

AN AUTOMATED APPLICATION TEMPLATE FOR DISSOLUTION STUDIES IN SDMS VISION PUBLISHER

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OVERVIEW

Dissolution studies during drug product manufacturing employ a standardized workflow that may be readily captured as a standardized template by using electronic report and authoring tools (see Figure 1 for workflow example). A standardized template both guides the analyst through the workflow and ensures reliable data capture without skipping necessary steps.⁴

SDMS Vision Publisher is a reporting and authoring module for NuGenesis SDMS. A Vision Publisher Dissolution Template provides a dissolution workflow and acts as a centralized document to record all aspects of a dissolution study.

INTRODUCTION

In vitro dissolution simulates *in vivo* drug release of solid dosage forms, transdermal patches, and suspensions.¹⁻³ For example, in the case of tablets and capsules, the acidic environment of the stomach is emulated and the rate of drug release is measured as a function of time. Quantitative measures are made by taking small aliquots of the dissolution medium from the dissolution device at defined time points, e.g., 5, 10, 20, 30 minutes.¹⁻³ The measurements can be performed by a number of standard analytical instruments with UV/Vis spectrometers and HPLC being some of the most common.¹ In particular, HPLC methodology offers the advantages of wide dynamic range and excellent selectivity because of the chromatographic separation aspect.¹

Dissolution testing may be performed during various phases of the drug development lifecycle of a dosage form, e.g., during Phases 0 and I to understand the dissolution mechanism; during Phases II and III to understand formulation; and as quality control (QC) during manufacturing.¹⁻² Maintaining good documentation of the dissolution studies is a common theme no matter what the stage of the product life-cycle but is particularly important during manufacturing due to the requirement to adhere to GMP guidelines for proper procedures and documentation.

The following example, illustrates how the Dissolution Template may be used to perform a HPLC based dissolution study.

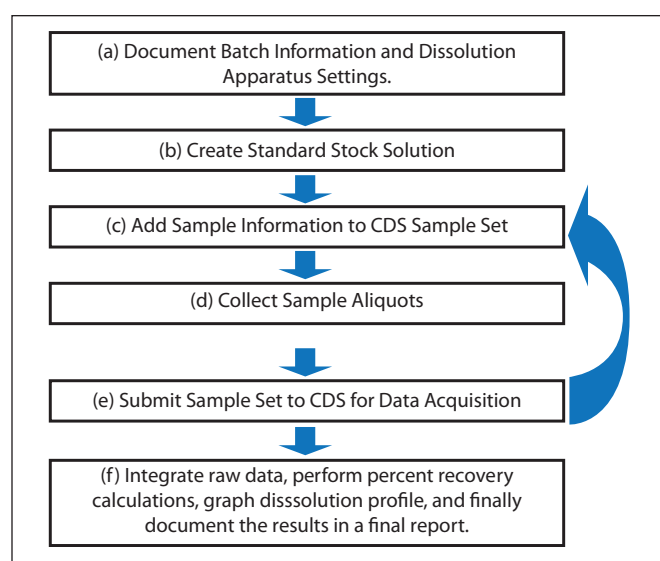


Figure 1. Typical dissolution study workflow when using HPLC for quantitative time point measurements where steps c through e are repeated for each time point.

HOW IT WORKS

Starting a Study

The Dissolution Template captures the workflow outlined in Figure 1 in a single organized electronic document. In order to perform a dissolution study when using SDMS Vision Publisher, a new document is created and the dissolution template is selected. The template consists of six sections (Figure 2): (a) sample and batch information, (b) dissolution bath parameters and sample collection times, (c) reference standard information, (d) dissolution Q-Factor criteria, (e) CDS sample set, (f) dissolution result section, (g) representative chromatograms (optional), and (h) a reference documents summary (i.e., a catalog section listing SOP documents, standard solution preparations, etc.).

[APPLICATION NOTE]

Adding links to representative chromatograms is optional (section g above), but may be useful if a dissolution study fails or to highlight degradation products.

To fill out the template, the analyst enters data both manually and by making use of external system interfaces accessed through Vision Publisher to automatically populate specific fields.

The Sample and Batch Information Section

The sample and batch information section will typically consist of the product name, active component, operator, lot/batch number, dissolution apparatus, and dissolution media (see Figures 2 and 3). This information can be entered manually or by using a Laboratory Information Management System (LIMS).

The screenshot displays the Waters Vision Publisher software interface. The title bar reads "Waters Vision Publisher - [080129_HPLC_0000(2)]". The menu bar includes File, Edit, Document, Tools, Workspace, Services, Administration, Options, Window, and Help. The toolbar contains icons for Message Board, Documents, New Document, Templates, Workspaces, New Workspace, External Systems, and SDMS Project Browser. Below the toolbar is a row of icons for Append, Delete, Replace, Properties, History, Sign, Options, Reload, Save, New, Transfer, and Print. The left sidebar features a "Filter:" section and a table with the following content:

Nr	Title
1	Sample and Batch Description
2	Dissolution Bath Parameters and Collection Times
3	Reference Standard (s)
4	Dissolution Q-Factor (Stage Pass/Fail)
5	CDS Sample Set
6	Dissolution Results
7	Reference Documents

The main workspace shows the "Title" field set to "Dissolution Template Example" and the "Document ID" field set to "080129_HPLC_0000". The "Sample and Batch Information" section contains the following fields:

Sample and Batch Information	
Method	USP-DISS-711
Project (Drug)	
Study	
Analytical Run Batch	
Comment	

The "Dissolution Parameters--Bath A" section contains the following fields:

Dissolution Parameters--Bath A	
Dissolution Vessel Range	1-6
Dissolution Media Volume	900.00
Dissolution Taken Volume	3.50
Dissolution Replaced Volume	0
Dissolution First Position	1
Dissolution Test Length	60.00
Dissolution Infinity Test?	No
Dissolution Media	
Dissolution Temperature	37.0
Dissolution Apparatus Speed	100.0
Dissolution Collect First?	No
Dissolution Sample Volume	1
Dissolution Rinse Volume	2.50
Dissolution Replace Media?	No
Dissolution Recirculate Media?	No
Dissolution Rapid Sampling?	No
Dissolution Pool Vessel Range	

The status bar at the bottom shows "080129_HPLC_0000(2)", "Jim Waters on wli-eu-demo", and "1/29/2008".

Figure 2. Illustration of a blank Vision Publisher Dissolution Template. The Sample and Batch Information sections as well as the dissolution parameters for Bath A are shown in this view.

[APPLICATION NOTE]

Sample and Batch Information	
Method	USP DISS-711
Project (Drug)	Excedrin
Study	Excedrin Dissolution
Analytical Run Batch	WAT-012345
Comment	Common Headache Medication

Figure 3. Entering the sample and batch information into the dissolution document.

The Standard Description Section

A USP reference standard of the active ingredient is required to determine the amount of drug compound released as a function of time. Typically, the quantity of released active ingredient during an HPLC dissolution study is determined by taking the ratio of the LCUV peak responses for the analyte (R_u) over the standard (R_s) multiplied by some factor, e.g., $2250C (R_u/R_s)$ where C is concentration.³ Hence, the preparation and the concentration of the standard must be recorded (Figure 4) in order to subsequently perform the necessary calculations.

The mass measurements for preparing the USP reference standard (and also for weighing the samples) can be captured automatically within the dissolution document by using an automated balance interface (Figure 5). Hence, accuracy of the measurement is improved since the automated tool eliminates the risk of a transcription error.

Description	Work sheet #	Lot #	Exp.Date
See Standard solutions preparation sheet:	071211_Bioanaly_0057	STSTK20071210224154	11/28/2008

Standards to be used for Stage:		1
Standard	Conc.	
1 Standard A	250 mg	

#	Component	Weight
1	Acetaminophen	250
2	Aspirin	250
3	Caffeine	65

Figure 4. The reference standard section captures the component weights for each standard.

Figure 5. Automatically recording a balance measurement for the dissolution study into Vision Publisher.

The CDS Sample Set Section

A predefined Empower™ dissolution sample set method is selected from within the dissolution document. Please note that Empower shown as an example, but the principle is the same for other chromatography systems. Subsequently, the sample and reference standard information are propagated down the sample set (Figure 6). For example, the batch number that was entered into the Sample and Batch Information section of the dissolution document, i.e., the first section of the dissolution document, is now automatically transferred to the sample set. After filling in the required information, the sample set can be submitted for acquisition by the Empower system.

[APPLICATION NOTE]

Open active SSM Search for an existing SSM Create a new SSM Balance Refreh SSM Save SSM Save as SSM Create Sample ID												
D1 PharmaceuticalDissolutionVP31												
CDS Project PharmaceuticalDissolutionVP3 Sample Set OC12100A												
CDS Date 12/11/2007 0:14 Stage 1 Version 1												
Sample Name	Vial #	Of Reps	Method Set / Report Method	Run Time (min.)	Inj. Vol. (ul)	Sample Weight	Dilution Factor	Analysis Function	Proc. Function	Level	Batch	
1 Diluent	4	1	Ch 241 Bicycle Dissolution	10.00	10.0	1.0000	1.0000	Inject Samples	Normal			
2			Ch 241 Bicycle Dissolution					Clear Calibration	Normal			
3 Std A	3	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Standards	Don't Proce			
4 S1 Disso 15min A1	7	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Samples	Don't Proce		AQVRD	
5 S1 Disso 15min A2	8	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Samples	Don't Proce		AQVRD	
6 S1 Disso 15min A3	9	1	Ch 241 Bicycle Dissolution	10.00	10.0	601	1.0000	Inject Samples	Don't Proce		AQVRD	
7 S1 Disso 15min A4	10	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
8 S1 Disso 15min A5	11	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
9 S1 Disso 15min A6	12	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
10 Std A	3	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Standards	Don't Proce			
11			Ch 241 Bicycle Dissolution					Clear Calibration	Normal			
12			Ch 241 Bicycle Dissolution					Calibrate	Normal			
13			Ch 241 Bicycle Dissolution					Quantitate	Normal			
14 S1 Disso 30min A1	13	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
15 S1 Disso 30min A2	14	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Samples	Don't Proce		AQVRD	
16 S1 Disso 30min A3	15	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Samples	Don't Proce		AQVRD	
17 S1 Disso 30min A4	16	1	Ch 241 Bicycle Dissolution	10.00	10.0	601	1.0000	Inject Samples	Don't Proce		AQVRD	
18 S1 Disso 30min A5	17	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
19 S1 Disso 30min A6	18	1	Ch 241 Bicycle Dissolution	10.00	10.0	600	1.0000	Inject Samples	Don't Proce		AQVRD	
20 Std A	3	1	Ch 241 Bicycle Dissolution	10.00	10.0	599	1.0000	Inject Standards	Don't Proce			

Figure 6. Selecting an Empower sample set method for desired dissolution study from within a dissolution document. The sample and standard information are transferred into the sample set. The buttons near the top of the window provide access to the Empower system, e.g., "Open active SSM", "Save SSM", etc.

DISSOLUTION COMPONENTS-BATH A			
	Component Name	Claimed Amount	Q-Factor (min) Q-Factor Percent
1	Acetaminophen	250.00	60 75.00
2	Caffeine	65.00	60 75.00
3	Aspirin	250.00	60 75.00

Figure 7. Calculating the Q-Factor deviation within the dissolution document provides an automated mechanism for deciding whether a subsequent dissolution stage is required. This example shows the Q-Factor criteria values that the acetaminophen, caffeine, and aspirin tablet dissolution study should meet.

The Dissolution Result Section

After the data acquisition on the Empower system has been performed, calculations are performed within Empower and the results are then returned to the Dissolution Result Section. These results are simply summarized within the Dissolution Result Section (Figure 8). If necessary, additional calculations and graphing can be performed within the dissolution document by using Microsoft Excel.

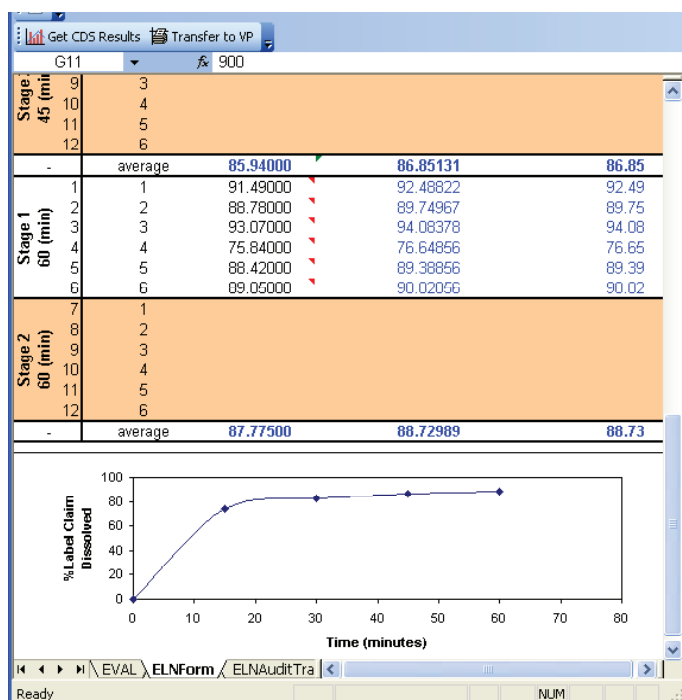


Figure 8. Transferring dissolution results from Empower into the dissolution document. The "Get CDS Results" pull information from the Empower system and the "Transfer to VP" button transfers the results to the dissolution document.

Calculation of Compendia Acceptance Criteria

The conformity to compendia acceptance criteria may not be calculated in some chromatography data systems; however, these calculations can be performed within the dissolution document providing an automated means of defining whether an additional dissolution stage is required. For example, the Q-Factor states that at 60 minutes during the dissolution study of Acetaminophen, Aspirin, and Caffeine tablets, 75% of the drug should be released

within during Stage 1. If the amount of drug released at 60 minutes doesn't meet the Q-factor criteria (within an acceptable error) then a Stage 2 dissolution study is required. Figure 7 shows the Q-Factor criteria for the acetaminophen, aspirin, and caffeine tablet dissolution study.⁵ This functionality allows the analyst to automatically update the CDS sample set to perform additional testing. Three stages are available including Stage 1 (6 replicates), Stage 2 (an additional 6 replicates, and Stage 3 (an additional 12 replicates).

Chromatograms Section (Optional)

Representative chromatograms may be imported into a dissolution document (Figure 9) in addition to the typical results (e.g., % API released) recorded during a dissolution study. This may be particularly useful to highlight degradation products.

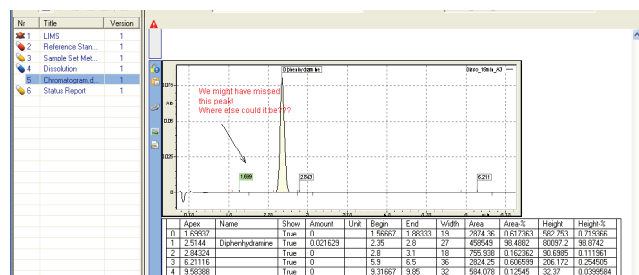


Figure 9. A chromatogram is added to the dissolution document indicating a unknown peak that is causing the study to fail.

Reference Documents Section

The reference documents summary provides an index of documents that are related to the present dissolution study. This index may include references to the original method, USP reference standard preparation protocols, etc.

CONCLUSION

The Dissolution Template within SDMS Vision Publisher provides a centralized electronic document to organize important data and results for a dissolution study. Advantages include: (1) direct electronic interface to data sources such as Empower 2, electronic balances, and LIMS; (2) records are searchable and traceable since they are stored electronically; and (3) the electronic record is 21 CFR Part 11 Compliant Ready. Hence, the QC analyst reduces both the time allocated to performing typical dissolution studies, as well as, the risk associated with transcription errors by using the Vision Publisher template.

Dissolution is a critical test for evaluating the performance of drug products. The process comprises a multi-step workflow where accurate documentation of results is an absolute necessity. The Waters Informatics suite provides an integrated solution that can dramatically streamline workflow, increase laboratory productivity, and facilitate product development and release.

References

1. Wang, Qingxi, et al. *Dissolution Technologies*. August: 6-13, 2006.
2. Gupta, Abhay, et al. *J Pharm Biomed Anal.* 46: 181-186, 2008.
3. United States Pharmacopoeia, USP30-N25, USP General Chapters: 711 Dissolution, 2008.
4. Ping Du, et al. *J. Assoc Lab Autom.* 12(3): 157-165, 2007.
5. United States Pharmacopoeia, USP30-N25, USP Monographs: Acetaminophen, Aspirin, and Caffeine Tablets, 2008.

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