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Calibration of the USP 3 (Reciprocating Cylinder) Dissolution Apparatus

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Summary

This article describes in detail the procedure for calibrating the USP 3 (reciprocating cylinder) dissolution apparatus. Included are the assay methods, calculations, and criteria for passing calibration. Also included are possible causes for calibration failure, as well as suggestions to make the process more efficient.

Introduction

In 1991, the USP included the reciprocating cylinder apparatus as an alternative to the basket and paddle apparatuses for drug release testing. [1] The reciprocating cylinder apparatus design is based on the disintegration tester described in the USP and BP and consists of six glass tubes fastened vertically to reciprocating pistons. The glass tubes contain the formulation to be tested and are enclosed by screens at the top and bottom of the tube. Dimensions may be found in reference 2. For general drug release testing, the tubes are immersed in thermostatted vessels containing dissolution media and may be dipped at a frequency ranging from 5 to 40 dips per minute (dpm). The tubes can be moved between successive rows of vessels during an assay with a short drain time allowed after removal from one row and before immersion in the next. Samples may be collected from vessels manually during pauses in testing or after rows are completed, or samples may be collected during testing by means of an attached autosampler. The history of the USP 3 apparatus has been recently summarized. [3] Both VanKel and Hanson have versions of the USP 3 apparatus on the market.

Calibration Requirements

To meet the calibration requirements, the apparatus must pass limits from three tests with two time points each. Chlorpheniramine maleate 16 mg extended-release tablets are tested at 5 dips per minute (dpm) with sampling at 1 and 4 hours, and at 30 dpm with sampling at 2 and 6

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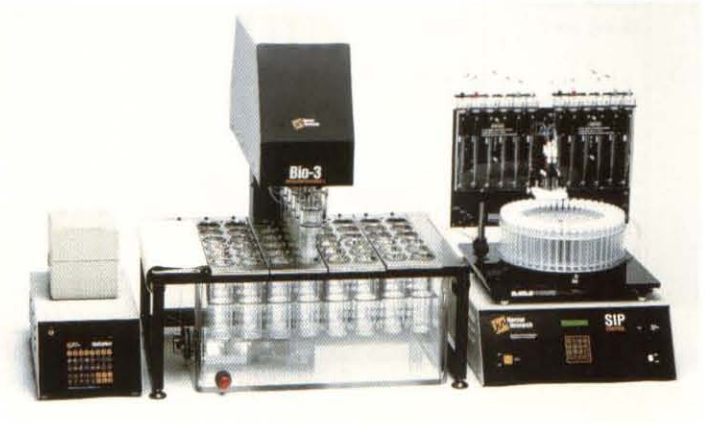
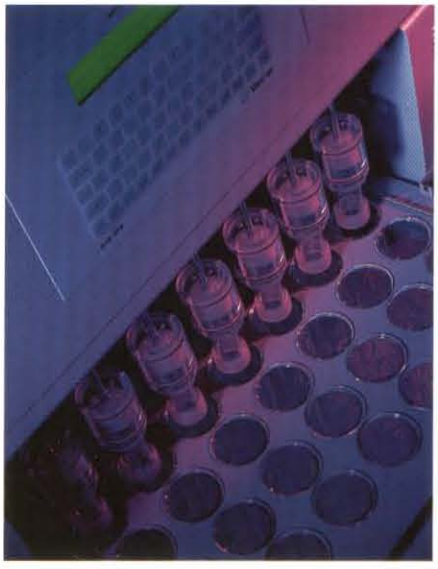


Above: Hanson's Model "B-3" USP Apparatus 3

Below: VanKel's Bio-Dis USP Apparatus 3



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hours. Theophylline extended-release beads are tested at 15 dpm with sampling at 2 and 6 hours. The system suitability ranges were established through a collaborative study conducted by the USP (described in detail in reference 4). Table 1 summarizes the tests and drug release limits for the current USP calibrator lots. All six limits must be met or the apparatus is not considered calibrated.

Table 1. Calibration criteria for the USP 3 (reciprocating cylinder) apparatus. The limits only pertain to the specific calibrator lots listed.

Dosage Form	Reciprocation Rate	Time Point	Limits (% Dissolved)
Chlorpheniramine Maleate Extended-release Tablets, 16 mg, Lot F	5 dpm	1 hr	22 - 30
		4 hr	51 - 67
	30 dpm	2 hr	37 - 61
		6 hr	79 - 100
Theophylline Extended-release Beads. Lot F-1	15 dpm	2 hr	16 - 25
		6 hr	61 - 92

Calibration Procedure: Chlorpheniramine Maleate Tablets

Apparatus set up:

Bottom screen: 20-mesh stainless steel.
Top screen: None.
Medium: 250 mL water at 37.0 ± 0.5°C.
Dose: One tablet per sample tube.

Sampling protocol:

Sample volume: 10 mL aliquot per test point.
Sample preparation: Filter sample with a 0.8 µm Millipore HA filter or equivalent. Discard the first 3 mL. To the remainder, add 60 µL of 6 N HCl.

In addition to the Millipore HA filters, we have found Gelman non-sterile acrodisc filters, either polysulfone or the acrylic copolymer on nylon support, to be acceptable. Filter bias can easily be checked by comparing the absorbance of a non-filtered solution to that of the same solution filtered. A difference of < 2% can be considered acceptable from a practical standpoint.

The 6 N HCl solution can be prepared by diluting concentrated (37%) hydrochloric acid with an equal volume of water. We use a digital microliter pipette to accurately add 60 µL to the sample.

Reference Standard Preparation:

The reference standard should be prepared to the equivalent of 16 mg/250 mL. The diluent should be 0.1 N HCl.

UV Endpoint Assay:

Wavelength: 264 nm.
Pathlength: 0.5 cm cell.
Blank: 0.1 N HCl.

The procedure that accompanies the tablets states that dilution is not needed if a 1.0 cm cell is used for the UV analysis. We found on our spectrophotometer that the solutions were too concentrated and the absorbance was > 1.0. A 0.5 cm cell brought the absorbance back into the 0 - 1.0 range for which our spectrophotometer was calibrated.

Calculation of Results:

In order to calculate percent dissolved, the sample concentrations need to be corrected for the fact that since 10 mL samples are taken, at later time points dissolution occurs into a volume smaller than the original 250 mL. The following are the general equations to be used for any method in which samples are pulled out of only one row initially containing 250 mL of dissolution medium.

The calculation involves four steps:

(1) Calculate the concentration in the samples relative to the standard.

$$C_x = (A_{smp}/A_{std})^*(W_{std}/V_{std})$$

where

A_{smp} = Sample Absorbance
A_{std} = Standard Absorbance
W_{std} = Weight of Standard
V_{std} = Volume of Standard Dilution

(2) Calculate the volume into which the 'xth' sample dissolves.

$V_x = 250 - [(Nx - 1)*Vsmp]$

where

N_x = Number of samples pulled from vessel

V_{smp} = Volume of sample pulled from vessel

For a 10 mL sampling volume, V_{smp} = 10 mL, V_x = 250 mL for the first sample, 240 mL for the second sample, etc.

(3) Calculate the percent of label in each sample aliquot.

$S_x = C_x*V_{smp}*(100/L)$

where

100 = Conversion factor to % of label

L = Label strength of tablet

C_x and V_{smp} are defined previously, **L** = 16 mg for the chlorpheniramine maleate calibrator tablets.

(4) Calculate the volume corrected percent dissolved.

$Px = Cx*Vx*(100/L) + \Sigma(S1 + ... + Sx-1)$

The result from this equation, **Px**, is the percent dissolved value which is compared to the calibration limits. The equation takes into account that after a sample aliquot is removed from the vessel, the remainder of the drug in the dosage form dissolves into a smaller volume. It then adds back the amount of drug that was removed in the previous aliquots to get the total percent dissolved.

These are the general equations if samples are pulled only from one row, as in the case of the calibrators. If developing a method using more than one row, add the amount dissolved in each previous row to the current row's result to get total percent of label dissolved.

Operating Notes for Chlorpheniramine Maleate Calibrators:

Tablets which stick to the bottom screen are reported to yield slower drug release profiles and should not be used for the limits test. [4] It has been our experience that at 5 dips per minute, the agitation rate is low enough that the tablets remain on the bottom screen of the sample tube during the test. Whether 'stuck' or not, drug release rates from these tablets have always met the calibration requirements. For the 30 dpm test, tablets contact the bottom screen during the up-stroke of the piston but are suspended in the medium during the piston down-stroke. A tablet stuck on the bottom screen can be loosened by a tap on the side of the metal piston which holds the sample tube.

Calibration Procedure: Theophylline Beads

Apparatus set up:

Bottom screen:	40-mesh polypropylene.
Top screen:	40-mesh polypropylene.
Medium:	250 mL 0.1 N HCl at 37.0 ± 0.5°C.
Dose:	Accurately weigh 200 ± 20 mg beads into each cylinder and record mass.

Sampling protocol:

Sample volume: 10 mL aliquot per test point.

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Sample preparation: Filter sample with a 0.8µm Millipore HA filter or equivalent. Discard the first 3 mL and collect the remainder.

As in the case of the chlorpheniramine maleate calibrators, we have found that in addition to the Millipore HA filters, Gelman non-sterile acrodisc filters, either polysulfone or the acrylic copolymer on nylon support, are acceptable for the theophylline samples.

Reference Standard Preparation:

The reference standard should be prepared to the equivalent of 58 mg/100 mL. Use 0.1 N HCl as the diluent.

UV Endpoint Assay:

Wavelength: 270 nm
Pathlength: 0.02 cm cell
Blank: 0.1 N HCl

Calculation of Results:

Theophylline sample concentrations need to be volume corrected. The following equations are used to calculate results.

(1) Calculate the concentration in the samples relative to the standard.

$$C_x = (A_{smp}/A_{std})*(W_{std}/V_{std})$$

where

A_{smp} = Sample Absorbance
A_{std} = Standard Absorbance
W_{std} = Weight of Standard
V_{std} = Volume of Standard Dilution

(2) Calculate the volume into which the 'xth' sample dissolves.

$$V_x = 250 - [(N_x - 1)*V_{smp}]$$

where

N_x = Number of samples pulled from vessel
V_{smp} = Volume of sample pulled from vessel

For a 10 mL sampling volume, V_{smp} = 10 mL, V_x = 250 mL for the first sample, 240 mL for the second sample, etc.

(3) Calculate the percent of label in each sample aliquot.

$$S_x = C_x*V_{smp}*[100/(0.72*W_{smp})]$$

where

100 = Conversion factor to % of label
0.72 = Theoretical weight fraction of theophylline in beads
W_{smp} = Weight of beads
C_x and V_{smp} are defined previously.

(4) Calculate the volume corrected percent dissolved.

$$P_x = C_x*V_x*[100/(0.72*W_{smp})] + \Sigma(S_1 + ... + S_{x-1})$$

The result from this equation, **Px,** is the percent dissolved value which is compared to the calibration limits. The equation takes into account that after a sample aliquot is removed from the vessel, the remainder of the drug in the dosage form dissolves into a smaller volume. It then adds back the amount of drug that was removed in the previous aliquots to get the total percent dissolved.

Operating Notes for Theophylline Bead Calibrator:

When weighing out beads, assemble the bottom cap, screen, and glass cylinder. Then tare the assembly and weigh the beads directly into it. If you try to weigh into just the bottom cap with screen, it is difficult to screw in the glass cylinder without trapping and crushing some of the beads between the cap and the cylinder.

General Notes

For the entire calibration procedure, we prepare 2 liters of 0.1 N HCl from standard volumetric concentrates which are commercially available. Of the 2 liters, 250 mL is used for the chlorpheniramine reference standard, 1.5 L for the theophylline bead dissolution medium, and 100 mL is used for the theophylline reference standard. The remaining 150 mL is available for UV blanks.

When tracking down the cause of calibration failures, consider the following suggestions. It has been shown that of all instrument parameters, sustained release formulations are most affected by reciprocation rate. [5] The reciprocation rate may be checked with a stopwatch, but it is anticipated that small deviations will not affect drug release rate of the calibrators to any great extent, especially for the theophylline beads. Unless there is a serious problem with the apparatus, a more likely cause of failure involves the analytical assay. Assure that the absolute absorbance is within the calibrated range of the detector. If not, the cell may be the

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wrong size. Check that the appropriate analytical wavelength is being used. Prepare an additional standard and check its relative absorbance against that of the original standard. If significantly different, the original standard may have been improperly prepared. If using a sipping device for the UV spectrophotometer, ensure there is no carryover by running a blank after the standard. If carryover occurs, increase the flush volume until carryover drops to an acceptably low level.

If the cause of the failure can be traced to one of the above or a similar analytical error, it may be appropriate to just document the deviation and reassay the samples using the corrected procedure. In the event that a specific cause for failure can not be identified, quantities of samples are not sufficient for reassay, or too much time has elapsed so sample integrity is questionable, then retest. It is only necessary to repeat the calibration test(s) which failed, although both time points per test condition should be measured.

References

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