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An Automated Application Template for Dissolution Studies in SDMS Vision Publisher

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Abstract

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. 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.

Experimental

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.).
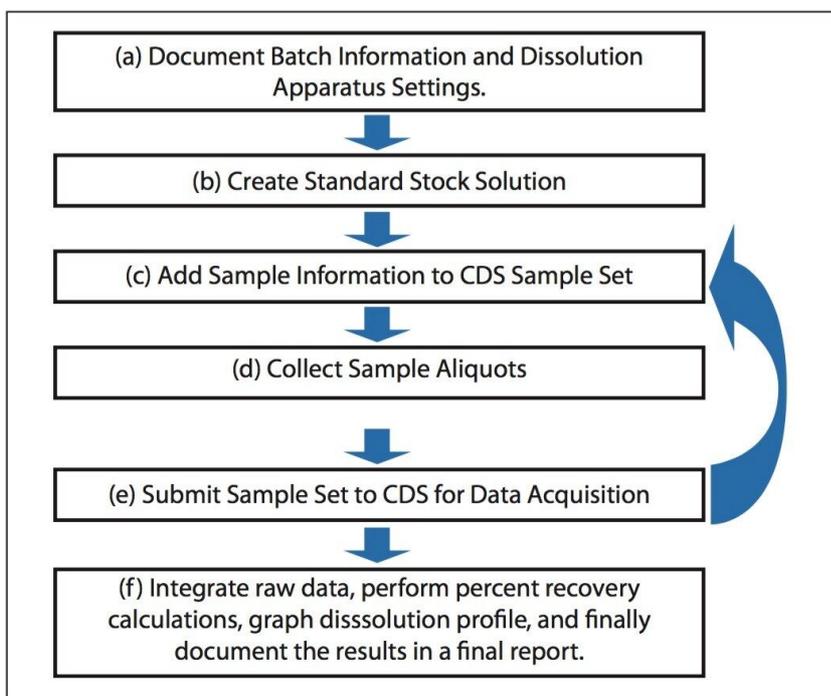

Figure 1. Typical dissolution study workflow when using HPLC for quantitative time point measurements where steps c through e are repeated for each time point.

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).
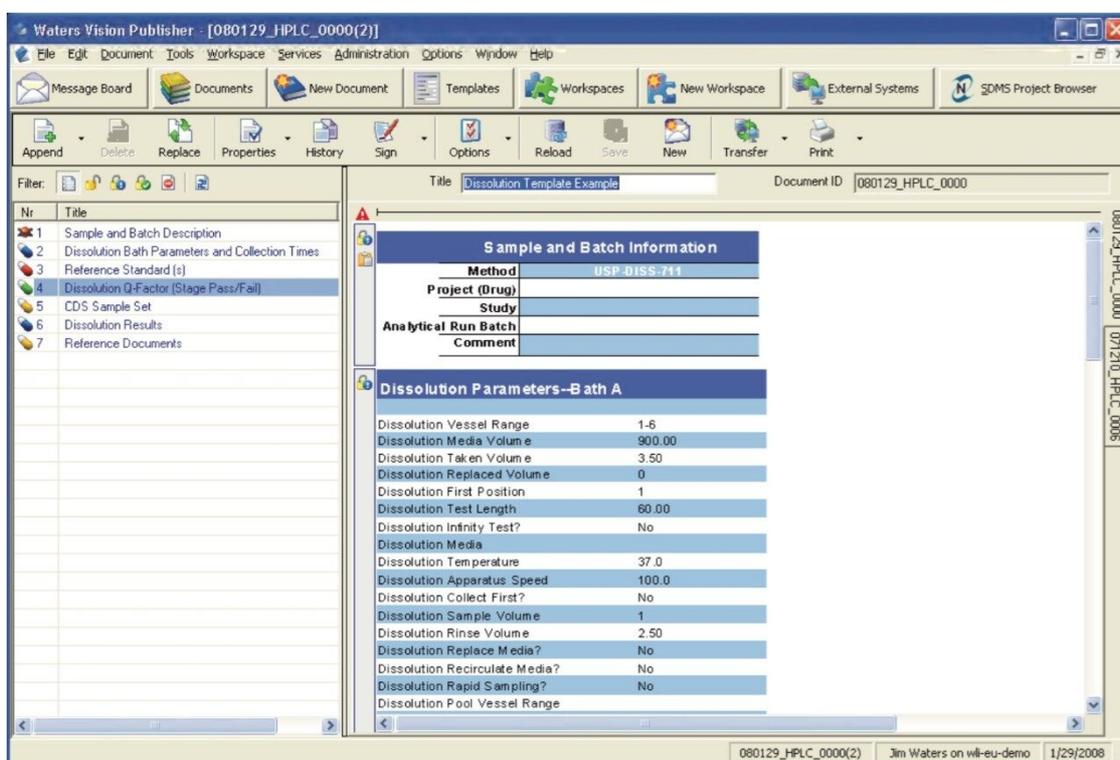

Figure 2. Illustration of a blank Vision Publisher Dissolution Template. The Sample and Batch Information sections as well as the dissolution parameters for Bath A are shown in this view.
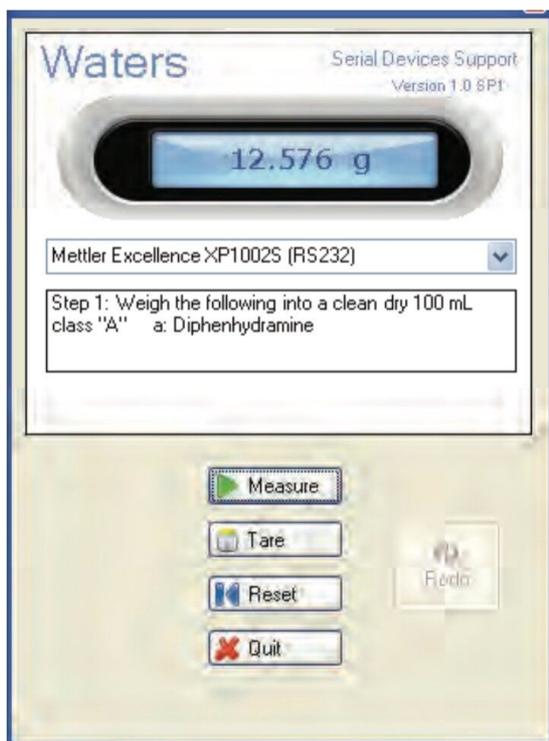
Figure 3. Entering the sample and batch information into the dissolution document.

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 (Ru) over the standard (Rs) multiplied by some factor, e.g., 2250C (Ru/Rs) 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.

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

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.

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.

D1   fx Pharmaceutical\DissolutionVP31

CDS Project Pharmaceutical\DissolutionVP3 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.

Results and Discussion

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.

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).

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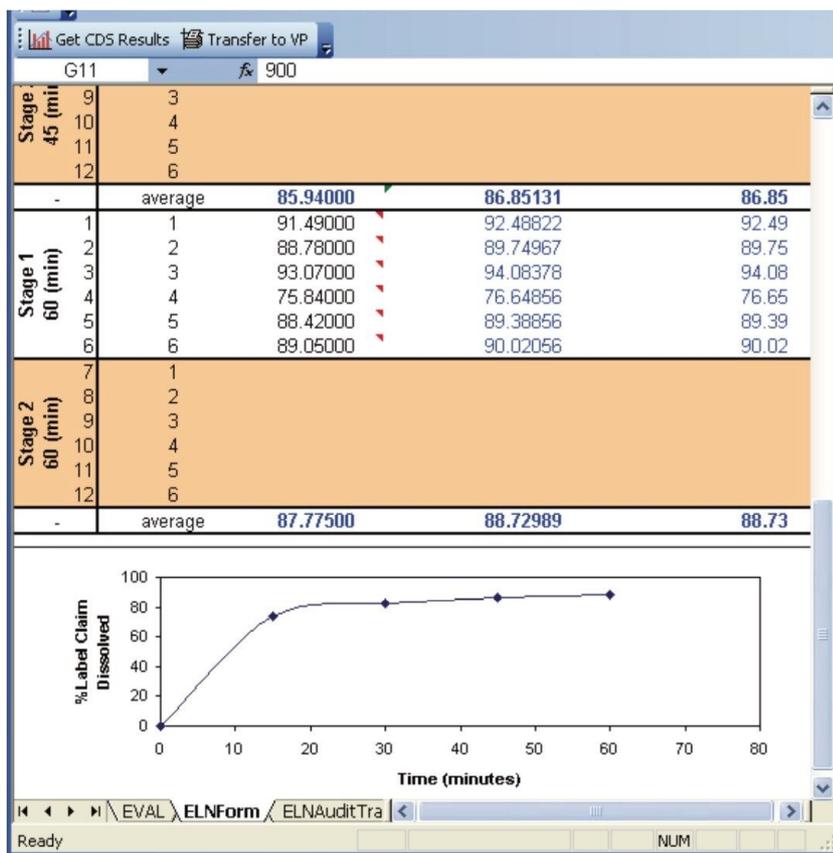
Figure 8. Transferring dissolution results from Empower into the dissolution document. The "Get CDS Results" pull information from the Empower system and the "Transfer to VP" button transfers the results to the dissolution document.

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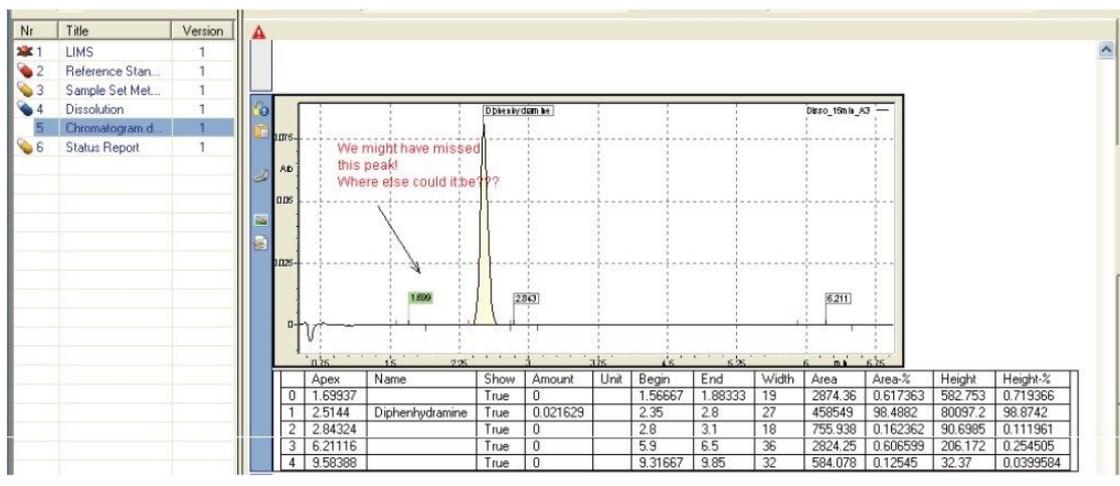
Figure 9. A chromatogram is added to the dissolution document indicating a unknown peak that is causing the study to fail.

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

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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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