Drug Development and Industrial Pharmacy, 22(12), 1187-1192 (1996)

Validation of a Computer Spreadsheet Used to Perform Dissolution Calculations

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ABSTRACT

Dissolution testing for various pharmaceutical dosage forms is an integral part of release and stability testing requirements. In order to assist in such testing, a spreadsheet has been written and validated to perform dissolution calculations using Microsoft Excel software. The spreadsheet has been written for a dissolution experiment where the volume of the dissolution medium is held constant for the vessel by replacing removed dissolution medium with fresh dissolution medium at each time point. The spreadsheet corrects for the amount of dissolved drug substance removed at each time point and reports results in terms of percent of label claim dissolved for each vessel. The use of computer software to assist in data manipulation in the pharmaceutical industry requires adequate documentation, and therefore a validation protocol has been written and is described. An example of the formulas used to generate the spreadsheet is also given and can be easily used by readers to implement design of their own spreadsheets for dissolution calculations.

INTRODUCTION

The role of dissolution testing in drug quality tests, bioavailability studies, and bioequivalence testing has been previously outlined (1). The importance of dissolution testing and its relationship to the stability of solid oral dosage forms has recently been reviewed (2). In addition, the Food and Drug Administration (FDA) has become increasingly more interested in replacing single-point test requirements with dissolution profiles containing multiple time points (3). The resource requirements to support dissolution testing can be reduced by automated calculations using a personal computer and spreadsheet software. A spreadsheet entitled "Dissolution Calculator" was written to perform dissolution calculations using Microsoft Excel software. Figure 1 dis-

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	A	B	C	D
1	ENTER DATA INTO SHADED AREAS:			
2		time 1	time 2	time 3
3	STD RESPONSE=	650029	642000	660230
4	CONC STD (MG/ML)=	0.002565		
5	PRODUCT STRENGTH (MG)=	1.25		
6	MEDIA VOLUME (ML)=	500		
7	VOLUME REMOVED (ML)=	20		
8				
9	CONC SAMPLE MAXIMUM=	0.0025		
10				
11	VESSEL	1	2	3
12				
13	SAMPLE RESPONSE (TIME 1)	125003	126565	123456
14	SAMPLE RESPONSE (TIME 2)	187504	193644	181881
15	SAMPLE RESPONSE (TIME 3)	325007	329069	322656
16	SAMPLE RESPONSE (TIME 4)	437510	442977	432106
17	SAMPLE RESPONSE (TIME 5)	525012	531573	512354
18	SAMPLE RESPONSE (TIME 6)	537512	542333	539565
19				
20	RESULTS			
21				
22	VESSEL	1	2	3
23				
24	% DISSOLVED (TIME 1)	19.73	19.98	19.49
25	% DISSOLVED (TIME 2)	30.75	31.75	29.85
26	% DISSOLVED (TIME 3)	52.49	53.17	52.08
27	% DISSOLVED (TIME 4)	72.82	73.76	71.91
28	% DISSOLVED (TIME 5)	89.63	90.77	87.54
29	% DISSOLVED (TIME 6)	94.89	95.80	95.04
30				
31				
32	% DISSOLVED	MEAN	STD DEV	%RSD
33	TIME 1	19.49	0.65	3.35
34	TIME 2	30.32	1.07	3.53
35	TIME 3	52.27	0.90	1.71
36	TIME 4	72.03	1.25	1.74
37	TIME 5	88.82	2.58	2.90
38	TIME 6	94.62	0.85	0.90
39				
40				
41	VESSEL	1	2	3
42				
43	FRACTION DISSOLVED T1	0.19730	0.19977	0.19486
44	MG REMOVED T1	0.00987	0.00999	0.00974
45	FRACTION DISSOLVED T2	0.30755	0.31746	0.29846
46	MG REMOVED T2	0.01498	0.01547	0.01453
47	FRACTION DISSOLVED T3	0.52494	0.53174	0.52083
48	MG REMOVED T3	0.02525	0.02557	0.02507
49	FRACTION DISSOLVED T4	0.72822	0.73756	0.71911
50	MG REMOVED T4	0.03441	0.03484	0.03398
51	FRACTION DISSOLVED T5	0.89630	0.90774	0.87538
52	MG REMOVED T5	0.04143	0.04195	0.04044
53	FRACTION DISSOLVED T6	0.94886	0.95797	0.95036
54	MG REMOVED T6	0.04241	0.04279	0.04257

Figure 1. Spreadsheet used for dissolution calculations with data for a hypothetical dissolution experiment displayed.

plays a portion of the spreadsheet with sample information entered for a hypothetical dissolution experiment. The input data are shown in rows 3 through 18, with results indicated in rows 24 through 54. The spreadsheet was written for a dissolution experiment where the volume of the dissolution medium is held constant for the vessel by replacing removed dissolution medium with fresh dissolution medium at each time point. The spreadsheet was written to assist in calculating percent dissolved values when multiple time points are being measured in a dissolution profile study. The spreadsheet allows for the input of different standard responses for each of the six time points. This feature is useful for high-performance liquid chromatography analysis of dissolution samples that may contain multiple bracketing standard sets. The spreadsheet corrects for the

amount of dissolved drug substance removed at each time point and reports results in terms of percent of label claim dissolved for each vessel. The spreadsheet also calculates the mean percent dissolved, standard deviation, and percent relative standard deviation for each time point.

The spreadsheet is opened by the analyst as a read-only document (the ability to enter the document and edit protected cells is controlled by a password). The spreadsheet portion which performs the calculations consists of protected cells. Other sections of the document where data are entered are not protected and will allow the analyst to enter data. The cells where data are to be entered can be shaded using simple Excel commands when writing the spreadsheet in order to assist the analyst in locating the data input cells.

Several publications address GMP documentation requirements for automated systems and computer system validation (4–6). In addition, the FDA has provided guidance in software development which focuses on methods and techniques for the management and development of software (7). The software life cycle has been categorized into (*a*) a requirement phase, (*b*) a design phase, (*c*) an implementation phase, (*d*) a test phase, (*e*) an installation and checkout phase, and finally (*f*) an operation and maintenance phase. This article explores the final two phases, which require two types of documentation:

1. The output of the procedure must be verified for accuracy. This verification is documented in the Methods section. This section is part of the check-out phase where the "system's ability to properly perform its control functions" is confirmed (7).
2. As part of the operation and maintenance phase, an approved validation protocol must be supplied. The validation protocol document describes a procedure to be followed at any point when it may be necessary to confirm the reliability of the spreadsheet. Appropriate times to confirm the reliability would be after an Excel software upgrade or after any modification to the spreadsheet calculation section. The validation protocol is described in the Results section.

METHODS

The calculations of the spreadsheet were validated against manual calculations using a hand-held calculator (TI-36X calculator from Texas Instruments). A detailed account of the spreadsheet validation (including a comparison of manual and computer calculations) would typically be given in a validation report. The validation report serves as the foundation for the validation protocol. The formulas used for the manual calculations are shown below.

Fx = fraction of active dissolved at time x.

$ASAM(x)$ = area of sample (HPLC peak) or absorbance at time x.

$ASTD(x)$ = area of standard (HPLC peak) or absorbance at time x.

$CONC\ STD$ = concentration of standard solution (milligrams/milliliter).

$CONC\ MAX$ = maximum theoretical concentration of sample (milligramd of dissolved drug substance/milliliter of dissolution medium).

$TAB\ STR$ = tablet or capsule strength (milligrams of drug substance/tablet or capsule).

$M(x - 1)$ = milligrams of dissolved drug substance removed at time point $(x - 1) = CONC\ (x - 1) \times mL$.

$CONC\ (x - 1)$ = concentration (milligrams/milliliter) of dissolved drug substance in dissolution vessel at time point $(x - 1)$.

$$= \frac{ASAM\ (x-1)}{ASTD\ (x-1)} \times CONC\ STD$$

mL = milliliters of medium removed at each time point.

$$Fx = \frac{ASAM\ (x)}{ASTD\ (x)} \times \frac{CONC\ STD}{CONC\ MAX} \times TAB\ STR + \frac{M(x-1) + \cdots M(x-m)}{TAB\ STR}$$

In the validation report, manual calculations were demonstrated to compare with the calculations generated by the spreadsheet. The spreadsheet was originally created by making column B (vessel 1), and then column B was filled across automatically using the appropriate Excel command to create columns for vessels 2 through 12. Data were input into the spreadsheet and concurrent manual calculations were carried out and shown to correspond to the computer outputs for time point 1 of vessel 1 through vessel 12.

The percent dissolved result cells for times 2 through 6 were originally made by using Excel fill down, and therefore a check of time 6 was made to assure that all lines were correct.

Additionally, the accuracy of the columns was validated by inputting the data from vessel 1 in each of the other columns to ensure that the generated results were the same for each vessel.

Figure 2 displays a printout of the spreadsheet formulas for vessel 1. From this printout, these basic formulas can be used to build an entire template for as many vessels as required.

RESULTS

A validation protocol was drafted to be used in the qualification of the software. The protocol was divided into functional sections for ease of use by the analyst involved in the validation.

I. Purpose
To evaluate the functionality of the Microsoft Excel spreadsheet "Dissolution Calculator" and determine compliance against stated criteria.

II. Identification: Validation Test Environment
The spreadsheet "Dissolution Calculator" may be

	A	B
1	ENTER DATA INTO SHADED AREAS:	
2		time 1
3	STD RESPONSE=	650029
4	CONC STD (MG/ML)=	0.002565
5	PRODUCT STRENGTH (MG)=	1.25
6	MEDIA VOLUME (ML)=	500
7	VOLUME REMOVED (ML)=	20
8		
9	CONC SAMPLE MAXIMUM=	0.0025
10		
11	VESSEL	1
12		
13	SAMPLE RESPONSE (TIME 1)	125003
14	SAMPLE RESPONSE (TIME 2)	187504
15	SAMPLE RESPONSE (TIME 3)	325007
16	SAMPLE RESPONSE (TIME 4)	437510
17	SAMPLE RESPONSE (TIME 5)	525012
18	SAMPLE RESPONSE (TIME 6)	537512
19		
20	RESULTS	
21		
22	VESSEL	1
23		
24	% DISSOLVED (TIME 1)	=B41*100
25	% DISSOLVED (TIME 2)	=B43*100
26	% DISSOLVED (TIME 3)	=B45*100
27	% DISSOLVED (TIME 4)	=B47*100
28	% DISSOLVED (TIME 5)	=B49*100
29	% DISSOLVED (TIME 6)	=B51*100
30		
31	% DISSOLVED	MEAN
32	TIME 1	=(B24+C24+D24+E24+F24+G24+H24+I24+J24+K24+L24+M24)/12
33	TIME 2	=(B25+C25+D25+E25+F25+G25+H25+I25+J25+K25+L25+M25)/12
34	TIME 3	=(B26+C26+D26+E26+F26+G26+H26+I26+J26+K26+L26+M26)/12
35	TIME 4	=(B27+C27+D27+E27+F27+G27+H27+I27+J27+K27+L27+M27)/12
36	TIME 5	=(B28+C28+D28+E28+F28+G28+H28+I28+J28+K28+L28+M28)/12
37	TIME 6	=(B29+C29+D29+E29+F29+G29+H29+I29+J29+K29+L29+M29)/12
38		
39	VESSEL	1
40		
41	FRACTION DISSOLVED T1	=(B13/$B$3)*($B$4/$B$9)
42	MG REMOVED T1	=((B$13/$B$3)*$B$4)*$B$7
43	FRACTION DISSOLVED T2	=(((B14/$C$3)*($B$4/$B$9)*$B$5)+B42)/$B$5
44	MG REMOVED T2	=((B$14/$C$3)*$B$4)*$B$7
45	FRACTION DISSOLVED T3	=(((B15/$D$3)*($B$4/$B$9)*$B$5)+B$44+B$42)/$B$5
46	MG REMOVED T3	=((B$15/$D$3)*$B$4)*$B$7
47	FRACTION DISSOLVED T4	=(((B16/$E$3)*($B$4/$B$9)*$B$5)+B$44+B$42+B$46)/$B$5
48	MG REMOVED T4	=((B$16/$E$3)*$B$4)*$B$7
49	FRACTION DISSOLVED T5	=(((B17/$F$3)*($B$4/$B$9)*$B$5)+B$44+B$42+B$46+B$48)/$B$5
50	MG REMOVED T5	=((B$17/$F$3)*$B$4)*$B$7
51	FRACTION DISSOLVED T6	=(((B18/$G$3)*($B$4/$B$9)*$B$5)+B$44+B$42+B$46+B$48+B$50)/$B$5
52	MG REMOVED T6	=((B$18/$G$3)*$B$4)*$B$7

Figure 2. Spreadsheet printout showing formulas used for calculation of results for vessel 1.

run with Microsoft Excel version 4.0 on a MacIntosh IICi with the appropriate system software (Version 7.0.1). The spreadsheet "Dissolution Calculator" may be run on other computer systems; however, the spreadsheet must be validated for each PC on which it is installed.

III. Overview

The spreadsheet "Dissolution Calculator" performs computations for the determination of percent label claim of drug dissolved for up to 6 time periods and 12 dissolution vessels. The spreadsheet has been written for a dissolution experiment where the volume of the dissolution medium is held constant for the vessel by replacing removed dissolution medium with fresh dissolution medium at each time point.

IV. Assumptions

The purpose of this validation protocol is to demonstrate that dissolution results reported by "Dissolution Calculator" conform to results obtained previously and confirmed by manual calculation as reported in the original validation report. In achieving this purpose, the spreadsheet "Dissolution Calculator" will be tested, verified, and validated.

V. Validation Methodology

1. Accessing "Dissolution Calculator" spreadsheet.
   1.1. The desktop will display several icons. Using the mouse, double click on the icon entitled "Dissolution Calculator."
   1.2. The next screen requires the input of a password to edit the document or selection of READ ONLY to perform the validation. Double click on the READ ONLY box to open the spreadsheet.
2. Entering the first data set into the spreadsheet
   2.1. The actual protocol should have attached a data set which contains the necessary numerical inputs to demonstrate that the software is functioning properly. This data set represents a collection of hypothetical data from a dissolution experiment for 12 vessels and 6 data points. Data are entered by using the mouse to select a cell by clicking on the cell of interest. The number is typed in the cell and the enter or return key is then pressed. As the data are entered in the shaded areas of the spreadsheet, calculated results will appear in the results section of the spreadsheet. The computer-outputted results will be compared (see Section VII) with manually verified calculations from the original validation report.
3. Printing the spreadsheet
   3.1. Under the file menu, select print and press return in order to print (1) the data input section and (2) the results section of the spreadsheet.
4. Exiting the spreadsheet
   4.1. Under the file menu select quit and respond NO to the question of saving changes.
5. Entering the second data set into the spreadsheet. (The second data set should also be attached to the protocol. The second data set contains the same numerical input for each vessel in order to demonstrate that each column performs the same calculation.)
   5.1. Repeat lines 1.1 and 1.2.
   5.2. Enter the data displayed in the second data set into the shaded areas of the spreadsheet in a fashion similar to that described in line 2.1.
6. Printing the spreadsheet
   6.1. Under the file menu, select print and press return in order to print (1) the data input section and (2) the results section of the spreadsheet.

VI. Criteria for Acceptance

The determination of acceptance for the validation of "Dissolution Calculator" will be based on the comparison of report printouts produced during the Validation Procedure to validated "Dissolution Calculator" printouts obtained during the original validation of the spreadsheet.

VII. Analysis

Verify that the report printouts from the validation protocol study match the printouts from validation report.

VIII. Results

Evaluate each report printout as outlined in the Analysis section against the Criteria for Acceptance of the protocol. All problems or discrepancies will be logged. Verify on each report acceptance or rejection and sign and date the data.

IX. Conclusion

Review and draw conclusions on the status of each of the report printouts created during the validation. Include all exceptions to the Criteria for

Acceptance that have been identified and any corrective action that was taken to correct the exception. Indicate the status of the "Dissolution Calculator" procedure for operational release.

X. Review Process
The individual responsible for the review process is listed here. Typically the lab manager is responsible.
1. Review validation report printouts and summarize conclusions after report generation has been completed.
2. Issue recommendation for operational release.

XI. Revalidation
Whenever hardware/software/communication problems, enhancements, or modifications are indicated, the software application manager will determine the extent of revalidation, document conclusions, and follow the review process.

XII. Validation Log
1. A validation log sheet will reside with the responsible manager. This log sheet will be completed for all scheduled and unscheduled validation tests. Copies of the validation log will be archived.
2. An archive will be maintained of unscheduled/scheduled protocol executions and corrective actions taken during each validation.

CONCLUSIONS

The use of spreadsheet software can greatly enhance the productivity of the laboratory. The use of such software requires the proper documentation to demonstrate that the software is correctly performing its desired task, and a protocol is necessary to properly evaluate the validity of the system.

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