

Development and Validation of Computer Spreadsheet Used to Calculate Dissolution Profiles without Media Replacement

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Abstract

Calculations carried out to generate dissolution profile data are complicated and subject to error to be performed manually, moreover and due to the repetitive nature of the dissolution testing experiments it is necessary to create a validated spreadsheet to replace and overcome the problems associated with manual calculations. A simple, user friendly spreadsheet was written to calculate dissolution profiles for a dissolution experiment where the volume of the dissolution medium for the vessel varies with time as the removed dissolution medium is not replaced with fresh one at each time point. The calculations of the spreadsheet were validated against manual calculations using a hand-held calculator; the results of the two methods were found to be comparable. The developed spreadsheet can be easily adapted for use in regulated environment after activating the security features embedded in Microsoft Excel software such as formulae hiding, cells block and password protection.

Keywords: Spreadsheet, Dissolution profiles calculation without media replacement.

1. Introduction

In vitro dissolution testing provides useful information at several stages of drug development process. Formulation scientists use dissolution to assess the dissolution properties of the drug itself and thereby by select appropriate excipients for the formulation. Dissolution testing is also employed to assist in choosing among candidate formulations, with the aim of selecting the dosage form with the most suitable and reproducible release profile. Dissolution tests are also used to establish *in vivo/in vitro* correlation between release of drug from dosage form and drug absorption [1].

Dissolution testing is also used to assure quality of the manufactured products and to ensure batch to batch reproducibility and adequate performance throughout their shelf lives [2].

In addition, there has been increasingly more interest in replacing single point test requirements with dissolution profiles containing multiple time points [3,4].

When sampling is carried out at multiple time points there are three potential scenarios:

- The sample is removed from the dissolution vessel and no replacement media is added resulting in a reduction in the dissolution volume.
- The sample is removed from the dissolution vessel and replacement media is added, resulting in the media volume remaining unchanged but there is a reduction in the concentration of the drug in the dissolution media in the dissolution vessel.
- The sample is returned to the dissolution vessel after analysis. This results in no changes to the dissolution volume or the concentration of the drug in the dissolution media.

In both of the first two scenarios it is necessary to take into account the amount of drug removed from the dissolution at previous time points in order obtain accurate release profiles. In the first scenario it is also necessary to take into account the changing dissolution volume.

The use of Excel spreadsheets in a regulated environment (cGXP = GMP, GLP, GCP) has to be controlled and validated. Also, periodic revalidation after defined intervals or changes has to be performed. This is consistent with EC guides on Good Manufacturing Practice (chapter 6.7, “Documentation” [5] and chapter 6.16, “Testing” [6]) and the FDA 21 CFR Part 11 electronic records and electronic signatures regulation [7].

Calculations carried out to generate dissolution profile data are complicated and subject to error to be performed manually, moreover and due to the repetitive nature of the dissolution testing experiments it is necessary to create a validated spreadsheet to replace and overcome the problems associated with manual calculations.

This spreadsheet will be written for a dissolution experiment where the volume of the dissolution medium for the vessel varies with time as the removed dissolution medium is not replaced with fresh one at each time point.

The sheet will assist in calculating the amount dissolved and the percent dissolved values when multiple time points are being measured in a dissolution profile study. 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.

To ensure the spreadsheet security, the ability to enter the document and edit protected cells will be controlled by a password. The spreadsheet portion which performs the calculations consists of protected and locked 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 will be shaded using simple Excel commands; when writing the spreadsheet in order to assist the analyst in locating the data input cells.

2. Methods

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 calculations of the spreadsheet were validated against manual calculations using a hand-held calculator (fx-100MS Casio Scientific Calculator). The formulas used for the manual calculations are shown below:

$$T_1 \% \text{ dissolved} = (((A_1 \times V) / A_s) \times C \times D) \times W \times 100$$

$$T_2 \% \text{ dissolved} = (((A_2 \times (V - (P \times n - 1))) + (A_1 \times P)) / A_s) \times C \times D) \times W \times 100$$

$$T_3 \% \text{ dissolved} = (((((A_3 \times (V - (P \times n - 1))) + (A_1 + A_2) \times P)) / A_s) \times C \times D) \times W \times 100$$

$$T_n \% \text{ dissolved} = (((((A_n \times (V - (P \times n - 1))) + (A_{n-1} + A_{n-2} + \dots) \times P)) / A_s) \times C \times D) \times W \times 100$$

Where,

A₁ = the absorbance or analytical response of the first sample pull

A₂ = the absorbance or analytical response of the second sample pull

A_n = the absorbance or analytical response of the nth sample pull

A_s = the average absorbance or analytical response of the standard

V = the initial media volume, ml

C = the concentration of the standard, mg/ml

W = the dose strength of the sample, mg

P = the volume of media being withdrawn for a single sample pull, ml

D = the withdrawn sample dilution factor (if diluted after pulling)

n = the number of the sample pull taken

3. Results

A spreadsheet entitled “Calculation of Dissolution Profiles” was written to perform dissolution calculations using Microsoft Excel software. Table 1 displays a portion of the spreadsheet with sample information entered for a hypothetical dissolution experiment.

Dissolution Profile Analysis

Enter data into shaded area

Product Name:	XYZ
Strength(mg)	40
Volume (ml)	900
Standard concn.(mg/ml)	0.008
Average std response	0.434
Sample pull volume (ml)	20.00
Sample dilution factor	5

Samples responses

Sample pull No.	Vessel number	
	1	
1	0.364	
2	0.462	
3	0.482	
4	0.488	
5	0.495	
6	0.499	

Results:

mg removed

Time (minutes)	Vessel number	
	1	
10	0.671	
20	0.840	
30	0.883	
40	0.893	
50	0.905	
60	0.911	

Table 1: Spreadsheet used for dissolution calculations with data for a hypothetical dissolution experiment

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.

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.

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

To further ensure the accuracy of the calculation a hypothetical dissolution profile calculation was carried out

for 12 vessels with 6 pulls of the samples from each vessel spanning from 10-60 minutes, the input data of vessels 4, 2 and 3 were intentionally used again as data for vessels 7, 11 and 12 respectively, the results of these each vessel were in full agreement with its corresponding one, Table 3 displays the data calculated for the twelve vessels as well as the mean percent dissolved, standard deviation(Stdv.), and percent relative standard deviation (RSD%) for each time point.

Results:

mg removed		Vessel number
Time (minutes)		1
10		=B15/\$B\$9*\$B\$8*\$B\$11*\$B\$10
20		=((((B16*(\$B\$7-(\$B\$10*(A\$17-1)))+(B15*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11*\$B\$10/\$B\$7)
30		=((((B17*(\$B\$7-(\$B\$10*(A\$18-1)))+(B15+B16)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11*\$B\$10/\$B\$7)
40		=((((B18*(\$B\$7-(\$B\$10*(A\$19-1)))+(B15+B16+B17)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11*\$B\$10/\$B\$7)
50		=((((B19*(\$B\$7-(\$B\$10*(A\$20-1)))+(B15+B16+B17+B18)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11*\$B\$10/\$B\$7)
60		=((((B20*(\$B\$7-(\$B\$10*(A\$21-1)))+(B15+B16+B17+B18+B19)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11*\$B\$10/\$B\$7)
Fraction dissolved %		
Time (minutes)		Vessel number
		1
10		=((((B15*\$B\$7/\$B\$9)*\$B\$8*\$B\$11/\$B\$6)*100)
20		=((((B16*(\$B\$7-(\$B\$10*(A\$17-1)))+(B15*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11/\$B\$6)*100)
30		=((((B17*(\$B\$7-(\$B\$10*(A\$18-1)))+(B15+B16)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11/\$B\$6)*100)
40		=((((B18*(\$B\$7-(\$B\$10*(A\$19-1)))+(B15+B16+B17)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11/\$B\$6)*100)
50		=((((B19*(\$B\$7-(\$B\$10*(A\$20-1)))+(B15+B16+B17+B18)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11/\$B\$6)*100)
60		=((((B20*(\$B\$7-(\$B\$10*(A\$21-1)))+(B15+B16+B17+B18+B19)*\$B\$10))/\$B\$9)*\$B\$8)*\$B\$11/\$B\$6)*100)

Table 2: Spreadsheet printout showing formulas used for calculation of results for vessel

mg removed		Vessel number											
Time (minutes)	1	2	3	4	5	6	7	8	9	10	11	12	
10	0.671	0.662	0.664	0.643	0.636	0.623	0.643	0.636	0.623	0.671	0.662	0.664	
20	0.840	0.839	0.870	0.812	0.845	0.792	0.812	0.845	0.792	0.840	0.839	0.870	
30	0.883	0.869	0.875	0.869	0.868	0.877	0.869	0.868	0.877	0.883	0.869	0.875	
40	0.893	0.882	0.888	0.880	0.885	0.872	0.880	0.885	0.872	0.893	0.882	0.888	
50	0.905	0.877	0.892	0.890	0.895	0.890	0.890	0.895	0.890	0.905	0.877	0.892	
60	0.911	0.892	0.897	0.903	0.905	0.904	0.903	0.904	0.920	0.905	0.892	0.897	
Fraction dissolved %													
Time (minutes)						Vessel number							
						6	7	8	9	10	11	12	
10	75.48	74.45	74.65	72.37	71.54	70.09	72.37	71.54	70.09	75.48	74.45	74.65	
20	94.45	94.44	97.92	91.35	95.03	89.08	91.35	95.03	89.08	94.45	94.44	97.92	
30	99.32	97.71	98.39	97.79	97.66	98.68	97.79	97.66	98.68	99.32	97.71	98.39	
40	100.48	99.26	99.94	98.95	99.59	98.10	98.95	99.59	98.10	100.48	99.26	99.94	
50	101.80	98.69	100.31	100.09	100.73	100.18	100.09	100.73	100.18	101.80	98.69	100.31	
60	102.54	100.35	100.87	101.56	101.83	101.65	101.56	101.65	103.50	101.80	100.35	100.87	
		Mean	Stdv.	%RSD									
10		73.10	2.00	2.73									
20		93.71	2.94	3.14									
30		98.26	0.63	0.64									
40		99.39	0.79	0.79									
50		100.30	0.96	0.96									
60		101.54	0.89	0.88									

Table 3: The data calculated for the twelve vessels, the mean percent dissolved, standard deviation and percent relative standard deviation for each time point.

4. Conclusion

The use of spreadsheets is a very helpful tool for data-organization, data-entry and data-calculations as such it is greatly enhancing the productivity of the laboratory.

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