeia, Rockville, MD); 10 mg prednisone tablets, USP, Lot 56967 (generic product from United Research Labs Inc., Philadelphia, PA); 20 mg famotidine tablets, Lot R5900 (Pepcid, Merck Inc., Whitehouse Station, NJ); 150 mg ranitidine hydrochloride tablets, Lot 6ZP7739 (Zantac, GlaxoSmithKline, Philadelphia, PA); and 500 mg metformin tablets, Lot 6D19083 (Glucophage, Bristol Myers-Squibb Company, New York, NY). Commercial drug products were purchased from McKesson Medical (San Francisco, CA). Dissolution profiles were determined for the selected products. Those products with a dissolution rate suffi-

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Table I. Dissolution Test Conditions

Product	USP Dissolution Apparatus	Dissolution Medium	Medium Volume (ml)	Rotation Speed (rpm)	Sampling Time (min)[a]	Monograph Tolerance	UV Absorbance (nm)
USP Lot P Prednisone RS Tablets	2 (paddle)	Water	500	50	30	N/A	242
Generic prednisone tablets	2 (paddle)	Water	500	50	–	NLT 80% in 30 min	242
Famotidine tablets	2 (paddle)	pH 4.5, 0.1 M phosphate buffer	900	50	–	NLT 75% in 30 min	265
Ranitidine hydrochloride tablets	2 (paddle)	Water	900	50	15	NLT 80% in 45 min	314
Metformin tablets	2 (paddle)	pH 6.8, 0.05 M phosphate buffer	1000	50	10	NLT 80% in 30 min	233

[a] Dissolution profiles were determined by sampling manually at 5-min intervals. The sampling time was chosen as the period at which about 40–60% of the drug dissolved. For the USP RS Tablets sampling was done at 30 min as specified in <711>
NLT Not less than

ciently slow to enable analysts to sample at a time (*t*) corresponding to about 50% dissolved were chosen for the variance study. Drug products that dissolve very rapidly were not selected because they did not provide adequate time to permit the detection of apparatus irregularities.

Chemicals

USP provided all RS, including Prednisone RS Lot M0D211, Prednisone RS Tablets Lot P0E203, Famotidine RS Lot I0E063, Ranitidine Hydrochloride RS Lot H0B268, and Metformin Hydrochloride RS Lot H0E136. Potassium phosphate monobasic, sodium hydroxide, and ethyl alcohol, USP (190 proof) were obtained from Fisher Scientific (Waltham, MA).

Dissolution Assemblies

The three dissolution assemblies used in this study were Hanson SR8Plus (Hanson Research, Chatsworth, CA), Distek Evolution 6100 (Distek Inc., North Brunswick, NJ), and VanKel 7010 (Varian Inc., Palo Alto, CA). They are identified by the Greek letters alpha, gamma, and epsilon (not in that order) to avoid disclosure of an individual assembly's performance. An integrated system consisting of the tester (bath), vessels, shafts, and paddles constitutes a dissolution assembly. In order to minimize the random experimental errors, the shafts, paddles and vessels were individually identified and were used in the same positions on the dissolution tester throughout this study. A *position* is defined as the location of a vessel in relation to other vessels in the tester.

Dissolution Procedure

Table I summarizes the dissolution test conditions for the study materials. Dissolution tests were performed at 37 °C using Milli-Q water (Millipore Corporation, Billerica, MA) for dissolution media preparation. Dissolution tests for the commercial dosage forms were carried out according to the procedure specified in the individual monographs in *USP 29* (8), and dissolution tests for USP Lot P Prednisone RS Tablets were conducted according to the procedure specified in General Chapter *Dissolution* <711>, *USP 29*.

Deaeration Technique

Dissolution medium (see Table I) was heated to about 41 °C with gentle stirring, and then a vacuum of 60 mbar was generated using a water aspirator (Model B-169, Brinkman Instruments, Westbury, NY) and monitored with an in-line vacuum gauge (Vacuubrand, Essex, CT). Medium was filtered under vacuum using a 0.45-µm membrane filter (Millipore Corporation) with vigorous stirring that continued for 5 min under vacuum following filtration (8).

Sampling

For the commercial dosage forms dissolution profiles were determined by sampling manually at 5-min intervals. The single sampling time chosen for comparison of repeatability was the period at which about 40–60% of the drug dissolved (see Table I). This sampling time was necessary because sensitivity to dissolution variables typically appears midway through the dissolution profile. At the designated sampling time point, samples of about 30 ml were manually collected.

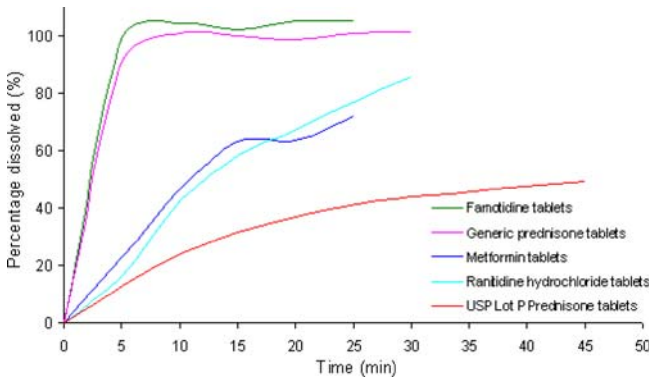

Fig. 1. Dissolution profiles for the study materials

Table II. Dissolution Results for USP Lot P Prednisone RS Tablets

Dissolution Assembly	Analyst	Percent Drug Dissolved (%)			
		Range	Mean	SD	%RSD
Alpha	A	40.5–44.3	43.0	1.4	3.2
	B	40.2–46.5	42.8	1.9	4.4
Gamma	A	38.6–44.6	41.6	1.9	4.5
	B	42.2–45.7	44.2	1.2	2.7
Epsilon	A	41.8–47.7	45.0	2.3	5.1
	B	40.4–47.0	42.8	2.0	4.6

The results reported are the summary of two dissolution experiments: $n=12$; 6 tablets were analyzed in each experiment

Table IV. Dissolution Results for Metformin Tablets

Dissolution Assembly	Analyst	Percent Drug Dissolved (%)			
		Range	Mean	SD	%RSD
Alpha	A	33.8–53.2	39.9	5.7	14.3
	B	32.4–52.8	42.6	5.6	13.2
Gamma	A	30.0–50.2	41.8	5.9	14.2
	B	38.6–51.1	43.0	4.2	9.7
Epsilon	A	33.2–49.6	40.7	5.6	13.8
	B	33.8–48.6	39.3	4.3	10.9

The results reported are the summary of two dissolution experiments: $n=12$; 6 tablets were analyzed in each experiment

Filtration

Samples were filtered with a syringe filter, discarding the first 5 ml, and filter suitability studies were performed for ranitidine hydrochloride tablets. Acceptable filters were those that showed less than 2% difference in drug recovery between filtered dissolution samples and unfiltered centrifuged dissolution samples. For metformin tablets, *USP* metformin revision files specified the type of filter. The filters used in the study were as follows:

- USP Lot P Prednisone RS Tablets—0.45 μm Millex HV hydrophilic (Millipore)
- Ranitidine hydrochloride tablets—0.45 μm Millex HV hydrophilic (Millipore)
- Metformin tablets—0.45 μm Puradisc Nylon (Whatman, Billerica, MA).

UV Analysis

Drug concentrations were measured by UV analysis (PerkinElmer Instruments, Wellesley, MA) and an external standard of USP RS solutions to determine relative drug concentrations. Dissolution samples were diluted if necessary in order to obtain absorbance values close to those of the standard solutions, and dissolution results were calculated as a percentage of the label claim dissolved.

Study Protocol

Two analysts (identified as A and B) performed dissolution variance studies for USP Lot P Prednisone RS Tablets, ranitidine hydrochloride tablets, and metformin tablets on three dissolution assemblies (identified as Alpha, Gamma, and Epsilon). For each product two analysts performed two experiments on each dissolution assembly, for a total of 12 experiments (72 tablets) per product.

Table III. Dissolution Results for Ranitidine Hydrochloride Tablets

Dissolution Assembly	Analyst	Percent Drug Dissolved (%)			
		Range	Mean	SD	%RSD
Alpha	A	46.6–66.8	57.9	6.4	11.1
	B	49.3–74.2	60.1	8.1	13.4
Gamma	A	43.8–80.1	60.7	8.3	13.6
	B	45.1–67.4	55.7	7.2	12.9
Epsilon	A	40.4–63.5	52.6	7.6	14.5
	B	39.0–66.1	56.9	8.0	14.1

The results reported are the summary of two dissolution experiments: $n=12$; 6 tablets were analyzed in each experiment

Statistical Analysis

Percent dissolved values were first summarized (mean and %RSD) by product, analyst, and assembly. To determine the contributors to variability, individual percent dissolved values were then transformed into the natural log scale to better approximate a normal distribution. The data were then analyzed using a mixed-effects model with analyst, experiment within analyst, and position within experiment treated as nested random effects using the default variance components covariance structure.

Preliminary analyses explored how to include assembly in the analyses. Including assembly as a fixed effect found no large or statistically significant assembly effects. Also, there was no indication based on the Akaike information criterion (AIC; 18,19) that variances differed between assemblies. The remaining analysis, including only random effects, estimated four variance components: interanalyst, interexperiment (intraanalyst), interposition (intraexperiment), and residual.

All results were transformed back to the original scale and the percent coefficients of variation (%CVs) for the

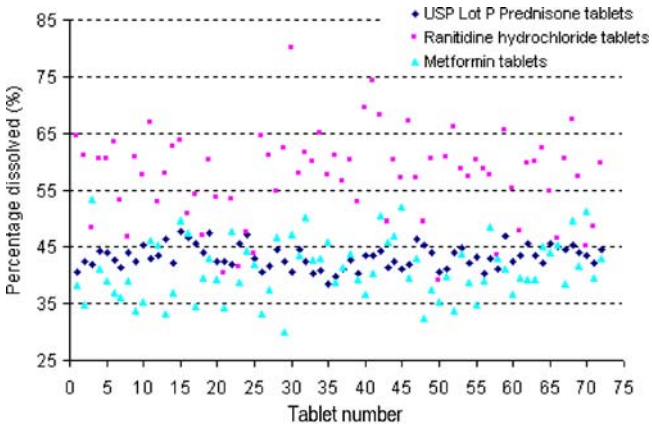

Fig. 2. This figure depicts the scatter of dissolution results for individual tablets. The overall mean for USP Lot P Prednisone RS Tablets, ranitidine hydrochloride tablets, and metformin tablets were 43.2, 56.8, and 40.9, respectively

variance components were calculated as $100\%\sqrt{\exp(S^2)-1}$, where S^2 is the variance component in the natural log scale. Repeatability reported here uses the International Conference on Harmonization/International Organization for Standardization/USP (ICH/ISO/USP) definition (20). The reported repeatability CV was found by first summing the variance components for experiment, position, and residual and then determining the %CV as given above.

All analyses were conducted using Proc Mixed of SAS 9.1.3 (SAS Inc., Cary, NC) on a Windows-based computer.

RESULTS AND DISCUSSION

Figure 1 illustrates dissolution profiles of the study materials. In the case of famotidine and generic prednisone tablets, more than 90% dissolution occurred within the first 5 min of the dissolution test. Therefore, they were not considered suitable for inclusion in the variance studies and are not considered further in this report. In this study the sampling time points selected for the variability analysis (i.e., the time at which 40–60% of the drug was dissolved) was 10 min and 15 min for metformin tablets and ranitidine hydrochloride tablets, respectively. The sampling time for USP Lot P Prednisone tablets was 30 min.

Tables II, III, and IV summarize the dissolution results for the USP Lot P Prednisone RS Tablets, ranitidine hydrochloride tablets, and metformin tablets, respectively. Disintegration and cone formation was observed with the film-coated ranitidine hydrochloride tablets. Metformin tablets were nondisintegrating. Figure 2 illustrates dissolution results for individual tablets. The overall mean percent dissolved for USP Lot P Prednisone RS Tablets, ranitidine hydrochloride tablets, and metformin tablets were 43.2, 56.8, and 40.9, respectively. The range for percent dissolved for USP Lot P Prednisone RS Tablets, ranitidine hydrochloride tablets, and metformin tablets were 38.6 to 47.7, 39.0 to 80.1, and 30.0 to 53.2, respectively.

Variance contributions of analyst, experiment, position, and residual were determined. No variance contributions from analyst and experiment were observed. The residual variance includes contributions from uncontrolled experimental parameters such as tablet placement and tablet assay in addition to inherent tablet-to-tablet variability. The residual %CV for ranitidine hydrochloride tablets, metformin tablets, and USP Lot P Prednisone RS Tablets were 14.2%, 11.7%, and 4.7%, respectively. The repeatability %CV for ranitidine hydrochloride tablets, metformin tablets, and USP Lot P Prednisone RS Tablets were 14.2%, 12.9%, and 4.7%, respectively. Therefore, with the exception of metformin, which demonstrated a %CV of 5.4% for position-to-position variability, the variability observed in this study was solely due to the tablets and uncontrolled experimental error.

This study sheds light on the challenges associated with the selection and use of in-house standards, namely rate of dissolution and sensitivity. This study was not designed to directly address a desirable property of a dissolution RS, namely that it should be sensitive to dissolution variables. Instead the authors considered a related factor, repeatability. For a candidate reference standard to be *detectably* sensitive, the response to changes in dissolution variables must exceed the background noise of the repeatability variability. Two of the initial choices, famotidine and the generic prednisone tablets, dissolved instantaneously. This is was not surprising because most immediate-release formulations are designed for instantaneous dissolution. This re-emphasizes that a product formulated for its clinical properties may not have the properties desirable for a dissolution RS—drug products that dissolve completely within a very short time period (<10 min) are not likely to show sensitivity to dissolution variables or abnormalities of dissolution assemblies.

SUMMARY AND CONCLUSIONS

This study determined the dissolution variability (repeatability) of commercial dosage forms and USP Lot P Prednisone RS Tablets. The repeatability %CV for USP Lot P Prednisone RS tablets was less than one-half that of Ranitidine hydrochloride tablets and metformin tablets. This study also provides insight into some of the challenges associated with the selection and use of in-house dissolution standards. In particular, tablets that dissolve very quickly are not suitable as reference standards.

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