



Author: Natalie E. Pagán Ramos
 Advisor: Rafael A. Nieves-Castro, PharmD.
 Manufacturing Competitiveness

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

In the manufacturing process of X's tablets, the current holding time for the coating suspension is limited to 24 hours. This constraint poses operational challenges, including material waste, increased downtime, and reduced flexibility in scheduling, particularly when unexpected delays such as equipment malfunctions or staffing shortages occur. These limitations result in inefficiencies and higher production costs.

To improve production resilience and reduce unnecessary material disposal, there is a critical need to validate an extended holding time of 72 hours for the coating suspension. This extension must ensure that microbial stability is maintained throughout the holding period without compromising the quality or safety of the final product. Validation under worst-case conditions—including the use of a formulation with a lower concentration of titanium dioxide (an ingredient with antimicrobial properties)—is essential to confirm compliance with established pharmacopeial microbial acceptance criteria and to support its application in routine commercial operations.

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 |

Methodology

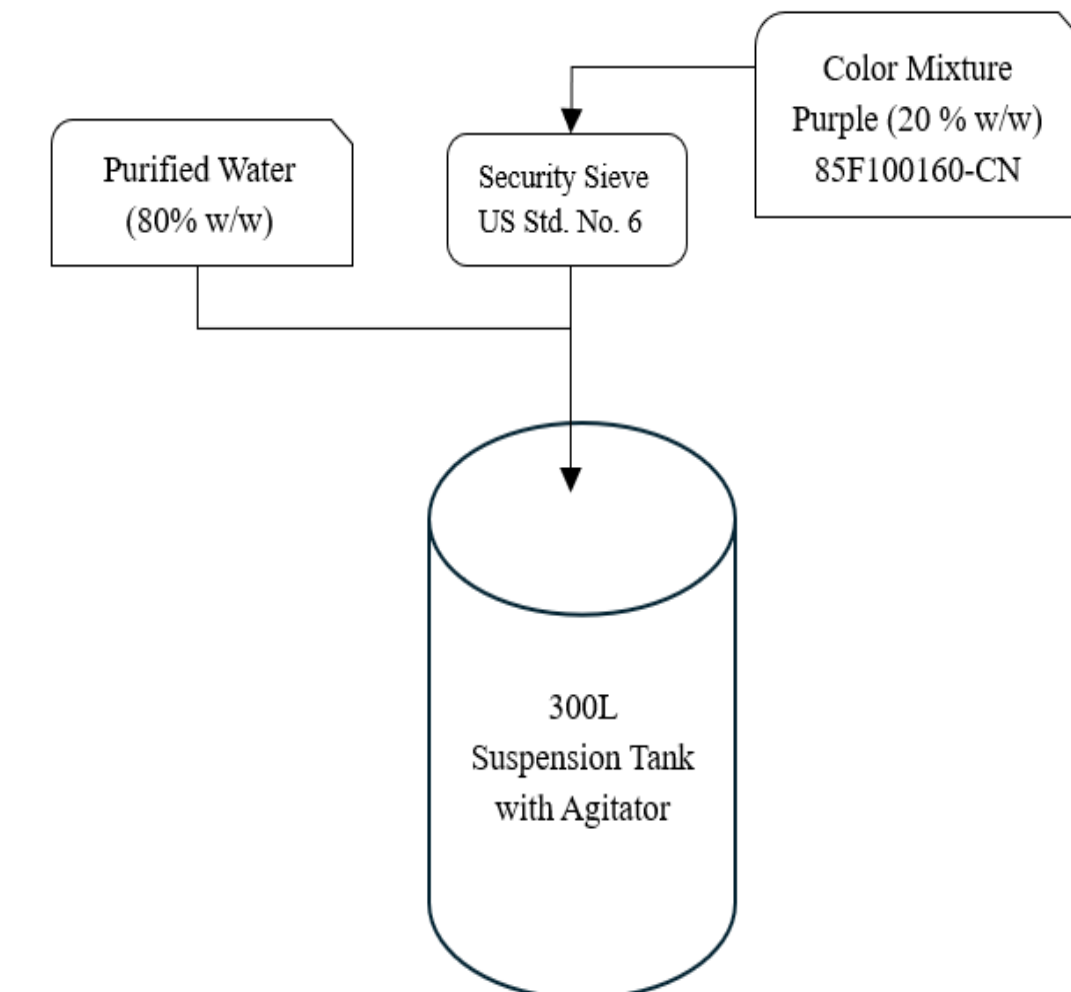
The study for the microbial stability of coating suspensions for X's tablets was held for 72 hours under worst-case conditions using purple color mixture (lowest titanium dioxide concentration). Three 300L batches were prepared using commercial manufacturing parameters. Samples were collected from the middle and bottom of the tanks immediately after mixing, and after 24, 48, and 72 hours. Sterile handling ensured no contamination during sampling. Microbiological testing followed USP guidelines and assessed Total Aerobic Microbial Count, Total Combined Yeast and Mold Count, and *Escherichia coli* presence.

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 |

Methodology Cont.

Figure 1. Coating Suspension Preparation Process Flow Diagram



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.

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 |

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 |
| <i>Pseudomonas aeruginosa</i> | None Detected | None Detected |
| <i>Salmonella</i> | None Detected | None Detected |
| <i>Staphylococcus aureus</i> | None Detected | None Detected |
| <i>Escherichia coli</i> | 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.

Results and Discussion Cont.

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.

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 |
| <i>Escherichia coli</i> | None Detected | Middle | Pass | Pass | Pass |
| | | Bottom | Pass | Pass | Pass |

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 |
| <i>Escherichia coli</i> | None Detected | Middle | Pass | Pass | Pass |
| | | Bottom | Pass | Pass | Pass |

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 |
| <i>Escherichia coli</i> | None Detected | Middle | Pass | Pass | Pass |
| | | Bottom | Pass | Pass | Pass |

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 |
| <i>Escherichia coli</i> | None Detected | Middle | Pass | Pass | Pass |
| | | Bottom | Pass | Pass | Pass |

Contributions

- Manufacturing Flexibility:** Allows production to continue smoothly despite delays from equipment issues, staffing shortages, or troubleshooting.
- Resource Optimization:** Reduces waste and rework, minimizing inefficiencies and unnecessary costs.
- Improved Scheduling & Batch Control:** Provides predictability, allowing manufacturers to align suspension preparation with production timelines.
- Minimized Downtime & Production Disruptions:** Helps maintain steady workflow and smoother transitions between production stages.

Conclusions

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.

Acknowledgements

I want to express my gratitude and appreciation to my processor and mentor, Dr. Rafael Nieves, for their able guidance and support in completing this project and through the courses. His constructive feedback has served as a significant contributor to the completion of this project.

References

- 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>.
- G. C. Cole, "Introduction and overview of pharmaceutical coating," in *CRC Press eBooks*, pp. 11–15, Oct. 1995. Doi: <https://doi.org/10.13109/9780203014356-1>.
- 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>.
- C. L. de Castillo, 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>.
- 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
- 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](https://doi.org/10.1016/j.nexres.2025.100180)