Optimization of On-Line Automated Dissolution System for Solid Dose Control Release Tablets

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Abstract — *An optimization of an automated dissolution system for control release tablets has been accomplished by the implementation of several variables using Six Sigma tools. Variables under evaluation includes: filter retention, baselines verification and addition of system suitability parameters. The implementation of the analyzed variables were compare before and after the optimization within 95% confidence interval generating statistically difference between them for three (3) out of four (4) sampling points. Additionally, after the statistical evaluation of the changes the dissolution profiles were evaluated by dissolution similarity factor (f_2) test, where the improvements shows an increase of fifteen (15) units against the same test before the implementation of the optimization.*

Key Terms *— Control Release Tablets, Dissolution profile, UV/VIS Spectroscopy.*

INTRODUCTION

Automated Dissolution System has been a very good alternative to improve laboratory capacity, testing reliability and lead time reduction in regular Quality Control laboratories [6]. Numerous vendors (e.g. Sotax, Horsham, PA Waters, Milford, MA Agilent, Santa Clara CA and Caliper Life Sciences, Hopkinton, MA) already manufacture a different variety of automated dissolution system with several interface were the instrument can be attached to analytical systems as Ultraviolet/Visible (UV/VIS) spectrophotometers and High Performance Liquid Chromatography (HPLC). More common automation lay-outs includes only off-line automation were the analyst after the test is completed, transfer samples to an HPLC, Gas Chromatography (GC) or other analytical equipment to complete the release or stability testing.

Currently a specific pharmaceutical manufacturing company of solid dosage control release bi-layer tablets in Puerto Rico uses an automated dissolution system for the dissolution testing required for profiles study as part of the release and stability testing specification. As part of the system implementation, several studies were performed to evaluated automation equivalency between manual and automated system. Nevertheless, the automation system has been showing discrepant results including atypical dissolution profiles as well as uncharacteristic baseline corrections and high dissolution values at the dissolution end points. Similarity factor (f_2) used to demonstrate equivalency were within Food and Drug Administration (FDA) established guidelines [4], however the similarity factor value was low compare with instrument capacity and product history.

This research is based in identification and control of critical parameters during the automated dissolution of control release tablet using a Zymark MultiDose G3 system from Caliper Life Sciences, Hopkinton, MA (Figure 1). Process understanding in addition to the control of internal and external variables provides adequate knowledge to end users and advances knowledge and technology transfer to product receiving site.

Dissolution test is used in the manufacturing industry to simulate dissolution or solubilization of drug product into the in vivo environment [2]. This test is a significant tool during the developmental phases of drug product mainly tablets or capsules. Additionally, the test is used by quality control laboratories for release purposes or stability

indicators. Dissolution test are controlled by major worldwide pharmacopeias (e.g United State Pharmacopeia (USP), European Pharmacopeia (EP), and Japanese Pharmacopeia (JP)) for those compendial products.

Figure 1
Zymark MultiDose G3 system from Caliper Life Sciences

EXPERIMENTAL

The methodology applied for the study consisted in the application of Six Sigma methodology. The tool used was the DMAIC (Define, Measure, Analyze, Improve and Control) strategy as presented in Figure 2..

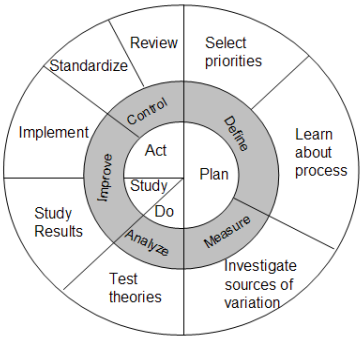

Figure 2
High-Level DMAIC improvement methodology including Plan, Do, Study and ACT

During the define phase, project stake holder in conjunction with the costumers were introduce to the project scope and overall project objectives which includes the improvements of similarity factor between manual and automated method.

In addition, as part of SIPOC (Supplier, Inputs, Process, Outputs and Customer) exercises the variables to be study were established and evaluated. Identified variables were then assessed using cause and effect diagram. Once variables were reviewed then the dissolution test were performed prior system modification "as is" and after system modification to complete a comprehensive statistical analysis which encompass a similarity facto evaluation against manual validated method.

RESULTS AND DISCUSSION

After the analysis of project scope and contributions, a list of variables was listed in order to take into consideration during automated system optimization for the control released tablet testing. The list of main variables and possible causes in the final dissolution process or compliance risk were listed and included in Table 1.

Table 1
List of main variables taken into consideration during the project and possible impact

Variable / Issue	Possible impact in the final dissolution result and/or compliance risk	Proposed Resolution
Baselines variation in dissolution vessels at the beginning of the test.	Unreal dissolution values since the final result is based in the baselines corrections made at the beginning of the testing.	Determine a maximum baseline difference allowance to confirm the validity of baselines values before start the dissolution test.
Filter changes within dissolution sampling points.	As results of filter de-aeration steps, after filter changes, few milliliters of solution is spill resulting in possible variation of sample concentration into the vessels.	Determine the possibility to use only one filter thru the dissolution test in order to avoid discrepancy in final volumes at each sampling points.
Discrepant standard verification	Misalignment practices between manual and	Include necessary standard evaluation e.g. pre

Variable / Issue	Possible impact in the final dissolution result and/or compliance risk	Proposed Resolution
suitability parameters according current company procedures.	automated dissolution practices.	and post analysis.
Short amount of time for the analyst to manually drop the tablets sinkers into the vessels.	Unreal dissolution time.	Add additional time or pause between sampling drop-in and start dissolution time.

Variables Evaluation and Resolutions

After variables evaluation it was determine that each one of them could be assess individually prior to determine if the whole group could be a contributing factor to improve similarity factor (f_2) which was the main objective of the project.

Dissolution Vessel Baselines Correction

In order to evaluate the baseline discrepancies observed during few testing in the automated system, the following actions were taken to evaluate system outputs. The instrument is capable to re-baseline vessels solutions; however a specific requirement to trigger the re-baseline reading and acceptance criteria is required. To evaluate the acceptance criteria it was determined which is the lower absorbance unit value allowed between system re-baselines readings that could not impact final dissolution results with the following results:

- Standard 100% absorbance units (AU) mean is 0.1500AU according method validation data.
- The maximum discrepancy allowed by company procedures is 1% from the final acceptance value due to individual variables e.g. filter and cleaning procedures.
- Having evaluated the maximum error allowed by procedure at the maximum dissolution rate, then, the maximum error allowed during the baselines readings is 1% of 0.1500 AU resulting in 0.0015 AU.
- As per system functionality the evaluation of baselines reading can be performed before start testing process. The analyst could determine if two consecutives baselines readings are within acceptance criteria (0.0015AU) and decide to continue with the testing or abort it.

The inclusion of this verification step prior start testing assure that final results will be within 1% of confidence regarding the baseline correction made by the instrument to evaluate dissolution media absorbance.

Filter changes within dissolution sampling points

A filter verification study was performed to evaluate the suitability of the filter thru the entire dissolution test (four different sampling points). To perform the test it was determine to select the worst case scenario and perform the test at the end point of the dissolution test, where is the maximum concentration of sample into the vessel. Filter A (filter already validated to perform the automated dissolution test) was selected to perform the test. The test was performed outside the automated dissolution system simulating the exact volumes used by the automated system. The test was performed as follow:

- Seven (7) milliliters (mL) of dissolution media were used to purge the filter prior to start filtering the samples.
- Twenty five (25) mL were then filtered four times (using same filter) to simulate the dissolution sampling points. Automated system used twelve (12) mL to purge the lines and thirteen (13) mL to collect samples, therefore 25 mL of sample is filter thru the filter at each time point.

The test was performed in triplicate and one sample taken from same dissolution vessels was centrifuged to be used as control sample. Acceptance criteria for the test was set to not more than (NMT) 1% difference between at each sampling point compared against the control

(unfiltered) sample. This criterion was taken from current validation company requirement. Table 2 resumes the results obtained during the test.

Table 2
Filter retention study evaluation results

Sampling point	Mean Percentage Dissolved
1	98% (25 mL filtered)
2	99% (50 mL filtered)
3	99% (75mL filtered)
4	99% (100mL filtered)
control sample	99% (centrifuge sample)

Results obtained from filter retention study demonstrated that filter A is suitable to filter 100% dissolution sample at four different sampling points without retaining sample from previous sampling point. This test confirms that one filter A can be used in the automated system for each vessel without affecting the final results. As a result of the test, the automated system can be set to not change filters at each time point avoiding the de-aeration step, which was leading into a sample spilling during collection process.

Discrepant standard verification suitability parameters according current company procedures

In order to assure the verification of suitability parameters according company procedures, automated method was set to include a post test evaluation at the end of the test. The evaluation consists of standard comparison between standards at the beginning of test and one standard at the end. The percent (%) difference between these two standards was set according to company procedures.

Reduce amount of time for the analyst to manually drop the tablets sinkers into the vessels

Similar to previous variable, the time before start the dissolution can be set as a pause in the automation method and it was set to add 30 second to the analyst before start the test. This additional time is enough to go from the computer in front to the instrument to drop the tablets sinker into the vessels prior to start the dissolution testing.

Dissolution Evaluation

Once the variables were evaluated it was determined that two of the variables were established to evaluated suitability of the instrument prior to start the test (baseline evaluation) and at the end of the test (standard verification). These two variables were not identified as possible cause of the low similarity factor (f_2) value between manual and automated dissolution. A retrospective evaluation show that previous validation baseline were very similar to the ones observed during the usage of the instrument for same product, therefore even the verification is an important step before start the test it was not an impacting factor in the original similarity evaluation. On the other hand, the standard verification was not identified as impacting factor since the dissolved percentage is calculated using the first standard of the run and the additional standard reading at the end was not, and will not be used to calculate the dissolved percentage. However, this verification assures the user that the instrument was suitable during the testing and could help in the identification of any atypical data during the test.

The addition of time before start the test (setting a 30 seconds delay) was design to allow the user to start the test once they are ready to initiate it. This enhancement was not identified as a possible contributing factor in the low similarity factor results since previous tests were started within the established timeframe ± 2% of dissolution time.

In contrast to previous variables, the leak observed during the purging step in the dissolution test could contribute in lower results of similarity factor since the sample concentrations are impacted due to variability is final volumes. In order to assess if this variable is impacting the similarity factors the following steps were performed.

- Four (4) dissolution tests were performed manually using one lot of control release tablets.
- Four (4) additional dissolution test were performed using automated system "as is" without the implementation of the variables identified in this project. The test was performed using same control release tablets lot.
- Four (4) dissolution tests were performed using the automated system with the implementation of the variables identified in this project.
- Dissolution test were performed using same lot and same dissolution sampling points as specified in the analytical method. Same solutions were also used for the all three testing.

A summary statistics for percentage released of these data are presented in Tables 3 and 4.

Table 3
Summary statistic for percentage released for automated dissolution prior modification and after modifications

Prior Modification (PM) Mean (SD)	After Modification (AM) Mean (SD)	95% Confidence Interval for Difference	Mean Difference p-value
1) 12.0 (2.9)	11.0 (1.4)	(-0.5, 2.4)	0.195
2) 40.2 (3.6)	37.9 (1.7)	(0.4, 4.1)	0.017
3) 83.0 (4.0)	78.3 (2.2)	(2.6, 7.0)	0.000
4) 101.1 (2.2)	98.1 (1.9)	(1.6, 4.3)	0.000

Table 4
Summary statistic for percentage released for automated dissolution after modification and manual method

Prior Modification (PM) Mean (SD)	After Modification (AM) Mean (SD)	95% Confidence Interval for Difference	Mean Difference p-value
1) 10.4 (2.4)	11.0 (1.4)	(-0.4, 1.8)	0.224
2) 35.7 (3.5)	37.9 (1.7)	(0.8, 3.7)	0.004
3) 76.8 (3.6)	78.3 (2.2)	(-0.7, 3.6)	0.168
4) 94.2 (1.3)	98.1 (1.9)	(2.,8 5.0)	0.000

After evaluation of 95% confidence interval for the mean dissolution profiles at every specific sampling point the following can be determine:

- The modifications in the automated method are significantly different at second, third and fourth sampling point. In addition, standard deviations observed for the results after automation modifications were lower than without modifications.
- When the modifications are compared with the manual validated method, there is a significantly difference at sampling points two and fourth. On the other hand, there is a statistical difference at sampling points one and third. The standard deviation for modified automated method produce lower standard deviation results for each of the first three sampling point. Only sampling point four was lower for manual method than automated.

Obtained results demonstrate that the elimination of filter replacement at each sampling point makes a significant contribution in the final dissolution percentage values. Dissolution results after modification shows closer values to those generated by manual validated method.

In order to evaluate the impact of the modification in the similarity factor (f_2), both similarity factors were evaluated. Table 5 show results for similarity factor calculations. Below is the equation that defines a similarity factor (f_2).

$$f_2 = 50\,LOG\left(\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} * 100\right) \qquad (1)$$

where R_t and T_t are the percent dissolved at each sampling point

Table 5
Similarity Factor (f_2) values for dissolution test prior and after automation modifications against the manual method

	Similarity Factor (f_2)
Automated Method Prior Modification / Manual Method	64
Automated Method After Modification / Manual Method	79

An f_2 value between 50 and 100 confirms that the two dissolution profiles are equivalent. However, as closer to 100 the value, more similar the profiles are. Values greater than 50 mean that both profiles does not differ more than 10%. In this specific case, similarity factor between the modified automated method and manual method is 15 unit greater than with the "as is" automated method which means that with modifications performed to the method provide closer values to the reference test (manual method). The results confirm that the variables evaluated and analyzed as part of this project increase the confidence of the automated dissolution method when it is compared against the manual method.

CONCLUSIONS

Based on the results obtained from this project it can be concluded that the identified and experimented variables improve the users' confidence with the automated dissolution system. The confidence was given by the improvement of similarity factor (f_2) value and alignment of current company practices (system suitability) between manual and automated systems. In addition, thru the design of experiment the final customers (analyst) participate and were engage in the project providing additional knowledge and poise to the automated system.

The removal of change filter set-up for each sampling point deliver closer dissolution values compare against the manual validate method which increase the similarity factor value within these two techniques. Additionally, this optimization represents the possibility of huge economical saving concerning the filters supplies used by the company. This variable (elimination of filter at each sampling point) reduces by 24 the amount of filters used by dissolution test. At the moment, the filter value is around $4.25 each resulting in $102.00 saving per lot tested. Taking into consideration ten lots tested per weeks (normal volume of lot for this product) its results in $53,040.00 of total economy per year. Also, the assurance given by the implementation of the results study in this project provides additional analyst flexibility to work in other testing or products meanwhile the automated dissolution system performs the dissolution test for them.

Other achievement that could be obtained by the implementation of the variables studied in this project could be the reduction in laboratory investigations because dissolution practices were aligned between automated and manual system providing additional confidence to the analyst at the time of automated system usage. Additionally, with the elimination of the leak observed during the de-aeration process of the filters the possibility of obtain results out of specification were reduced drastically.

As part of project recommendations it is suggested to adopt the practices described in this study for other products/strengths that could present the same automated dissolution diagnosis.

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