Water Technologies & Solutions
application note

real time, low flow, pharmaceutical soil cleanability profiling with TOC and conductivity

introduction

Designing a robust cleaning process for pharmaceutical drug manufacturing is critical to successful cleaning validation and verification. Historically, cleaning process design for pharmaceutical manufacturing was focused on reducing active pharmaceutical ingredients (API) with the highest potency or toxicity down to or below the maximum allowable carryover (MAC) limits. The Food and Drug Administration (FDA) as well as industry experts have placed an increasing emphasis on reducing risk and demonstrating process control and process understanding for validated cleaning processes. The concept of total cleanability and master soil identification is an emerging area of interest for risk reduction when developing a validated cleaning process.[1]

A traditional total cleanability study can be achieved by isolating each potential soil and, under worst case cleaning conditions (e.g. concentration, temperature, etc.) ranking all soils based on time until clean. Using the time until clean metric, a master soil is identified and the cleaning process is optimized around reducing the master soil. This method assumes that by reducing the master soil, all other soils will be reduced even further. Traditionally, these cleanability studies are performed using visual clean as the qualitative metric for ranking.[2] The studies can be time and resource intensive, do not provide adequate sample frequency, and rely on subjective rankings such as visually clean.

With these considerations in mind, a novel cleanability study was designed using the Sievers* M9 Total Organic Carbon (TOC) Analyzer to mimic equipment rinse down during a cleaning cycle and quantitatively rank soils for cleanability profiling. This solution enables more efficient and quantitative studies for master soil identification and effective cleaning process design.

real time soil cleanability profiling

To perform this study, the Sievers M9 TOC Analyzer was deployed online in turbo mode with a low flow sampling block to profile a representative series of pharmaceutical soils. Turbo mode on the Sievers M9 allows for near real-time data acquisition with a TOC measurement taken every four seconds. This innovative feature uniquely allows the Sievers M9 to measure the rinse down profiles on a piece of equipment as it is being cleaned. This feature, in tandem with the low flow sampling block, enables rinse down profiling even when the final rinse volume or flow rate is limited. The standard Integrated On-Line Sampling system (iOS) for the Sievers M9 has a minimum flow of 30 mL/min whereas the low flow sampling block has a minimum flow of 3 mL/min.

The novel proposals within this cleanability study are:

1. leveraging real time TOC and conductivity measurements through Turbo mode to characterize various soil rinse down profiles
2. ranking soils based on their profile tailing factor (TF) rather than simply time to clean.

Traditionally a chromatography parameter, TF is a metric for quantifying the undesirable interaction between analytes and column stationary phase. For the purposes of this cleanability study, the TF metric is applied to the TOC results to identify the master soil to optimize a cleaning process around (**Figure 1**).

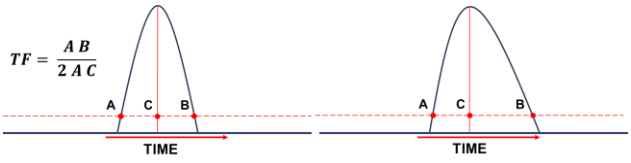


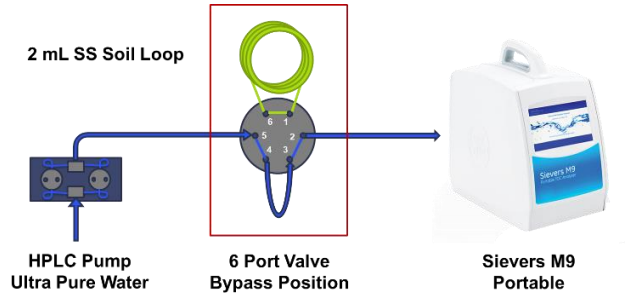
Figure 1. Sample chromatograms demonstrating tailing factor (TF) ranking points

methods

To mimic the rinse down of soiled pharmaceutical equipment, a Sievers M9 Portable TOC Analyzer was configured with a six port, two position valve and a pre-soiled 2 mL stainless-steel sample loop (**Figures 2a** and **2b**). An HPLC pump was also connected to the valve to pump Ultra Pure Water (UPW) through the soiled sample loop and into the M9 for measurements.

First, baseline measurements of the UPW were obtained by rotating the valve into the bypass position (**Figure 2a**) so that UPW flowed into the M9 sampling block without contacting the soiled sample loop. Once the UPW baseline reading was stable, the valve was rotated into the run position (**Figure 2b**) to allow the UPW to pass through the soiled sample loop and into the instrument. The Sievers M9 in Turbo mode was then used to measure TOC and conductivity to generate a cleanability profile for each soil tested.

a.



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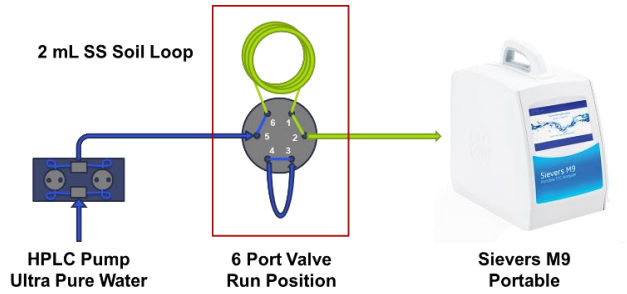

Figure 2a. Valve bypass position
Figure 2b. Valve run position

The following compounds were analyzed using this method:

- Starch
- Lactose
- Ibuprofen
- Bovine Serum Albumin (BSA)
- Hemoglobin
- Ethanol (EtOH)

results

The real time, low flow, soil cleanability TOC and conductivity profiles for the six compounds tested are shown in **Figures 3** and **4**, respectively. In **Figure 4**, the lower level conductivity profiles are shown magnified in the upper right corner. Based on the TOC TF, the soils are ranked from worst case to best case in terms of cleanability (**Table 1**).

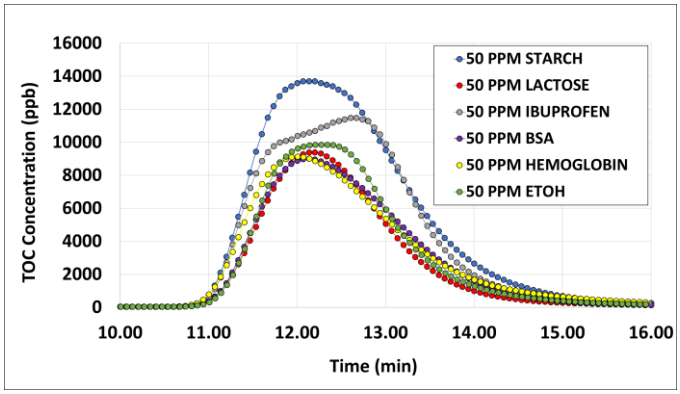

Figure 3. TOC soil profiles collected in Turbo mode with the Sievers M9

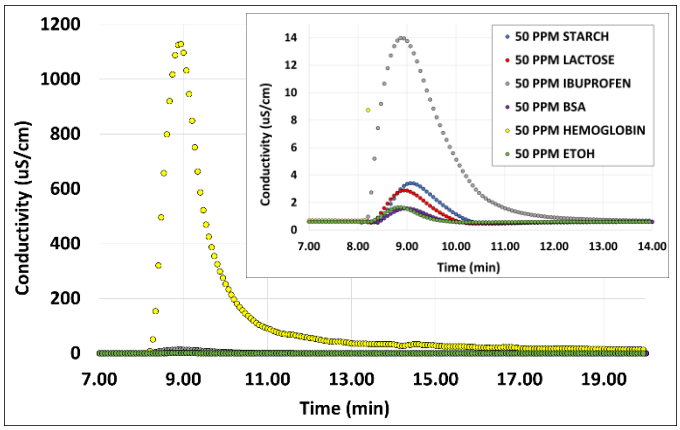

Figure 4. Conductivity soil profiles collected in Turbo mode with the Sievers M9

Table 1. Soil profile rankings based on tailing factor (TF)

Soil	A (min)	B (min)	C (min)	TOC TF	Rank
Hemoglobin	10.935	15.430	12.000	0.643	1
Starch	10.988	15.010	12.130	0.619	2
BSA	11.023	14.853	12.130	0.612	3
Ethanol	11.063	14.775	12.270	0.602	4
Lactose	11.020	14.453	12.200	0.592	5
Ibuprofen	10.998	14.925	12.670	0.589	6

The data from this study indicate that out of the six soils tested, the worst case, master soil is hemoglobin (**Table 1**). Traditional cleaning process design would have identified the most toxic or most potent soil as ibuprofen and designed a cleaning process around its reduction/elimination while neglecting the other soils as inconsequential.

The data from this research indicate that ibuprofen is the most cleanable soil of all of those tested. If the traditional approach to cleaning process design was taken, all other soils tested would not be reduced to optimal levels and may have prevented the process from being be validated.

conclusion

With the increased emphasis from the FDA and industry experts on demonstrating process control and understanding, factoring soil cleanability into cleaning process design has never been more important. Performing cleanability studies to identify master soils is critical in designing a robust and effective cleaning process.

By leveraging a non-specific method such as TOC, cleanability studies can now efficiently and quantitatively identify worst case master soils. Additionally, the use of non-specific methods for cleaning validation and verification enables process control and understanding through total soil monitoring of APIs, detergents, degradants, excipients, and any other contaminants. Specific methods such as HPLC only provide information about single APIs or specific analytes and offer a limited view of the entire cleaning process.

This research successfully demonstrates real time cleanability soil profiling using a Sievers M9 TOC Analyzer deployed online at a low flow rate in Turbo mode to measure TOC and conductivity. Additionally, this research demonstrates the successful application of tailing factor to rank soil profiles to identify the worst case, master soil. Through its Sievers product line, SUEZ offers complete TOC analysis solutions for all your cleaning application needs.

References

1. "Guidance for Industry. Process Validation: General Principles and Practices." U.S. FDA Pharmaceutical Quality/Manufacturing Standards (CGMP), fda.gov, www.fda.gov/downloads/drugs/guidances/ucm070336.pdf. Accessed 15 May 2018.
2. Jordan, Kelly, et al. "Cleanability of Pharmaceutical Soils from Different Materials of Construction." Pharmaceutical Technology, vol. 38, no. 7, 2 July 2014, www.pharmtech.com/cleanability-pharmaceutical-soils-different-materials-construction. Accessed 15 May 2018.

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