Coating Suspension Holding Time Validation for X's Tablets in 300L Tanks

Natalie E. Pagán Ramos
Master in Manufacturing Competitiveness
Advisor: Rafael Nieves Castro, PharmD.
Polytechnic University of Puerto Rico
Graduate Project EXPO, May 2025

Abstract *— The validation of the 72-hour holding time for coating suspensions used in the production of X's tablets is crucial for improving manufacturing efficiency and reducing costs. X's tablets, which treat type 2 diabetes and obesity, are produced in six different strengths using a continuous, direct compression platform followed by an aqueous non-functional color coating process. The current 24-hour holding time leads to material waste and production interruptions. Extending the holding time to 72 hours ensures the microbial stability of the suspensions. The validation process involves preparing three suspensions in 300L tanks and assessing microbial growth at various intervals. The study confirms that the suspensions meet microbial growth acceptance criteria over the extended period, supporting sustainable large-scale production while maintaining high-quality standards.*

Key Terms *— Coating, Hold Time, Suspension, and Titanium Dioxide.*

PROBLEM STATEMENT

When a patient encounters a tablet, their first impression often depends on various factors, such as how easy it is to swallow, the absence of unpleasant odors, and how visually appealing it may look. A well-designed coating doesn't just make a tablet look better, but it also adds a touch of elegance and practicality. In pharmaceutical manufacturing, the tablet film coating process plays a key role in improving the appearance of tablets, providing protection, and meeting important functional standards. This process involves applying a polymer-based liquid coating to the tablet surface, which is then dried to create a uniform and protective film [1]. The final coated tablet's quality depends on the uniformity and stability of the film coating suspension, a composition typically including polymers, plasticizers, and pigments. Ensuring the homogeneity of these suspensions throughout the coating process is critical for consistent application and defect prevention [2]. Additionally, maintaining microbial limits within the suspension is essential to ensure compliance with pharmaceutical safety standards, safeguarding the coating solution's physical consistency and microbiological integrity.

X's, a glucagon-like peptide-1 receptor agonist (GLP-1RA), treats type 2 diabetes and obesity/overweight. It promotes weight loss and improves glycemic control by slowing gastric emptying, stimulating insulin secretion, and inhibiting glucagon secretion [3]. The product will be manufactured in six different strengths as immediate-release tablets in a continuous, direct compression platform, followed by an aqueous non-functional color coating process. To support the large-scale production of these tablets, 300L tanks are utilized to prepare coating suspensions. Currently, the holding time of these suspensions is limited to 24 hours, leading to material waste, production interruptions, and increased costs. Extending the suspension time to 72 hours is essential for improving production efficiency and aligning with regulatory and operational standards.

The validation of the suspension's 72-hour holding time is a critical prerequisite for the process validation scheduled for Q4 of 2025. Ensuring that the suspension complies with microbial growth acceptance criteria over the extended period will allow the process validation to proceed, confirming that all manufacturing stages meet safety, quality, and compliance requirements before the process validation. This effort is expected to support the sustainable, large-scale production of X's, optimizing operations while maintaining the highest quality standards.

Research Description

The validation process addresses the holding time of the coating suspensions used for X's tablets. An approach will be followed to select the representative color mixture based on the titanium dioxide concentration in the formulation. That ingredient exhibits antimicrobial characteristics; therefore, a lesser concentration increases the chance of microbial growth recovery [4]. The suspensions will be prepared with approved raw materials. All 300 L tanks available for this study have the same design and operational principles. In addition, all coating suspensions will be prepared at the same solid concentration, utilizing the same materials, manufacturing processes, major equipment, and facilities intended for the commercial routine production of the tablets. Samples will be taken throughout the 72 hours to confirm bioburden activity. The materials used and generated are for holding time validation purposes only and are not intended for human consumption.

Research Objective

The primary objective of this research is to validate that the holding time for the coating suspension utilized in X's coating process in 300L tanks, when operated within its specified parameters at the intended commercial scale, can produce coating suspensions in compliance with microbial growth acceptance criteria over a 72-hour holding period. Specific microbial indicators, such as Total Aerobic Microbial Count, Total Combined Yeast and Mold Count, and Escherichia coli, will be rigorously assessed through microbiological testing to confirm the stability of the suspension. The identification of Salmonella, Pseudomonas Aeruginosa, and Staphylococcus Aureus will not be performed since these microorganisms are not required for oral use dosage forms [5]. This research aims to bridge the gap between microbial safety standards and operational efficiency by providing evidence-based solutions for extending the suspension's holding time without compromising product quality.

Research Contributions

This validation process will greatly improve the adaptability and effectiveness of batch production, ensuring the suspension meets microbial standards for an extended time. By validating the extended holding time, we aim to achieve several key benefits that will improve both operational efficiency and process control within the production environment.

In manufacturing, unexpected issues like equipment breakdowns, staff shortages, or troubleshooting problems can sometimes delay coating spray completion within the usual 24-hour timeframe for the suspension. Extending the validated holding time to 72 hours provides the company a crucial buffer, ensuring the suspension stays stable, effective, and microbiologically safe for longer. This added flexibility helps avoid wasting resources or having to redo work, which can lead to inefficiencies and unnecessary costs. Furthermore, it ensures that production schedules can be adhered to more easily, even with unexpected disruptions.

Extending the coating suspension's validated holding time gives the production team greater predictability and control over the scheduling of batches. With a 72-hour validated holding time, manufacturers will be able to plan suspension preparation with a more anticipatory approach, knowing that the suspension can be safely prepared for an extended period before application. The extension enables better alignment of batch production with overall manufacturing timelines, reduces the likelihood of downtimes, and facilitates smoother transitions between different production stages.

As part of the extended holding time validation, we will confirm that the coating suspension meets the required microbial acceptance criteria throughout the 72 hours. This validation will create a reliable reference for addressing future microbial-related deviations, should they arise, allowing for a more systematic approach to investigating any quality issues. Extending the holding time for a coating suspension from 24 hours to 72 hours allows for better handling of unexpected delays, supports

smarter scheduling, and provides more room to address and manage any issues that might come up. This added flexibility strengthens the manufacturing process, helping to maintain consistent product quality, meet microbial safety standards, and make the best use of resources.

RESEARCH BACKGROUND

X's tablet coating suspensions are formulated with non-functional coating for aesthetic purposes only. The three-color mixtures are manufactured by Colorcon™ and share a similar formulation, using Polyvinyl Alcohol (PVA) as the main film-forming polymer. The other major components include titanium dioxide, macrogol (PEG), and talc. Refer to Table 1 for Colorcon's Color Mixture formulation.

Table 1
Colorcon's Color Mixture Formulation

Product Strengths	A	B	C	D	E	F
Color Formulation	85F640054	85F220280	85F100160	85F640054	85F22028	85F100160
Color	Pink	Yellow	Purple	Pink	Yellow	Purple
Material	% w/w					
Polyvinyl Alcohol (PVA)	40.000	40.000	40.000	40.000	40.000	40.000
Titanium Dioxide	24.314	24.800	23.830	24.314	24.800	23.830
Macrogol/PEG	20.200	20.200	20.200	20.200	20.200	20.200
Talc	14.800	14.800	14.800	14.800	14.800	14.800
Iron Oxide Red	0.373		0.330	0.373		0.330
Iron Oxide Yellow	0.313	0.200		0.313	0.200	
Iron Oxide Black			0.840			0.840

Titanium dioxide (TiO_2), a commonly used excipient in tablet film coatings, serves multiple functions beyond its role as an opacifying and whitening agent. Emerging evidence highlights its potential antimicrobial properties, which can be leveraged to enhance the microbial stability of coating suspensions. TiO_2 exhibits photocatalytic activity under ultraviolet (UV) light, generating reactive oxygen species that disrupt microbial cell membranes and inhibit bacterial proliferation [6]. In the context of extended holding times for coating suspensions, titanium dioxide's antimicrobial activity offers an additional safeguard against microbial contamination. This dual-purpose role ensures that the suspension remains compliant with microbial growth acceptance criteria, particularly for critical pathogens such as *Escherichia coli*, while preserving the aesthetic and functional qualities of the film coating. Based on the similarities in the composition of the color mixture and the antimicrobial characteristics of titanium dioxide, the color mixture purple was determined to represent all strengths, which is the "worst case scenario."

Preparing coating suspensions is a meticulous process crucial in ensuring the quality and performance of coated tablets or other pharmaceutical forms. It begins with selecting appropriate coating materials, which can include polymers (like hydroxypropyl methylcellulose), plasticizers, colorants, and additives. These materials are mixed with a solvent, such as water, to create a uniform suspension. The key to achieving an optimal suspension lies in thorough mixing, which ensures homogeneity and prevents sedimentation or clumping. This is typically done using equipment like high-shear mixers or tanks with impellers. The resulting suspension must have the proper viscosity and stability to allow for smooth application during coating processes. In practice, the suspension is applied onto tablets using advanced methods, such as spray systems in coating pans or fluidized beds. Coating suspensions are widely applied to enhance aesthetic appeal, protect active ingredients from environmental factors (i.e., light or humidity), improve swallowing, mask unpleasant tastes, or modify drug release profiles, such as in enteric-coated or sustained-release formulations. Proper preparation ensures the coating adheres effectively, delivering functionality and a polished finish.

Preparing coating suspensions involves challenges that can impact their quality and functionality, such as microbial issues. In addition to common problems like achieving homogeneity, controlling viscosity, and maintaining stability, microbial contamination poses a significant challenge, particularly when aqueous solvents are used. Microbial growth can compromise the suspension's stability, alter its physical and chemical properties, and ultimately reduce the efficacy and safety of the coated product. To address this, stringent hygiene measures must be applied during

the preparation process, including proper cleaning of equipment, the use of purified or sterile water, and the use of antimicrobial agents or preservatives in the color mixtures. By proactively managing these microbial challenges, manufacturers can ensure that the coating suspension is effective and safe for pharmaceutical and other applications.

X's tablets coating suspensions are prepared at a 20% w/w solids concentration, consisting of 200 kg of purified water and 50 kg of the applicable color mixture. As shown in Figure 1, the same basic procedure applies for every preparation: purified water is filled into the tank, agitation is turned on for vortex formation, and materials are incorporated into the vortex through our security Sieve US Std. No. 6. After incorporation, agitation is applied until no lumps/agglomerations are observed. The agitation speed is reduced after the material is incorporated to mix the coating suspension. After some time, the agitation will be reduced even more to eliminate bubbles from the suspension that could affect the coating process.

Table 2
Quantity of Color Mixture and Purified Water per Coating Suspension

Component	w/w %	Qty per batch (kg)
Color Mixture	20	50
Purified Water	80	200

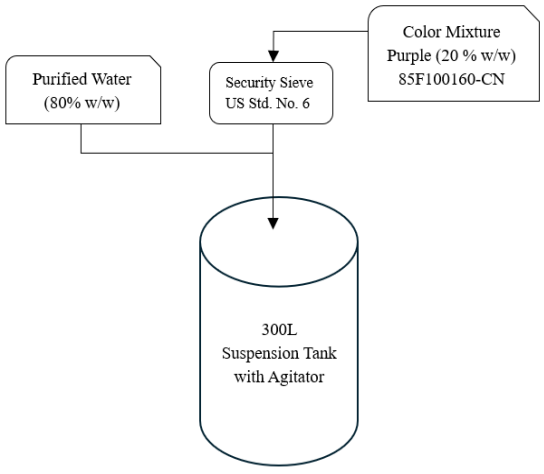

Figure 1
Coating Suspension Preparation Process Flow Diagram

Suspension preparation parameters for 300 L tanks are shown in Table 3. The mixing speed and mixing times vary throughout the preparation process to allow for solids' incorporation and continued suspension.

Table 3
300 L Tanks Coating Suspension Preparation Parameters

Equipment	Stage	Process Parameter	Set Point	Range / Tolerance	Success Criteria
300 L Tank	Incorporation	Mixing Speed	450 rpm	400 – 500 rpm	The process is executed normally. Batch processed according to batch record parameters with no process upsets or anomalies observed in product appearance or quality.
		Incorporation Time		≤ 5 minutes	
	Mixing	Mixing Speed	340 rpm	276 – 400 rpm	
		Mixing Time		≥ 90 minutes	
	De-aeration	Mixing Speed	240 rpm	150 – 300 rpm	
		De-Aeration Time		≥ 90 minutes	

METHODOLOGY

This study aims to validate the microbial stability of tablet film coating suspensions stored for 72 hours under worst-case conditions. Color Mixture Purple was selected for the validation studies since it shows a reduced titanium dioxide concentration compared to the others. Since Titanium Dioxide has antimicrobial properties, this formulation ensures that the study rigorously evaluates microbial growth in challenging conditions. The hold time for the coating suspension used to manufacture X's tablets is defined as the period when purified water is initially drawn for the coating suspension preparation to the maximum expected time to complete the film coating process.

The coating suspension hold time study will consist of preparing three (3) coating suspensions in the 300 L tank. After de-aeration, samples will be taken at different time points: after initial mixing, 24-hour, 48-hour, and 72-hour intervals to monitor microbial bioburden over time. The acceptance criteria for the suspensions correspond to those established for the final drug product and conform with the pharmacopeia requirements for non-sterile oral products.

Sterile disposable liquid thieves and containers will be used to collect samples from both the middle and bottom of the tanks, ensuring an accurate representation of microbial distribution within the

suspension. These sterile handling procedures will be strictly adhered to prevent contamination and maintain the validity of the results. Once collected, samples will be transported to the Microbiology Laboratory under controlled conditions to preserve integrity. The microbial stability will be evaluated against established acceptance criteria, specifically analyzing Total Aerobic Microbial Count, Total Combined Yeast and Mold Count, and Escherichia coli. Testing methods, such as plate counting or alternative validated detection techniques, will be employed to ensure reliable and precise measurement of microbial growth. It must comply with all the acceptance criteria detailed in Table 4 to determine the longest acceptable hold time.

Table 4
Microbiology Acceptance Criteria for Hold Time Study

Test	Acceptance Criteria
Total Aerobic Microbial Count	NMT 1,000 CFU / mL
Total Combined Yeast and Mold Count	NMT 100 CFU / mL
Escherichia coli	None Detected

RESULTS AND DISCUSSION

The holding time for the X's coating suspension is defined as when purified water is initially drawn into the tank to prepare for the maximum expected coating process completion time. The actual holding times for all suspensions are shown below.

Table 5
Actual Hold Time for Coating Studies

Sample	After Mixing	24 h	48 h	72 h
	Suspension 1			
Start (Water Incorporation) Date/Time	Mar-31-2025 1104			
Sampling Date / Time	Mar-31-2025 1133	Abr-01-2025 1113	Abr-02-2025 1128	Abr-03-2025 1122
Actual Hold Time (h, min)	0h, 29min	24h, 9 min	48h, 24 min	72h, 18 min
	Suspension 2			
Start (Water Incorporation) Date/Time	Mar-31-2025 1157			
Sampling Date / Time	Mar-31-2025 1227	Abr-01-2025 1201	Abr-02-2025 1207	Abr-03-2025 1219
Actual Hold Time (h, min)	0h, 30min	24h, 4 min	48h, 10 min	72h, 22 min
	Suspension 3			
Start (Water Incorporation) Date/Time	Mar-31-2025 1236			
Sampling Date / Time	Mar-31-2025 1309	Abr-01-2025 1238	Abr-02-2025 1241	Abr-03-2025 1255
Actual Hold Time (h, min)	0h, 33min	24h, 2 min	48h, 5 min	72h, 19 min

The following table summarizes the analytical results for the raw material used in this study.

Table 6
Raw Material Analytical Results for Color Mixture Purple

Test	Acceptance Criteria	Results
Physical Acceptability	Meets the method limits by the visual method	Pass
Physical Appearance	A purple powder by the visual method	Pass
Pseudomonas aeruginosa	None Detected	None Detected
Salmonella	None Detected	None Detected
Staphylococcus aureus	None Detected	None Detected
Escherichia coli	None Detected	None Detected
Total Aerobic Microbial Count	NMT 1,000 CFU / g	< 10 CFU / g
Total Combined Yeast and Molds Count	NMT 100 CFU / g	< 10 CFU / g
Identity Titanium	Must qualitatively demonstrate the presence of titanium by the ignition method	Pass
Identity Iron	Must qualitatively demonstrate the presence of iron by the ignition method	Pass
Identification	The IR sample spectrum most qualitatively compares favorably with that of a reference sample using a suitable spectrometer.	Pass

A major cleaning was performed according to local procedures on all tanks before use. The coating suspension preparations were performed in a room where a major cleaning was performed per local procedure before conducting the study. The coatings suspensions were prepared following the exact manufacturing instructions and parameters intended for commercial manufacturing. Microbiology testing results of each suspension are presented in Tables 7 - 10. All the samples tested for microbial content comply with the pre-established acceptance criteria regarding the absence of *Escherichia coli*, a USP indicator Organism. In addition, the total count of aerobic microbes and the total combined yeast and mold of samples comply with the required limits of up to 72 hours of hold time. This data demonstrated that the holding time for the coating suspension for X's tablets can be held up to 72 hours and ensure that the microbial content will be maintained within the acceptance criteria.

Table 7
Microbiology Results of Samples Collected Immediately After Mixing

Test	Acceptance Criteria	Location	Color Mixture Purple (85F100160)		
			S1	S2	S3
Total Aerobic Microbial Count	NMT 1,000 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Total Combined Yeast and Mold Counts	NMT 100 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Escherichia Coli	None Detected	Middle	Pass	Pass	Pass
		Bottom	Pass	Pass	Pass

Table 8
Microbiology Results of Samples Collected After 24 Hours of Holding Time

Test	Acceptance Criteria	Location	Color Mixture Purple (85F100160)		
			S1	S2	S3
Total Aerobic Microbial Count	NMT 1,000 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Total Combined Yeast and Mold Counts	NMT 100 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Escherichia Coli	None Detected	Middle	Pass	Pass	Pass
		Bottom	Pass	Pass	Pass

Table 9
Microbiology Results of Samples Collected After 48 Hours of Holding Time

Test	Acceptance Criteria	Location	Color Mixture Purple (85F100160)		
			S1	S2	S3
Total Aerobic Microbial Count	NMT 1,000 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Total Combined Yeast and Mold Counts	NMT 100 CFU / ML	Middle	<10	<10	<10
		Bottom	<10	<10	<10
Escherichia Coli	None Detected	Middle	Pass	Pass	Pass
		Bottom	Pass	Pass	Pass

Table 10
Microbiology Results of Samples Collected After 72 Hours of Holding Time

Test	Acceptance Criteria	Location	Color Mixture Purple (85F100160)		
			S1	S2	S3
Total Aerobic Microbial Count	NMT 1,000 CFU / ML	Middle	350	230	<10
		Bottom	220	310	<10
Total Combined Yeast and Mold Counts	NMT 100 CFU / ML	Middle	10	20	<10
		Bottom	15	30	<10
Escherichia Coli	None Detected	Middle	Pass	Pass	Pass
		Bottom	Pass	Pass	Pass

CONCLUSION

The process was executed with no events. Studies were processed according to batch record parameters, with no process upsets or anomalies observed in product appearance or quality. All acceptance criteria established in this holding time validation have been met with the three suspensions with a maximum of 72 hours of hold time in 300 L tanks. The validated 72-hour hold time for the coating suspensions was based on bioburden evaluation at specified intervals. The suspension evaluated in this study represents the worst-case scenario for microbial growth. Therefore, this study supports the implementation of a 72-hour holding time.

REFERENCES

[1] C. Christodoulou, E. Sorensen, A. S. Khair, S. García-Muñoz, and L. Mazzei, "A model for the fluid dynamic behavior of a film coating suspension during tablet coating," in *Process Safety and Environmental Protection*, vol. 160, pp. 301–320, Jun. 2020. Doi: https://doi.org/10.1016/j.cherd.2020.05.021.

[2] G. C. Cole, "Introduction and overview of pharmaceutical coating," in *CRC Press eBooks*, pp. 11–15, Oct. 1995. Doi: https://doi.org/10.3109/9780203014356-1.

[3] A. Moiz, K. B. Filion, M. A. Tsoukas, O. HY. Yu, T. M. Peters, and M. J. Eisenberg, "Mechanisms of GLP-1 receptor agonist-induced weight loss: A review of central and peripheral pathways in appetite and energy regulation," in *The American Journal of Medicine*, Jan. 2025. Doi: https://doi.org/10.1016/j.amjmed.2025.01.021.

[4] C. L. de Dicastillo, M. G. Correa, F. B. Martínez, C. Streitt, and M. J. Galotto, "Antimicrobial Effect of Titanium Dioxide Nanoparticles," in *Antimicrobial Resistance - A One Health Perspective*, Jan. 2020. Doi: https://doi.org/10.5772/intechopen.90891.

[5] United States Pharmacopeia, "General Chapter, ⟨1111⟩ Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use," in *USP-NF*, Rockville, MD: United States Pharmacopeia, 2024. Doi: https://doi.org/10.31003/USPNF_M99830_01_01

[6] K. Nagaraj *et al.*, "Photocatalytic advancements and Applications of Titanium dioxide (TIO2): Progress in biomedical, environmental, and energy sustainability," in *Next Research.*, pp. 100180, Jan. 2025. Doi: 10.1016/j.nexres.2025.100180.