In-Process Pharmaceutical Manufacturing Aqueous Coating Suspension Hold Time Study

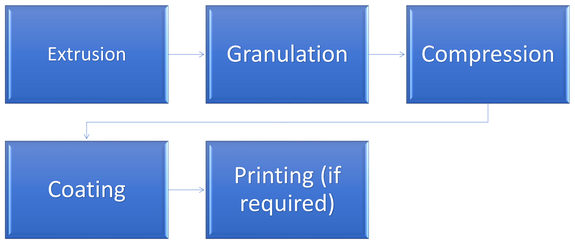
Author: Yarelys Soto Echevarria
Advisor: Rafael Nieves, Pharm D
Industrial Engineering Department

Abstract

A hold time study is established in the development phase of any product. All the In-Process unit operations require a hold time study to protect the integrity and quality of the final drug product. This study will analyze the hold time study of the collating suspension in a new product to be launched at the pharmaceutical site. The composition of the solution is 20% dye in 80% water. The samples were taken in duplicate to perform the microbiology test; Total Aerobic Microbial Count (TAMC), Total Yeast and Mold (TY&M) and E. coli presence. The solution was performed in 5 lots of equivalents components. The lots were executed on different days, rooms, equipment and operators. All the lots complied with the microbiology bioburden level. It can be established that a 72 hour hold time of color suspension preparation at GMP conditions is capable of reproducibly manufacturing product within predetermined quality attributes.

Introduction

The pharmaceutical industry establishes in process hold times of the associate unit operation in the production of solid products. Hold-time studies help ensure the quality of the pharmaceutical product as they determine a time in which product quality does not deteriorate significantly during the hold time. Additionally, times are established for the holding of materials at various stages of production. During the product development phase all of these In-Process hold time studies are executed and these times are determined. The solids manufacturing process consists of extrusion, granulation, compression, coating, and then printing.



Objectives

The main research objective is to validate a color suspension hold time for a new product being transferred to a pharmaceutical manufacturing site. To validate the hold time microbial testing will be performed for 72 hours in different sampling time points.

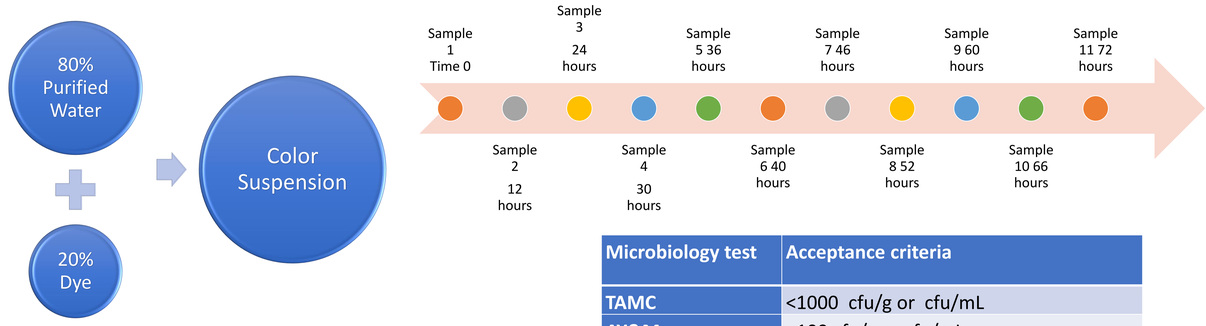
A validation study defines maximum allowable hold times for all intermediate process stages based on product-specific data obtained during a hold study. A systematic risk assessment can determine which intermediate hold points should be validated.

Good manufacturing practices require that the maximum allowable hold time should be established to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material. These time periods must be supported by adequate data to demonstrate that the product will be stable throughout the approved shelf-life.

Background

Since there are many products in the pharmaceutical site that defer in formulations and compositions the manufacturing site must validate an appropriated hold time for each manufacturing operation of each product. As areas are not dedicated for specific product manufacturing it is important to establish correct In-Process hold times to allow flexibility for manufacturing operations scheduling. Manufacturers should ensure that the products that they manufacture are pure, integral, effective, and safe. [1] This level of quality is required to be in compliance with regulations such as FDA, EP, JP and the code of regular federation, and deliver a high degree of assurance to consumers that the products they consume will adhere to their intended use. It is primordial that manufacturing processes are capable of consistently manufacturing pharmaceutical products with the required quality attributes that comply with their specifications [2]. There are many things to consider in the process validation like the design of the facility and the qualification of the equipment and utilities. The process must always follow GMP-compliant procedures. Enough data must be accumulated in order to have a statistical sample of the process large enough that knowledge about the commercial product processes are expected and accounted for and are not discovered during validation [3].

Methodology



Microbiology test	Acceptance criteria
TAMC	<1000 cfu/g or cfu/mL
AY&M	<100 cfu/g or cfu/mL
E.coli	Absence of Escherichia Coli (1g or 1mL)

Results and Discussion

Microbiology Results for Lot. 1

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL) TAMC (CFU/mL)	<100 (CFU/mL) TYMC (CFU/mL)	Not detected E. coli Presence
1	<10	<10	Not Detected
2	<10	<10	Not Detected
3	<10	<10	Not Detected
4	<10	<10	Not Detected
5	<10	<10	Not Detected
6	<10	<10	Not Detected
7	<10	<10	Not Detected
8	<10	<10	Not Detected
9	<10	<10	Not Detected
10	<10	<10	Not Detected
11	<10	<10	Not Detected

Microbiology Results for Lot. 2

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL) TAMC (CFU/mL)	<100 (CFU/mL) TYMC (CFU/mL)	Not detected E. coli Presence
1	<10	<10	Not Detected
2	<10	<10	Not Detected
3	<10	<10	Not Detected
4	<10	<10	Not Detected
5	<10	<10	Not Detected
6	<10	<10	Not Detected
7	<10	<10	Not Detected
8	<10	<10	Not Detected
9	<10	<10	Not Detected
10	<10	<10	Not Detected
11	<10	<10	Not Detected

Microbiology Results for Lot. 3

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL) TAMC (CFU/mL)	<100 (CFU/mL) TYMC (CFU/mL)	Not detected E. coli Presence
1	<10	<10	Not Detected
2	<10	<10	Not Detected
3	<10	<10	Not Detected
4	<10	<10	Not Detected
5	<10	<10	Not Detected
6	<10	<10	Not Detected
7	<10	<10	Not Detected
8	<10	<10	Not Detected
9	<10	<10	Not Detected
10	<10	<10	Not Detected
11	<10	<10	Not Detected

Microbiology Results for Lot. 4

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL) TAMC (CFU/mL)	<100 (CFU/mL) TYMC (CFU/mL)	Not detected E. coli Presence
1	<10	<10	Not Detected
2	<10	<10	Not Detected
3	<10	<10	Not Detected
4	<10	<10	Not Detected
5	<10	<10	Not Detected
6	<10	<10	Not Detected
7	<10	<10	Not Detected
8	<10	<10	Not Detected
9	<10	<10	Not Detected
10	<10	<10	Not Detected
11	<10	<10	Not Detected

Microbiology Results for Lot. 5

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL) TAMC (CFU/mL)	<100 (CFU/mL) TYMC (CFU/mL)	Not detected E. coli Presence
1	<10	<10	Not Detected
2	<10	<10	Not Detected
3	<10	<10	Not Detected
4	<10	<10	Not Detected
5	<10	<10	Not Detected
6	<10	<10	Not Detected
7	<10	<10	Not Detected
8	<10	<10	Not Detected
9	<10	<10	Not Detected
10	<10	<10	Not Detected
11	<10	<10	Not Detected

Results and Discussion (cont.)

The aim of this validation study was to support the longevity of the color solution for up to 72 hours. The new solid drug product must be free from hazardous microbes to be considered safe. The results show that <10 CFU/mL of Total Aerobic microbial or fungi grew in Soybean-Casein Digest Agar Medium. The yeast and mold results yielded <10 CFU/mL in the Sabouraud Dextrose Agar Medium. The TYMC is a test to detect mesophilic fungi in pharmaceutical ingredients that range from raw materials and water to the finished products. In this study <10 CFU/mL was obtained for all five lots. The presence of Enterobacteriaceae bacteria is not allowed in pharmaceutical product as per USP<1111> . The results demonstrates no growth of E.coli or gram-negative colonies in MacConkey medium. The results for all five lots comply with USP <1111> and the guide for hold time establishment in pharmaceutical industry.

Conclusion

All the lots of the color suspension hold time study were successfully completed for up to 72 hours. Therefore, the color suspension of the new product can reach the 72 hour of preparation within acceptable bioburden and endotoxin level. Also, the results demonstrate that the raw material, the purified water and the equipment used during the manufacturing of the lots complies with the qualitative microbial requirements.

The process validation was completed, documented and closed in the quality systems. No amendments or deviations were generated in the protocols. The process demonstrated robustness with different operators, days, rooms, supplied utility system, and validated tanks. The cleanness of the tank was achieved through a cleaning protocol notebook. The in-process control equipment was not monitored during the study, but the facilities and water used was within parameters.

The hold time coating suspension study complies with the regulatory agency to which the product will be sold and with all internal procedures, specifications, and quality requirements. A maximum of 72 hour can be established without affect the quality of the color suspension.

Future Work

A global protocol will be developing to established In-Process hold time for the following unit operations: milling to blending, blending to compressing, compressing to coating and the coating to shipment. Also, different packaging configuration study will be conducted for this product.

References

[1]Sandle, Tim. "Assessing Process Hold Times for Microbial Risks: Bioburden and Endotoxin." Journal of GXP Compliance 19, no. 3, 2015.

[2] World Health Organization (WHO), Good regulatory practices: Guidelines for national regulatory authorities for medical products, Working document QAS/16.686, Draft for comment prepared by EMP/RSS, Switzerland: WHO Geneva, 2016.

[3] USP <1111>, “Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use,” in The United States Pharmacopeia Convention, USP Rockville, MD.