In-Process Pharmaceutical Manufacturing Aqueous Coating Suspension Hold Time Study

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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.*

Key Terms *— Color Suspension, E.coli, GMP, Hold Time, TAMC, TY&M.*

PROBLEM STATEMENT

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 manufacturing process is a product specific. The manufacturing will depend of the development and the filling. Some product will require more steps for the finish good. Also, the process will be determined by the final dosification and deliver. The oral solid dose form preferred are tablets and capsules. The primary unit operation for tablet manufacturing process consists of extrusion, granulation, blending, compression, coating, and then printing. Also, in the manufacturing the process is divided by extrusion and post extrusion.

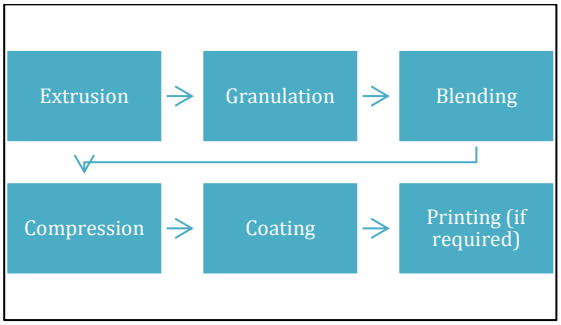

Figure 1
General Manufacturing Process of Solids Goods

The hot melt extrusion process consists of form an intermediate solid product. The active pharmaceutical ingredient is mixed with the excipients. Then melted at high pressure and high temperature. The material moves through twin-screw shear and them through the dies. The blend material melt down to break up into particles. This solid product can be a continuous line or beads (lentils).

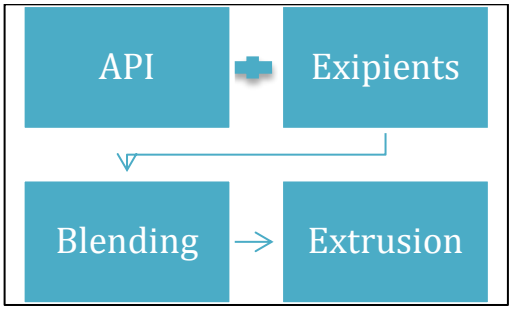

Figure 2
Manufacturing Extrusion Process

In-Process hold time is established to pass from one operation to other. The manufacturing process is

not a continuous line. From one unit operation to other is important to establish an appropriated time when the product is not at risk related to chemical stability and microbiological growth. The hold time is also established in case of equipment issues. This study intent is to establish a color coating suspension hold time used during the coating operation. The pharmaceutical industry establishes that 24 hours is the default hold time of color suspension when validation is not performed. If more time is required a study to determine the suspension stability must be executed. The risk of the color suspension hold time is based on the water capability to grow microbial substances when held for prolonged time periods. Since no active product is included in this phase analytical tests are not required.

Research Description

The aim of the study is to establish a hold time for the In-Process coating suspension of a tablet pharmaceutical product. This study will be provide flexibility to the manufacturing schedule without compromising the quality of the product. Also, the pharmaceutical industry requires that the In-Process Hold times complies with the regulations established by the Federal Drug Administration (FDA), European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP), for example. The color suspension hold time study will be evaluated for up to 72 hours.

The Code of Federal Regulations (CFR) established [1]:

1. Bioburden in-process testing must be conducted pursuant to written procedures during the manufacturing process of drug products.
2. “Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.”
3. “Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.”
4. “When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.”

The FDA established [1]:

1. In relation to processing, it is a requirement that sterilized holding tanks and any contained liquids should be held under positive pressure or appropriately sealed to prevent microbial contamination.
2. The hold time validation is referred to when the time limits established for the various production phases should be supported by data. Bioburden and endotoxin load should be assessed when establishing time limits for stages such as the formulation processing stage."

The USP <1115>"Bioburden control of nonsterile drug substances and products" [2], determined that manufacturers should consider whether processing steps and hold periods could result in changes to bioburden. Furthermore, manufacturers must properly establish processing hold times.

Research 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.

Research Contribution

The study results will validate the hold times used to establish In-Process controls for the pharmaceutical product that is to be manufactured. These studies are typically conducted to define

acceptable hold times for process intermediates to determine acceptable hold times for in-process production. 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.

LITERATURE REVIEW

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. In case that a commercial strategy changes unexpectedly, the hold time will allow that any given manufacture stage will not be discarded if it is held up to its validated maximum hold time.

Manufacturers should ensure that the products that they manufacture are pure, integral, effective, and safe. 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. Products should be consistently manufactured to quality standards appropriate to their intended use as required by the world market jurisdiction they will be sold in. Systems should ensure that pharmaceutical products are produced according to defined procedures that are validated and continuously monitored. It is primordial that manufacturing processes are capable of consistently manufacturing pharmaceutical products with the required quality attributes that comply with their specifications [3].

Sampling intervals and hold time period should be determined by the possible hold time in the manufacturing stage. For example, binder and coating solution are used in periods of hours and not days. Thus, hold times are validated for hours and not days. This requires that the maximum testing period may be 8 hours and have test intervals of 2, 5 and 8 hours. However, granules (core tablets) are held for days and sometimes months. Thus, the validation strategy contemplates having maximum testing between 60 to 90 days for example. A sampling strategy according to this length will have intervals 15, 30, 45, 60 and 90 days [4].

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 [5].

The film coating process is applied to the surface of a dosage form to protect the tablet from moisture and light. Also, the coating it's used to protect the tongue from the sometimes acid flavor the tablet may have. For film coating processes, the advantage of reduced processing times must be balanced against the uniformity requirements for the finished product. Reduced processing times can eliminate defects such as edge chipping and erosion by decreasing the overall mechanical stress experienced by the tablets. Ultimately, reduced processing times greatly improve productivity in manufacturing [6].

METHODOLOGY

A change control will be designed to initiate the study. The validation plan will consist of the quality actions that has to be taken in order to approve the

study. The protocol has to be approved by Manufacturing & Science, Quality Assurance, Engineering, Manufacturing Operations and Quality Control. Once the protocol is approved the planning schedulers will coordinate the activities in order to have the appropriate resources available.

The hold time study will be defined through 5 different dyes of similar composition. In this study the tanks used are comparable in design, manufacture and qualification. Also, the rooms used have similar utilities being supplied such as HVAC and purified water systems.

The aqueous coating suspension will be prepared at 20% dye of the solution. The solution will be mixed at high agitation for 15 minutes. Then, the agitation will be lowered until the end of the study.

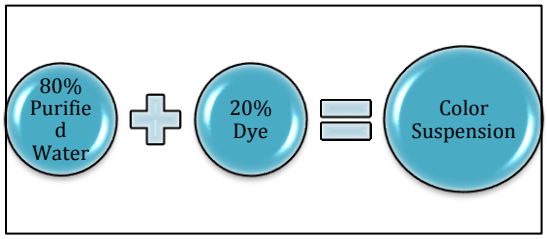

Figure 2
Color Suspension Preparation

Coating suspension samples will be taken during 72 hours at 11 time points in duplicate. As established in the United States Pharmacopeia (USP) the coating suspension samples are distributed as: Initial, 12, 24, 36, 48 and 72 hours and tested for Total Aerobic Microbial Count (TAMC), Aerobic Yest and Mold (AY&M) and *E.coli.* Microbial specific criteria for non-sterile product will not be considerer

As per USP<1111> [7] the acceptance criteria for non-sterile products for non-aqueous product such as tablets: is the following:

Table 1
Hold Time Study Acceptance Criteria

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)

The laboratory methodologies will be the same for a total of the 5 lots. Study will be conducted on different days, using different operators and manufacturing rooms. No critical process parameter is established for this unit operation.

RESULTS AND DISCUSSION

This section presents the microbial results for the 5 lots color suspension. The color suspension preparation were performed on GMP facilities and validated equipment. Since there was no critical process parameter a in process control data is not available.

Table 2
Microbiology Results for Lot. 1

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL)	**<100 (CFU/mL)**	**Not detected**
	Total Aerobic Microbial Count (CFU/mL)	Total Yeast and Mold Count (CFU/mL)	*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

Table 3
Microbiology Results for Lot. 2

Sample Number	Acceptance Criteria		
	<1000 (CFU/mL)	**<100 (CFU/mL)**	**Not detected**
	Total Aerobic Microbial	Total Yeast and Mold	*E. coli* Presence

	Count (CFU/mL)	Count (CFU/mL)	
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

Table 4

Microbiology Results for Lot. 3

Sample Number	**Acceptance Criteria**		
	<1000 (CFU/mL)	**<100 (CFU/mL)**	**Not detected**
	Total Aerobic Microbial Count (CFU/mL)	Total Yeast and Mold Count (CFU/mL)	*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

Table 5

Microbiology Results for Lot. 4

Sample Number	**Acceptance Criteria**		
	<1000 (CFU/mL)	**<100 (CFU/mL)**	**Not detected**
	Total Aerobic Microbial Count (CFU/mL)	Total Yeast and Mold Count (CFU/mL)	*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

Table 6

Microbiology Results for Lot. 5

Sample Number	**Acceptance Criteria**		
	<1000 (CFU/mL)	**<100 (CFU/mL)**	**Not detected**
	Total Aerobic Microbial Count (CFU/mL)	Total Yeast and Mold Count (CFU/mL)	*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

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.

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.

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.

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