Estudio de Validación de limpieza y recuperación (Swab) Mediante un Analizador basado en oxidación UV/Persulfato

Aplicación 017

RESUMEN

La Validación de limpieza farmacéutica es un proceso multi paso. La Organización FDA lleva publicando guías para la validación de limpieza desde 1963 en las regulaciones de buenas prácticas de fabricación (GMP) (Part 133.4). La organización FDA dispone de instrucciones (Standard Operating Procedures) SOP detallando el proceso de limpieza de fabricación y los equipos productivos.

Estas Instrucciones SOP incluye el entrenamiento de analistas y su documentación generada. Esta aplicación recoge la validación de la limpieza y el estudio de recuperación mediante "swab". La disposición de materiales de referencia para simular el protocolo de limpieza validación del analista y su entrenamiento mediante el Analizador basado en la oxidación con persulfato /UV Teledyne Tekmar Modelo Fusion.

Introduction

The FDA has published guidelines on cleaning validation as part of Good Manufacturing Practices (GMP) as far back as 1963. The 1963 GMP Regulations (Part 133.4) stated "Equipment*** shall be maintained in a clean and orderly manner ***." A similar section was included in the 1978 cGMP regulation concerning cleaning.[1] In general, the FDA expects firms to have written procedures detailing their cleaning processes to ensure that undesirable compounds are not transfer from one batch to a new product batch using the same manufacturing equipment.

Pharmaceutical cleaning validation typically involves multiple methods for determining the suitability of the manufacturing equipment for use. One of the methods employed for ascertaining the cleanliness of the manufacturing equipment is total organic carbon (TOC) analysis of rinse water and swab samples. The UV/Persulfate method can measure the oxidizable carbon from carbon-containing cleaning agents, manufacturing excipents and active pharmaceutical ingredients (APIs).

Pharmaceutical manufacturers require passing or failing results in a timely manner. This allows them to initiate corrective actions, typically called corrective action preventative action (CAPA), to help minimize costly equipment downtime.

This application note will examine eight compounds typically used in the pharmaceutical industry. The compounds will be evaluated for their ability to be oxidized with the UV/Persulfate method by processing them as standards. The compounds will be spotted onto 304/2B stainless steel coupons and allowed to dry. The stainless steel coupons will then be swabbed following typical manufacturing processes. The instrument software will also be evaluated for its ability to determine if a sample passes or fails criteria, and to add samples during the analytical run.

Experimental-Instrument Conditions

Parameters		Advanced Parameters	
Variable	**Value**	**Variable**	**Value**
Sample Volume	9.0mL	Baseline Stabilization Time	0.70 min
Dilution	1:1	Detector Pressure Flow	500mL/min
Acid Volume	0.5mL	NDIR Pressurization	50psig
Reagent Volume	0.8mL	NDIR Pressure Stabilize	0.50 min
IC Sparge Time	1 min	Low Level Filter NDIR	Off

Table 1: Fusion UV/Persulfate TOC Instrument Parameters

Sample Preparation

The compounds used for this application note include l-ascorbic acid, benzoic acid, ceftazidime pentahydrate, cimetidime, metformin HCl, sulfaguanidine, l-tryptophan, and vitamin B12. Stock solutions of approximately 125ppm Carbon for each compound were prepared in TOC quality water. The stock solutions will be used to spot 304/2B stainless steel coupons for the swab study.

The stock solutions were diluted to a final concentration of approximately 2.5ppm. This final dilution will be used to calculate the linearity curve data for each compound. Table 2 list the compounds used for this study and the dilutions made.

Compound	% Carbon	Sample Weight	Stock Dilution	Volume Stock	Final Dilution
l-Ascorbic Acid	40.92	152.5mg	500mL	10mL	500mL
Benzoic Acid	68.85	91.3mg	500mL	10mL	500mL
Ceftazidime Pentahydrate	41.50	148.8mg	500mL	10mL	500mL
Cimetidine	47.60	132.4mg	500mL	10mL	500mL
Metformin Hydrochloride	29.01	216.0mg	500mL	10mL	500mL
Sulfaguanidine	39.61	158.4mg	500mL	10mL	500mL
l-Tryptophan	64.70	96.2mg	500mL	10mL	500mL
Vitamin B12	55.83	53.4mg	250mL	10mL	500mL

Table 2: % Carbon Values and the Sample Dilutions of the Compounds Assayed for the Application Note/Poster

The swab study was performed in two stages. First, 40mL of TOC grade water was added to ten 40mL VOA vials which had previously been tripled rinsed with TOC grade water. A 1ppm solution of the compound was prepared by adding 320µL of the Stock standard into seven of the vials.

A 1ppm concentration was prepared on the stainless steel coupons by spotting 320µL of the stock standard in triplicate onto coupons and allowed them to air dry, similar to a manufacturing site. These three coupons were swabbed individually with separate large Alpha® CleanTips® swabs wetted with TOC grade water. The swab tips were then broken off into the three remaining vials. Five blanks swabs were prepared to determine the swab background for the TOC analysis.

One swab coupon was spiked at a higher level to imitate a swab failure. This high level swab sample will be used to test the ability of the software to allow a rapid CAPA analysis of the failed swab sample.

Samples were analyzed with the Fusion UV/Persulfate TOC instrument utilizing the parameters in Table 1. The other parameters were the standard Fusion TOC Pharmaceutical Water method parameters that were loaded with the Fusion software at the time of installation.

The instrument was calibrated with a 2.5ppmC potassium hydrogen phthalate (KHP) standard. The calibration curve was prepared by using the auto dilution feature to create a 0.050ppmC to 2.500ppmC curve (n=2). A blank was included in the calibration curve. The instrument suitability was determine by comparing the results of a 0.5ppmC sucrose solution to a 0.5ppmC 1,4-benzoquinone solution.

Results

The UV/Persulfate analyzer was successfully calibrated with KHP from 0 to 2.5ppmC. The linear correlation coefficient (r^2) was 0.99998. The system was confirmed to be suitable for pharmaceutical water from the response efficiency of the 0.5ppmC sucrose to the 0.5ppmC 1,4-benzoquinone. The response efficiency was 95.4 % and passed the USP<643> Total Organic Carbon requirement of between 85% to 115%.

The 2.5ppmC standards of the eight compounds were assayed as if they were standards. Their correlation data along with the KHP standard are listed in Table 3. The data indicates that the compounds are readily oxidizable with the UV/Persulfate TOC method. Benzoic acid and cimetidine HCl required sonication to dissolve the sample.

Compound	Correlation Coefficient (r^2)
KHP	0.99998
l-Ascorbic Acid	1.00000
Benzoic Acid	0.99992
Ceftazidime Pentahydrate	0.99996
Cimetidine	0.99950
Metformin Hydrochloride	0.99979
Sulfaguanidine	0.99880
l-Tryptophan	0.99982
Vitamin B12	0.99997

Table 3: Correlation Coefficients for the Compounds Assayed as a Standard Curve

The stock standards of the compounds that had been spiked into 7 VOA vials and spotted in triplicate on stainless steel coupons were assayed as samples. The MDL was calculated for the 7 VOA vials. The Percent Recovery of the 3 swab samples were calculated against the average of the 7 VOA vial solutions. The % RSD of the 3 swab samples was also calculated.

Compound	MDL	% Recovery	%RSD
l-Ascorbic Acid	0.05	87.8	2.5
Benzoic Acid	0.05	36.7	28.5
Ceftazidime Pentahydrate	0.03	84.2	2.5
Cimetidine	0.03	89.6	9.5
Metformin Hydrochloride	0.05	79.5	2.9

Sulfaguanidine	0.11	80.0	1.8
l-Tryptophan	0.03	85.2	0.7
Vitamin B12	0.02	112.4	3.1

Table 4: Minimum Detection Limit of the Seven VOA Vail Solutions and the % Recovery and %RSD of the

Three Swab Samples

The high level swab sample was assayed with other swabs. The software was tested to determine its ability to allow changes to be made during the assay run. Figure 1 is a screen capture of the run in progress.

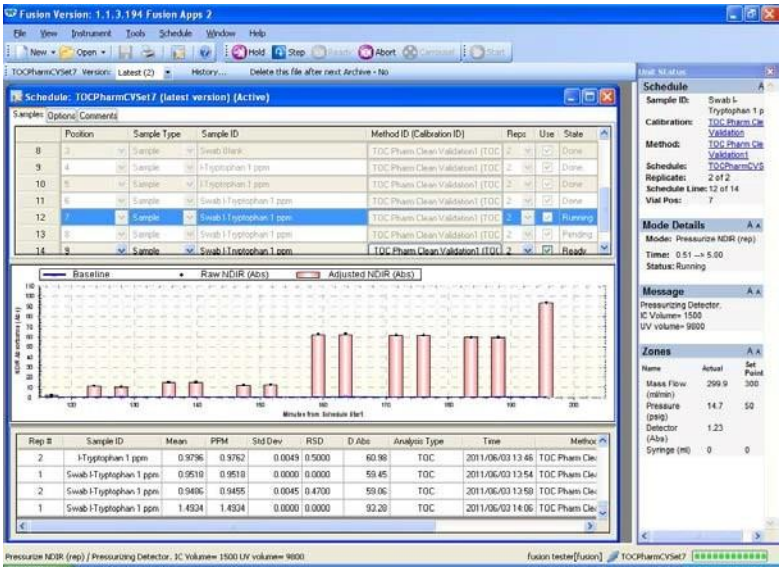

Figure 1: Screen Capture of the High Level Swab Sample Assay

The Fusion software allowed the analyst to observe the results with a color graph to quickly determine if the current sample was greater than allowable limits. The table below the graph also allowed the analyst to see the failing data and to scroll through previous samples not in the current graph. The sample table at the top of the window allowed the analyst to change the next pending sample to support a corrective action preventative action (CAPA) process.

Conclusions

Pharmaceutical cleaning validation is a multistep process, one of which is the analysis of rinse waters and swab samples with TOC by the UV/Persulfate method. Eight compounds used in the pharmaceutical environment were studied. The compounds include l-ascorbic acid, benzoic acid, ceftazidime pentahydrate, cimetidime, metformin HCl, sulfaguanidine, l-tryptophan, and vitamin B12.

All of the compounds were oxidizable with the UV/Persulfate method. The correlation coefficients of the compounds for a low level sample range from 0 to 2.5ppmC were greater than 0.999. The compounds when assayed for MDLs were within the detection range of the Fusion instrument capability.

Six of the eight compounds had swab recoveries greater than 80% with %RSD of three swab samples less than 3.1%. This indicates that these six compounds were detected with water swabbing.

Two of the compounds, benzoic acid and cimetidine had higher %RSD and benzoic acid had a swab recovery of approximately 40%. Both of these compounds required sonication to dissolve the standards. This study would alert the cleaning validation methods development scientist that a solvent other than water would be required to efficiently remove these compounds from the swab surface.

The Fusion software was tested to determine the ability of the laboratory scientist to make fast decisions during the run to initiate the manufacturers' required CAPA system. This permits the facility to quickly turn around the equipment cleaning process. The Fusion software allows the laboratory personnel to determine the passing or failure of a sample during the run and to change the samples in the sequence to address the failed sample.

References

1. Guide to Inspections Validation of Cleaning Processes, http://ww.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm