Oliver
HEALTHCARE PACKAGING

Reducing Airborne Particulate During Manufacture of Prefilled Syringes

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Contributors and Sources:

Goff, J. (2019) World Pharma Today, New Independent Study proves Coated Lidding Significantly reduces Packaging-related Particulate in Drug Delivery Systems*

Oliver Healthcare Packaging Internal Report (2018): *Airborne Particulate Testing Coated Tyvek Lids;* Unpublished.

International Organization for Standardization [ISO] (2015) Prefilled syringes – Part 7: "*Packaging systems for sterilized subassembled syringes ready for filling,*" ISO 11040-7; retrieved from https://www.iso.org/standard/59937.html

ISO (2018) Determination of Particle Size Distribution -- Single Particle Light Interaction Methods – Part 4: *Light Scattering Airborne Particle Counter for Clean Spaces,* ISO 21501-4:2018, retrieved from https://www.iso.org/standard/58073.html

ASTM F88/F88M (2015) *Standard Test Method for Seal Strength of Flexible Barrier Materials*

Background and Purpose

As demand for prefilled syringes in the pharmaceutical industry continues to increase, the packaging industry has recognized the need for a greater understanding of airborne particulate risks associated with coated drug delivery packaging systems.

Drug delivery system sterility is essential for pharmaceutical companies and manufacturers. Choosing the right sterile barrier system can be an afterthought, primarily due to the immense demands of the development and launch process. To help combat this potentially detrimental trend, Oliver Healthcare Packaging (OHCP) organized this independent third-party study. The study would apply scientific methods to quantify and compare the particulate generated by three coating technologies applied to DuPont™ Tyvek® lids. The coatings would be tested to determine particulate generation using three lid peel methods: mechanical, heated and manual. The outcomes would provide factual data to manufacturers as they consider the safest packaging options.

The prefilled syringe manufacturing process typically applies Tyvek® lids to tubs filled with sub-assembled syringes that are nested in glass vials. The opening

process is performed in an ultra-clean environment where the Tyvek® lid is peeled back, exposing the sterile syringes for filling.

Performance of the sterile barrier, which in the case of prefillable syringes is the coated lidding over the tubs, must comply with ISO 11040-7, Prefilled Syringes – Part 7.
The standard states that the packaging system shall have acceptable microbiological and particulate levels to support the introduction of sterilized sub-assembled syringes into an aseptic filling environment.

This study sought to test and demonstrate variances in particulate levels produced by different types of coating technologies. Results are intended to promote greater understanding among pharmaceutical developers, packaging engineers and manufacturers in material selection for coated lidding. The study also supports compliance with ISO 11040-7 by reporting the efficacy of the subject coatings and peel methods.

Research Approach and Study Design

An independent third-party lab conducted the study using certified testing methods based in the U.S.A. Testing was conducted in an ISO 7 certified cleanroom. Baseline cleanroom measurements were considered as a part of data collection prior to the study.

All apparatus and work surfaces were disinfected using 99% IPA and Polyester ISO 7 Cleanroom Wipes.

Environmental considerations were an important element in the efficacy of this study. The most laminar airflow was identified, and the ISO 7 cleanroom recently demonstrated the performance of significantly below the ISO 1464401 requirements (average 352,000 particles/m3), thus qualifying as a suitable environment for the study.

In preparation, three airborne particulate readings were taken within the vicinity of the test station in the ISO Class 7 cleanroom. The readings were taken to confirm ambient cleanliness levels within the cleanroom. The particle counter was set to measure for five minutes per reading. Results demonstrated conformance to ISO Class 7 or better.

NOTE: Additional ambient measurements were added beyond those stipulated in the protocol, due to observed conditions in-test (i.e., to ensure comparison

between sets). These measurements were defined as "control" readings and documented as such throughout the study.

It is also of note that ISO Class 7 cleanroom conformance was identified as the optimal environment for testing over a Class 8 cleanroom compliant facility. The determination was due to the high airflow pressure from top to bottom in a Class 8 environment, which prevented the particle counter equipment from detecting any particulate due to airflow.

Materials, Methods, and Procedures

Acceptance criteria were recorded as met regarding training protocols. Confirmation of individually specified acceptance criteria and deviation documentation showed that no deviations were observed during the study.

Three peel protocols were established for testing, as shown in Figure 1:

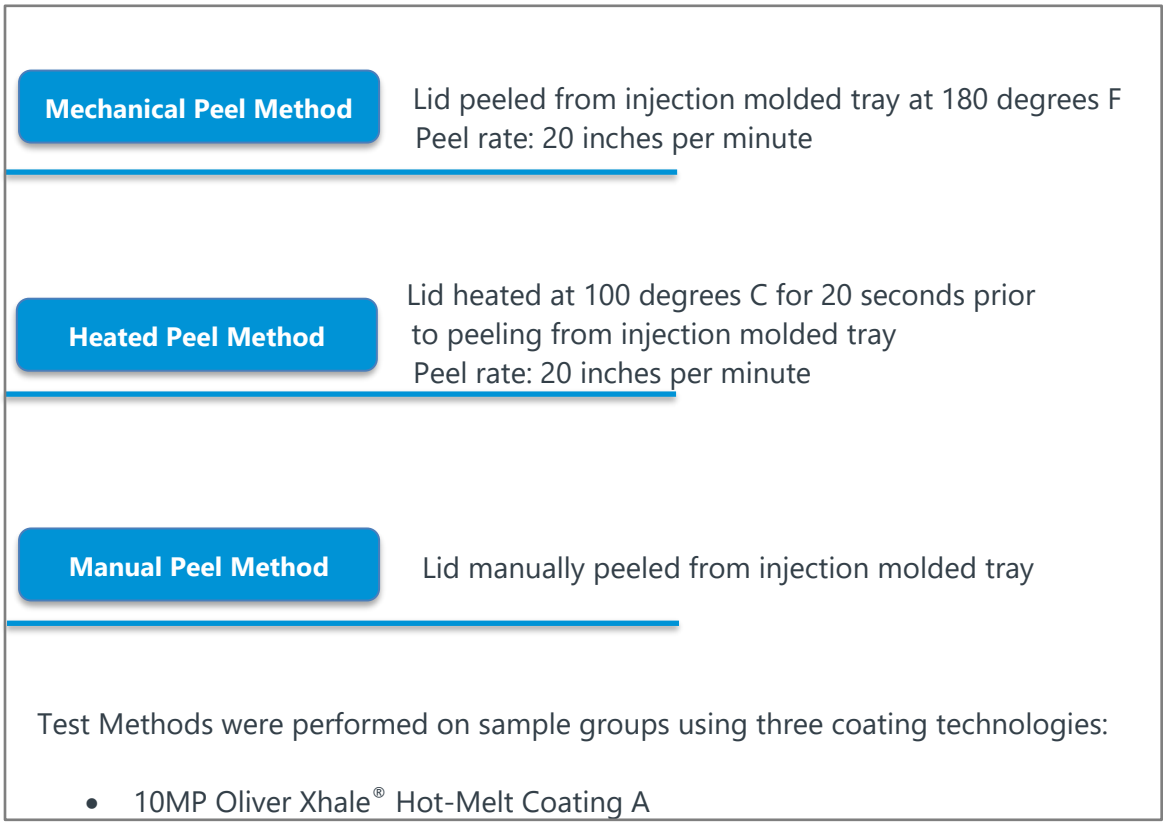


Figure 1: Peel Test Methods and Coating Technologies.

The study design was implemented per OHCP specifications and scope, using OHCP-provided production representative samples, received at testing facility as follows:

Universal Sample Components

- Injection molded Polystyrene Tray 45 mil HIPS, 261mm L x 229mm W x 98 mm D (*new trays, visibly clean and double bagged*)

- DuPont® Tyvek® 1073B Tray Lids, 262mm L x 230mm W

Sample trays and lids were received and recorded for test setup.

All unsealed trays were cleaned using a reverse osmosis water system and Steelco DS500 CDL Automatic Washer Disinfector in a secured chamber with dual washing and drying control.

Within the prepared Class 7 cleanroom, the injection molded polystyrene trays were heat-sealed with coated lids according to coating type and sample group. Heat sealing was performed using Sencorp Tray Sealer MD2420. Parameters set were 250'F, 60 PSI, 3.0 Seconds for all sample groups.

Universal components were assigned into test groups based on coating type, with numbered sample ranges of five units each representing peel methods, as shown in Figure 2:

Coating Technology[1]	Mechanical Peel	Manual Peel	Heated Peel
Oliver 10MP Xhale® Hot-Melt Coating Group A	Samples 1-5	Samples 6-10	Samples 11-15
Oliver 18B Xhale® Hot-Melt Coating Group B	Samples 1-5	Samples 6-10	Samples 11-15

Competitor Water-Based Coating Group C	Samples 1-5	Samples 6-10	Samples 11-15

[1]A control group was also assigned and tested, applying identical criteria, materials, apparatus and methods.

Figure 2. Test Group, Method and Sample Labeling

Trays were labeled according to study design protocols by sample groups. Sample groups were determined by coating type and peel method. Sealed sample trays were created for each group, with parameters recorded. The trays were allowed to acclimate a minimum of four hours in an ambient cleanroom environment.

Upon acclimation and before the commencement of testing, label accuracy verification was completed. Baseline particulate readings in the position of the test were completed according to established protocols.

The testing station was prepared and baseline particulate measurements of 0.3 µm, 0.5 µm and 5.0 µm were taken using TSI Alnor 9303 AeroTrak Particle Counter.

Technicians were in-room, with no activity, for 10 minutes. Data was recorded for comparison to the ambient environment before commencing actual test activity. No cleanroom interlock breach or opening was allowed at any time during testing. Figure 3 shown here represents the visual scenario of the test setup:

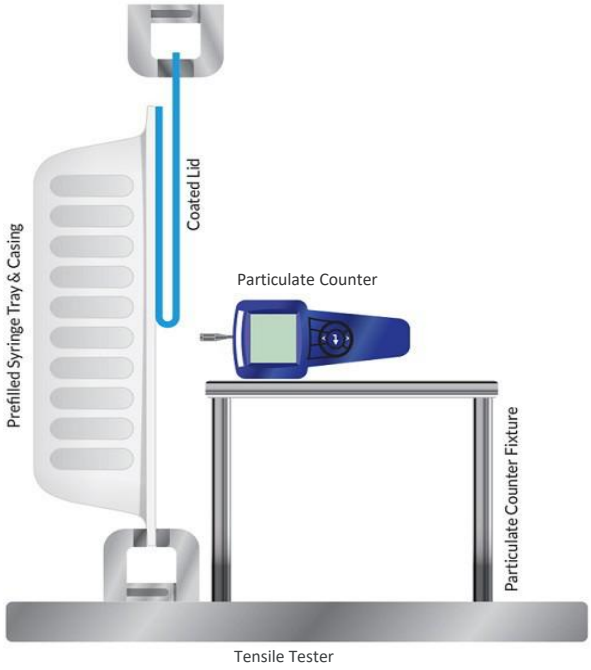


Figure 3: Visual Orientation of Test Setup for Mechanical and Heated Peel Methods

Mechanical and Heated Peel Testing

Formal test activities were performed on mechanical and heated peel groups. The Admet peel tester synched to Mtest Quattro software was set up in the Admet 7601 test stand to travel for thirty seconds at the identified peel rate (see Fig. 3 Mechanical and Heated methods).

For testing the Heated Peel sample group, the sealed tray was returned to the tray sealer within the cleanroom. Teflon (glass cloth) was applied, and the shuttle actuated to heat lid to 212F (100C) for 20 seconds at 30 psi.
To ensure consistency and accuracy in data collection and particulate measurements, the particulate counter fixture and meter were positioned in the same location for all peel actions, at a distance of 1" from the sealed flange (+/- 1/8").

Manual Peel Group Testing

Gowned and gloved laboratory technicians conducted manual peel testing. Operators followed the same basic protocols as Mechanical and Heated Peel groups. Additional work instructions to address the manual test operation

required technicians to stand in the same location in relation to the test stand for all tests.
To commence testing, the technician peeled one corner of the tray open approximately ¼". The particle counter was started, and the technician would lift the sample from the work surface, to duplicate the expected action during manufacturing practice. The tray was then manually peeled back, with the open corner facing the particulate counter.

Manual peel rates resulted in approximately 50 percent of the tray being opened in <5 seconds. A 1-2 second pause was counted before the remaining portion of the lid was removed (due to large tray size). The particulate counter was stopped after 30 seconds minimum up to 50 seconds maximum.

Results of each sample group and particulate generation rates for each specified particulate size (0.3 µ, 0.5 µ and 5.0 µ) were recorded.

Discussions and Considerations

This is the first study known to analyze and demonstrate reduced rates of particulate in association with a particular type of coated Tyvek® lid as compared to competitor products in the market. Note that while it specifically considered the pre-fillable syringe market as its subject, the findings are applicable to a much broader industry segment.

Material selection during the product development phase can impact particulate generation. Coating can often help reduce the volume of particulate generated. Coating technologies also play an important role in maintaining the sterility of the drug delivery packaging system. These factors underscore the importance and value of inclusion from the earliest stages of development.

During the typical manufacturing process for pre-fillable syringes, the syringe tub and lid are brought into a production location and opened. Once the lid is peeled and removed from the syringe tub, the syringes are then prepared and filled with the applicable drug. During the peel process, particulate generation must be minimized to prevent contaminants from entering the syringes. It is highly recommended that lidding used for this application be coated to lower particulate levels.

The test was conducted applying the technical assessment procedure and apparatus associated with ASTM F88/F88M – 15 and ISO 21501-4:2018. This testing is not a normative standard or validated test method and is intended to measure and compare the airborne particulate generated during subject lid peeling.

The coating type selected, as demonstrated in this study, can impact particulate risks to the syringe contents.

Hot-Melt vs. Water-Based Coatings

The two coating technologies currently available in sterile barrier packaging are water-based and hot-melt. Hot-melt coatings use a process to apply 100 percent solids in a uniform dot pattern. The application process maximizes coating anchorage and substrate breathability while decreasing particulate generation during peeling. The reaction of the coating during the sealing process causes the coating dots to merge. This results in consistent peel properties. Because they are waterless, hot-melt coatings have an inherently low endotoxin population when compared to water-based coatings.

Additionally, hot-melt coatings show considerably less variability in particulate generation than the competitor water-based formula. This consistency is of particular interest to industry since variability parameters set from a quality perspective could lead to regulatory standards establishing allowable levels of particulate generation.

These properties make hot-melt coatings a potentially more effective protectant for specific applications, including drug delivery systems such as the prefillable syringe market, as was the subject of this study.

Results

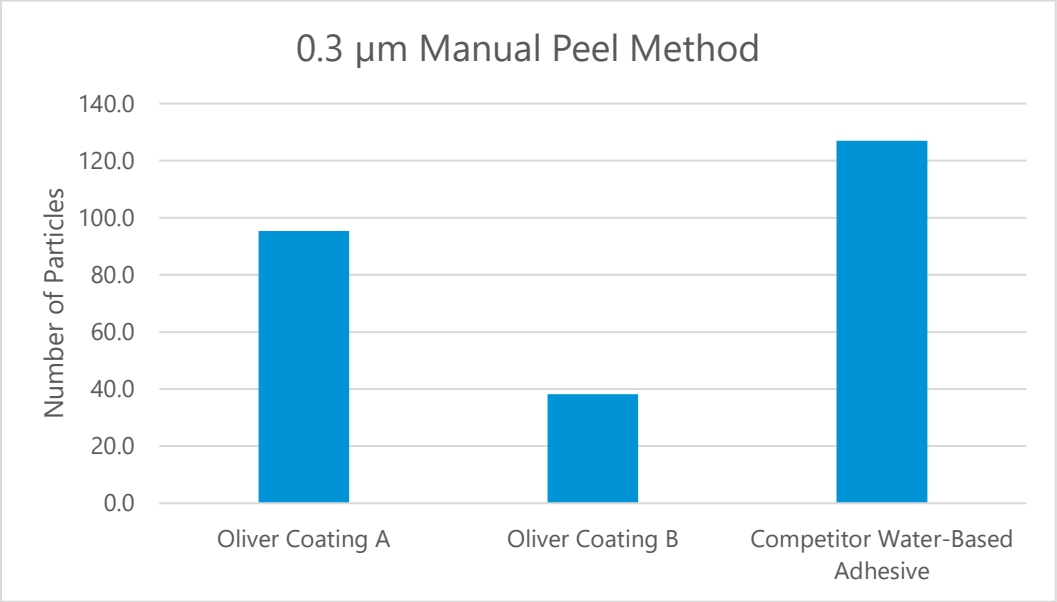
Key findings evidenced by the data collected demonstrate that:

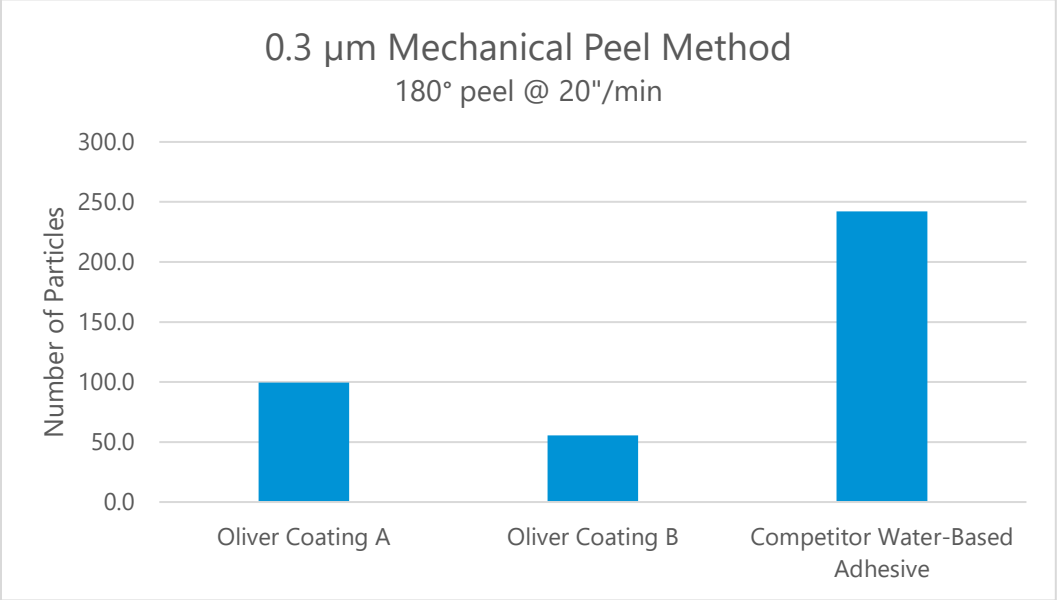
- Hot-melt coating technologies reduce particulate generation by up to 96% when peeled from polystyrene trays.

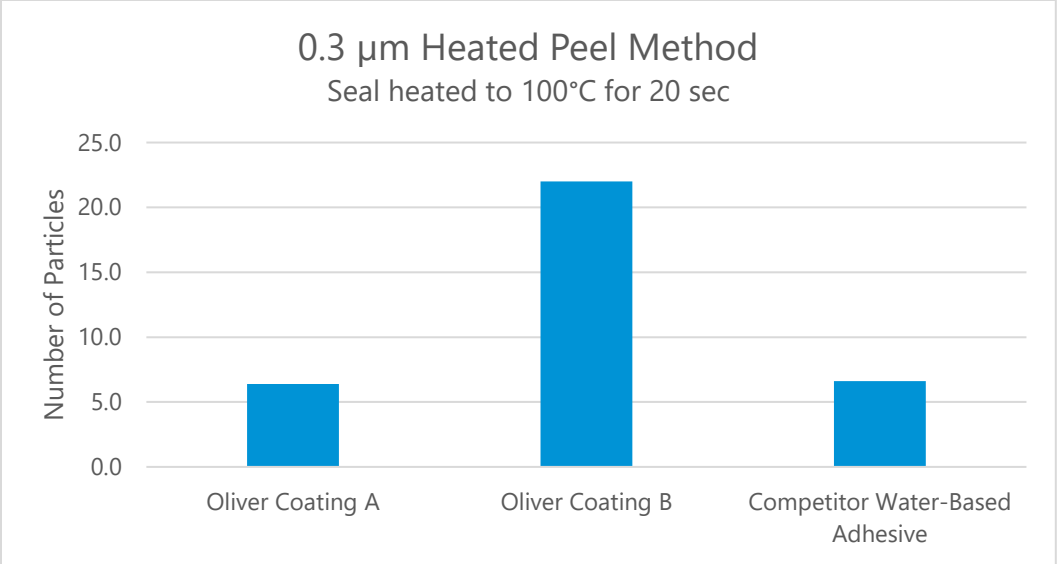
- Hot-melt coatings perform more effectively at lowering particulate generation than water-based in the application tested (pharmaceutical manufacturing of prefilled syringes).

The charts below show individual results for each test method and particulate measurement represented in the study.

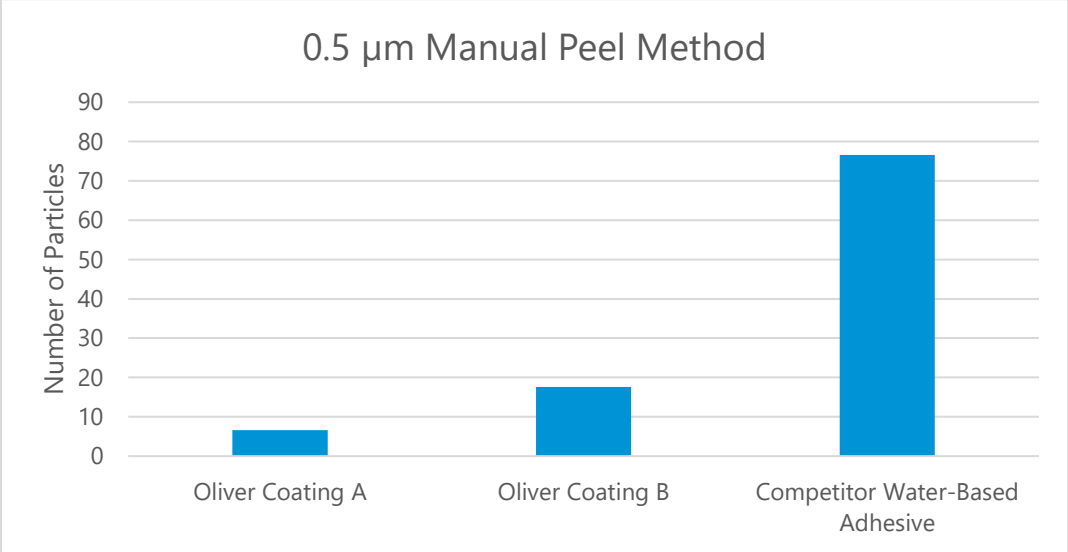
0.3 Micron Particulate Generation Results All Methods and Coatings

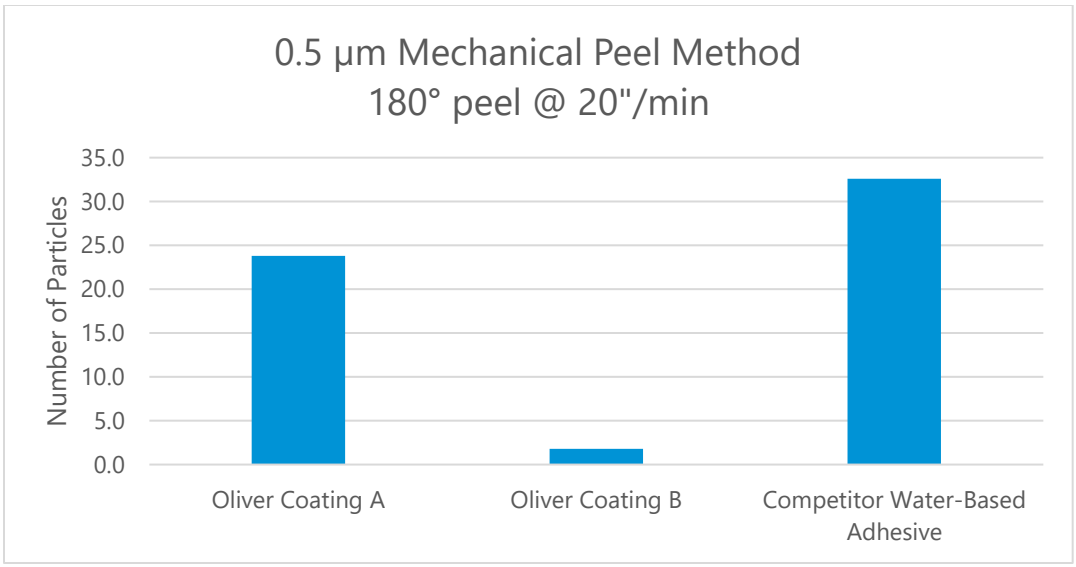


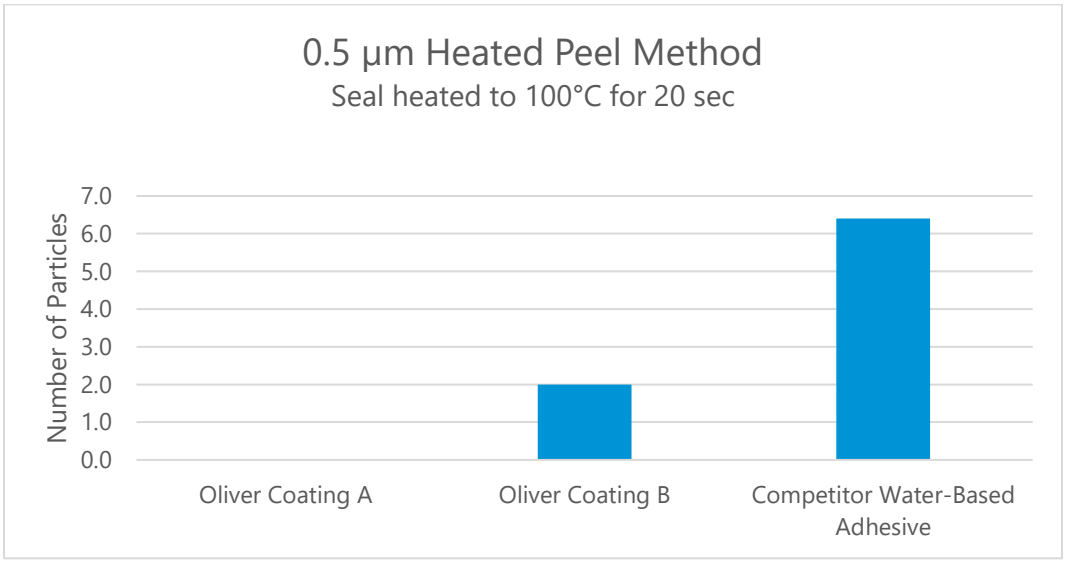




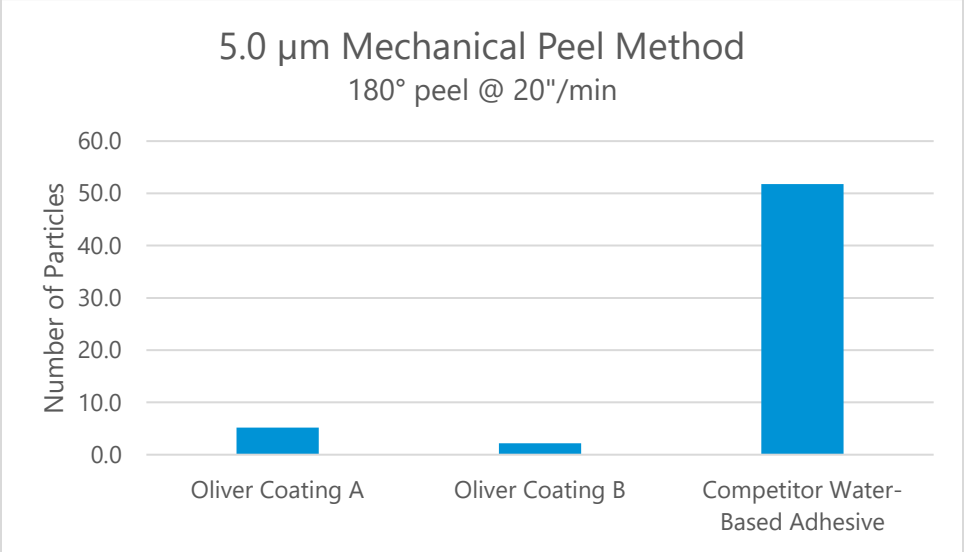
0.5 Micron Particulate Generation Results All Methods and Coatings

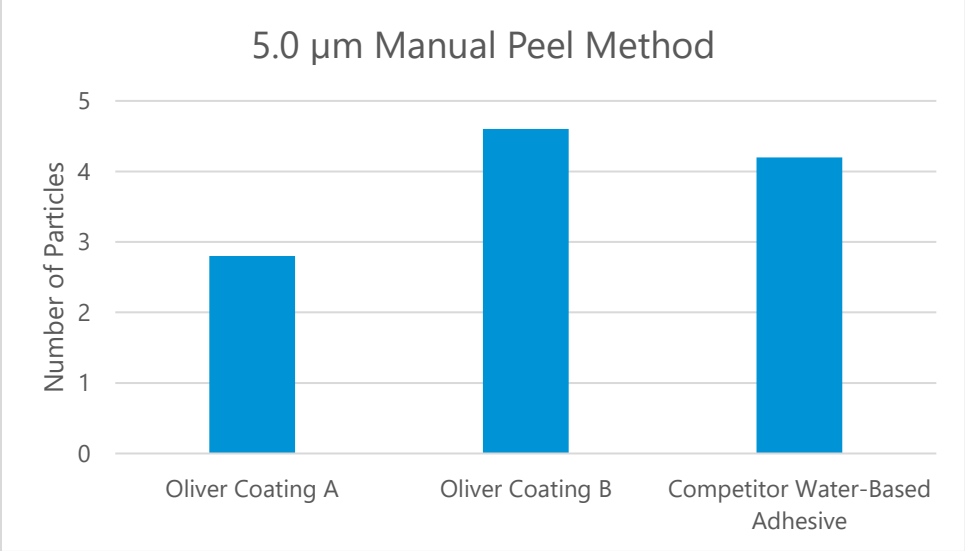


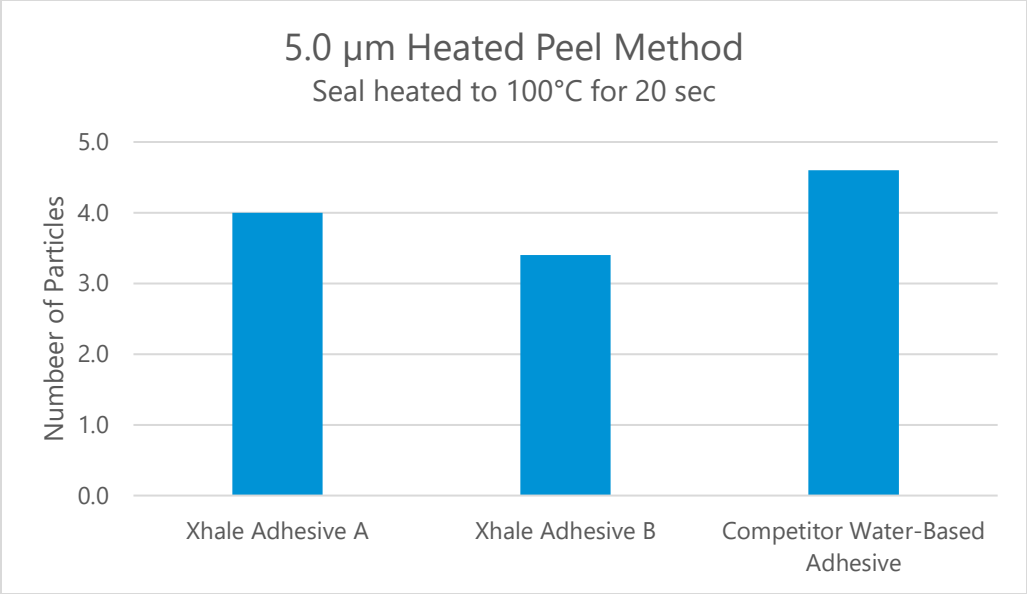




5.0 Micron Particulate Generation Results All Methods and Coatings







Conclusion

Though additional testing is recommended, and other industry applications could benefit from individual investigation, the initial results show potentially far-reaching manufacturing, clinical and patient safety benefits to the use of hot-melt coating technology in pharmaceutical manufacturing.

If you have questions or would like more information regarding this study, Oliver coating technologies, or your pharmaceutical manufacturing initiative, please contact us.