



**TELEDYNE
INSTRUMENTS**
Analytical Services

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Title:

Why Total Organic Carbon (TOC) Is Often Superior to HPLC for Cleaning Validation Sample Analysis: A Real World Example

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Introduction:

As TOC has grown in acceptance in recent years, its versatility has evolved to include cleaning validation/verification analysis; an application typically reserved for single-product assays like HPLC. This has been quite slow to occur however, and in those applications where it is found, it is almost always the case that TOC was used in a new validation scheme rather than as a replacement for HPLC.

If a facility is already using HPLC for cleaning validation, the economics of a change from HPLC to TOC may seem attractive at first, but when considering the actual costs of the change to company quality and validation groups, the attractiveness can fade. While TOC is cheaper, easier and faster, the costs of migrating to an alternative analytical method and revalidating are high and the process sometimes burdensome. A blockbuster drug (\$1B or more) can expect millions of dollars in lost time to equipment and employee lost hours with HPLC and yet the best possible support for making a switch to TOC belies economics and instead rests in its advantages as a non-specific technique.

Disadvantages of HPLC?

Advantages to using HPLC in cleaning validation from an analytical perspective include, but are not limited to: sensitivity, specificity and robustness. These qualities are generally desirable in an analytical technique but are best exploited within a highly specified static method development.^{1,2} As manufacturers of drugs and biologics consider active ingredients and compounds in their products for limit establishment, chromatographic methods are often developed to test for the products and elicit the best possible system response; it is within this method development and optimization that danger may reside.

Because method parameters are honed to best detect the one or two analytes of greatest interest, validated methods may in fact be quite ineffective for accurately detecting other sources of contamination.

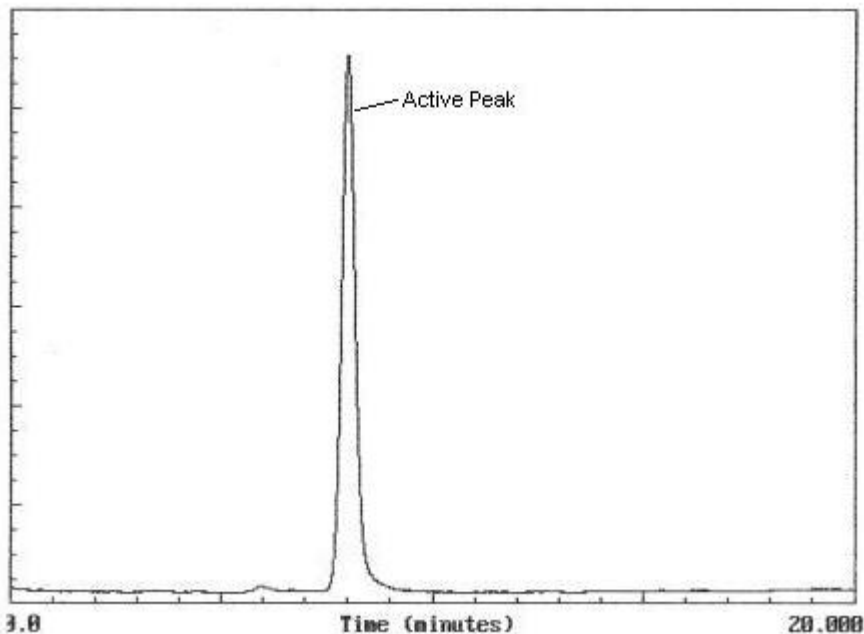
Customer Example

Data volunteered by one customer of a system excursion revealed that the TOC value obtained from one cleaning validation analysis exceeded their system alarm limit, prompting a follow-up investigation. Table 1 shows the results obtained from the analysis, where the equipment train represented in AF-33 was found to be in question with respect to potential contamination.

Equipment	TOC Result	Limit	Action Required (Yes/No)?
C2 (Blend, Mix, Win)	304 ppb	1.1 ppm [C]	No
AF-33 (Hold, Mix, x-fer)	21.9 ppm	2.0 ppm [C]	Yes
C1 (Stor, x-fer, Blnd, Pass)	96 ppb	2.0 ppm [C]	No

Table 1 – Results obtained using Tekmar Phoenix TOC analyzer

Employed as a supplemental “specific” technique in the event of failures, HPLC was performed on a backup sample, but yielded no additional information in that no contamination was discovered (Graph 1). A second TOC analysis yielded a TOC result of 21.2 ppm; similar to the first result and far exceeding the established limits.



Graph 1 – Sample chromatogram depicting result of backup sample.

More than two weeks of investigative work can be summarized by stating that the contamination was eventually traced to a component in a hand sanitizer used by the

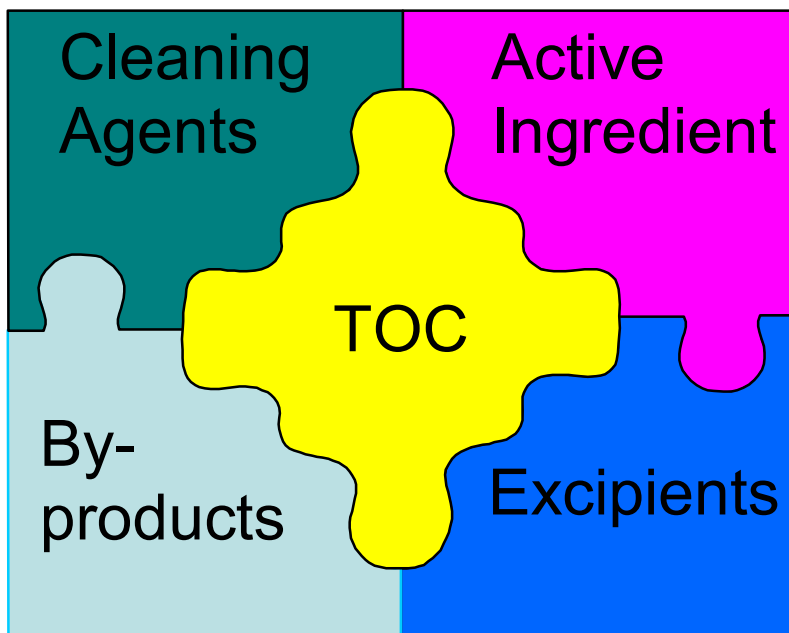
manufacturing personnel that acquired the cleaning verification samples. It was eventually identified using an LC-MS system and several method refinements. Even though the contamination was eventually determined to be a sample contamination and not a true system contamination, this was a very important exercise for the customer with respect to the analytical methodology employed in their cleaning verifications.

For the customer, it was clear that their TOC instrument “saw” contamination that their HPLC did not. It mattered little what the source or nature of the contamination was; it validated the power of TOC in cleaning applications to detect contamination outside their active pharmaceutical ingredients. After considering the general operation of their HPLC instrument and the properties of the contaminating compound, the customer concluded that the two were poorly suited. The validated HPLC utilized a UV detector, yet the contaminant was only very slightly polar and possessed almost no UV chromophores – a mismatch as far as a viable detection scheme. Beyond this however, the gradient elution methodology of the LC system for the active ingredients matched up rather poorly with the elution properties of the contaminant as far as its polarity was concerned. In this particular situation, the HPLC system was essentially doomed to fail.³

The Power of Non-specificity

As a non-specific technique, TOC has been criticized as inappropriate for use in pharmaceutical cleaning validation applications. The truth is though, that because validated facility cleaning procedures do an excellent at eliminating carry-over and cross-contamination between product batches, there is typically no need for qualitative information. Making an analogy to the testing of bulk pharmaceutical waters in accordance with USP <643>, the source of the contamination is insignificant so long as the TOC levels do not exceed established limits. Similarly, if residue limits are properly established, TOC is perfectly appropriate for use in cleaning validation applications.⁵⁻⁷ The FDA is fully accepting of its use pending a full analytical methodology justification and validation.⁸ It should not only be acceptable to manufacturers in cleaning applications, but rather seen to provide a distinct advantage as a non-specific technique.

Because TOC measures carbon irrespective of its source, it can provide a system snapshot that is much more revealing than results from a compound-specific chromatogram. The simple illustration below illustrates how TOC can provide information about not simply the active ingredient in a manufacturing system, but also about cleaning agents, by-products, excipients and more. As was illustrated in the customer example, a qualitative technique such as LC should always be employed in the event of a limit excursion investigation, but the frequency of this will likely be very low due to the general efficiency of most cleaning programs.



Conclusion:

Total Organic Carbon has a myriad of advantages over single-product assays in cleaning validation. Not only is the technique less expensive to implement and maintain as compared to LC, its non-specific nature allows it to detect contamination from any source, regardless of its nature. Additionally, it should be noted that because of the complexity of HPLC and its widespread use, it is generally accepted as the most oft-targeted assay by inspectors. Certainly it the lower costs of purchasing, validating and operating a TOC analyzer in cleaning validation applications should not be overlooked, but it should be more important to manufacturers that its non-specificity provides distinct informational advantages over qualitative techniques like HPLC.

References:

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