Cleanability of Pharmaceutical Soils from Different Materials of Construction

The authors look at the cleanability of pharmaceutical soils from a variety of materials of construction to determine the relative ease of cleaning and explore potential grouping strategies as part of a comprehensive cleaning validation program.

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A cleaning procedure is expected to remove soil from product-contact equipment surfaces. A validated cleaning procedure has been shown to reliably remove soils from these surfaces. One of the accepted approaches to cleaning validation is to identify a worst-case soil for validation. A worst-case soil is one that is the most difficult to clean in relation to all other soils manufactured in a pharmaceutical facility. If the worst-case soil can be cleaned to an acceptable level, it can be concluded that the other soils in the facility can also be cleaned to an acceptable level using the validated cleaning procedure.

Identification of a worst-case soil can be accomplished through equipment-washer and formulator experience. Those involved in manufacturing formulations, cleaning, and maintaining the equipment are in the best position to identify the hardest-to-clean soil. This approach is a practical but subjective determination and would leave a facility open to question until ongoing data supports the initial conclusions on the worst-case soil.

A second approach is a comparison of API solubility. Solubility data for APIs are typically generated in water and organic solvents as part of the physical and chemical characterization workup for the API. Those APIs that are least soluble in the cleaning solvent are considered

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the hardest to clean. This approach neglects the formulation excipients, which are often insoluble, comprise a much greater percentage of the formulation, and can be more difficult to clean than the API.

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A more empirical method to determine a worst-case soil is to spot coupons with the soils, allow them to dry, and clean them using the identical conditions encountered in the cleaning cycle. Equipment surfaces, however, encounter different types of cleaning action depending on their location in the manufacturing equipment. Soils could be subjected to manual scrubbing, impingement under the cleaning solvent, turbulent flow from a pump forcing cleaning solvent through piping, or a cascade action as the cleaning solvent moves across equipment surfaces.

Cleanability studies are typically conducted using dried residue spotted on a coupon dipped into a beaker containing water or the cleaning solvent or solution. The cleaning solvent is stirred, creating a less rigorous cleaning action than encountered during actual cleaning, and would be considered a worse-case condition. The experiment can be conducted at room temperature or an elevated temperature. The soil with the longest cleanability time can be considered the worst-case soil for cleaning validation within the variability of the test parameters. Numerous studies have been conducted to demonstrate cleanability. Studies range from a paper-based evaluation of a facility's soils (1) to basic laboratory conditions, such as suspending the coupons in a beaker of cleaning solvent, all the way up to a sophisticated cleanability bath (2). Cleaning parameter variations have been characterized using cleaning process design on bench-scale studies (3), but for this study the cleaning parameters were held constant. Statistical equivalence testing for assessing cleanability (4) can show that soils are cleaned to an equivalent extent. If potential worst-case soils demonstrate comparable cleanability, it would be prudent to use more than one worst-case soil for further testing.

A well-executed cleanability study is one part of a comprehensive cleaning validation program. The experimental cleanability can be preceded by an evaluation of the formulation components to narrow the number of soils tested. The selected soils and materials of construction can be tested using a matrix approach to determine a worst-case soil and a hardest-to-clean material of construction.

Complementary studies can include—rinse recoveries and swab recoveries for analytical testing, and visible residue limits (5) for inspection of cleaned equipment. The studies can be conducted in parallel, often using the same coupon samples for multiple studies. All studies might not be necessary, based on the number of formulation soils and the manufacturing equipment involved, but a comprehensive picture of the physical properties of the soils during cleaning, and the ability to test and detect residual soils after cleaning, form a sound basis for a validated cleaning program.

Methods

The cleanability study was conducted to determine ease of cleaning for a variety of soils on a range of material-of-construction coupons using the following parameters. **Table I** lists 10 material-of-construction coupon types, which are among the commonly used materials of construction in pharmaceutical and biopharmaceutical manufacturing. All 10 materials of construction were tested during the study.

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Table I. Material-of-construction coupon types.
316 stainless steel
Glass
Polypropylene
Acrylic
Polytetrafluoroethylene (Teflon)
Silicone
Synthetic fluoropolymer rubber (Viton)
Nickel-steel alloy (Hastelloy)
Ethylene propylene diene monomer (EPDM)
Polyether ether ketone (PEEK)

The cleanability study to determine the worst-case soils was conducted using three buffers and three media under the following parameters. The coupons were weighed and soils were spotted in triplicate for each of the material-of-construction coupon types listed in **Table I.** Each individual coupon was spotted with 1 ml of the soil. The soil was allowed to dry for at least 4 hours, or until visually dry, but no longer than 3 days, which was the established dirty hold time. Following drying, the coupons were reweighed and the coupon weight was subtracted to determine the weight of the residue. The coupons were immersed in a 600-ml beaker containing 400 ml of room-temperature purified water. The 600-ml beaker was the smallest beaker that would hold the 2.5” x 2.5” coupons without impeding flow around the coupons during testing and 400 ml was the minimal volume necessary to completely cover the coupons. The water was agitated on a magnetic stirrer at a fixed rotation and did not generate a vortex during testing. The cleanability endpoint was defined as the time at which the soil was no longer visible to the observer under defined conditions: distance 18 inches, optimal viewing angle dependent on the material-of-construction coupon type, and 700 lux light intensity. The coupons were removed from the beaker immediately after the visual endpoint was determined.

The visual endpoint was confirmed analytically through conductivity, total organic carbon (TOC), and gravimetric testing. The cleaning solution in the beaker was tested for conductivity. A sample of the cleaning solution was taken and tested for TOC. Positive controls were tested for conductivity and TOC by pipetting 1 ml of soil directly into a beaker and testing for conductivity and TOC. After drying, the coupons were again weighed and the weight was compared to the initial weight to determine cleanability of the soils gravimetrically.

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