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Downsides to TOC?

After HPLC, TOC (Total Organic Carbon) is one of the most widely used analytical methods for measuring residues in cleaning validation protocols. TOC is used because of its simplicity of method development, and because it measures degraded as well as undegraded organic chemical species. As with other analytical methods, TOC does have it downsides. Both advantages as well as possible disadvantages of any analytical method should be considered in a decision to use it.

One downside to TOC is that the residue must be water soluble. I have discussed this feature many times, but it bears repeating. The issue of water solubility for cleaning validation protocols usually means that the target residue must be soluble in water at a level of about 10-30 ppm (equivalent to about 5-15 ppm TOC). In other words, in most cases, residue limits as measured by TOC are going to be less than 15 ppm. The usual definitions of solubility, as given in the pharmacopeias or in the Merck Index, define "practically insoluble" as solubility of 1 part in more than 10,000 parts of solvent. This is equivalent to solubility less than 100 ppm. Therefore, just considering this definition of solubility may be misleading; determination of adequate water solubility needs to be assessed individually for each compound listed as "practically insoluble". I have discussed ways to document adequate solubility in my December 2004 Cleaning Memo. Note further that if a compound is listed as "very slightly soluble", it is soluble in the range of 100 ppm to 1000 ppm, and should be amenable to measuring by TOC. In addition, if the target residue (for example, the active) is degraded in the cleaning process, then perhaps it is not the solubility of active itself which should be considered, but rather the solubility of the degraded fragments of the active. In other words, the issue of water solubility may be a downside, but it probably is not as severe a limitation as is sometimes believed.

A second possible downside to TOC is that measuring residues using TOC is, in most cases in cleaning validation protocols, a worse-case situation as compared to measuring the same residue with a specific analytical method. In other words, if I am measuring residues of the active (API) using an HPLC method, I will generally measure a lower value for that active than if I measured the same active using TOC. For clarification, this generally applies to measuring that active in a cleaning validation protocol where there are sources of organic carbon in addition to the active. For example, in a protocol execution, other sources of organic carbon might be the excipients and the cleaning agent. If I were just measuring a solution of the active alone in a laboratory study, I should obtain the same values (within experimental error) using either method (TOC or HPLC). This phenomenon of being a worse case means that other things being equal, I would be more likely to measure values below my preestablished residue limit using a specific method. Of course, I could put a positive spin on this by saying that obtaining passing results with TOC means my cleaning procedure is even more robust.

A third possible downside to TOC relates to the practical limit that can be calculated based on carryover considerations and swab sampling considerations. Assuming that a surface area limit of M $\mu g/cm^2$ is established, then the limit in the desorbed swab sample (what I currently call L4) depends on the swabbed area and the amount of solvent (such as water) the swab is desorbed into. The mathematical expression of this is:

where SA is the swabbed area in cm^2 and SDA is the "solvent desorption amount" in grams (or mL).

For methods such as HPLC, it is possible to desorb a swab in a very small amount of solvent, such as 2 to 5 grams of solvent. As a practical matter for TOC, the minimum amount of solvent that is required for an analysis is about 17 grams (or 17 mL). This is required because most TOC instruments will perform four injections, with the values from the last three injections averaged as the reportable value. Assuming that with both HPLC and TOC we swab the same surface area (cm^2), then the controlling factor for determining the L4 value is the value for SDA, which is determined to an extent by the amount that must be injected into the instrument (another determining factor is the amount that is required to wet the swab so the residue can be removed from the swab to the solvent). Assuming that our L3 value is 1.6 $\mu g/cm^2$ and the swabbed area is 25 cm^2, then the L4 limit value will be about 2.4 ppm active with TOC (SDA of 17 mL), which assuming that the active were 50% carbon would be about 1.2 ppm TOC. However, the L4 value for the HPLC technique would be about 10 ppm (with a SDA of 4 mL). In this example, 1.2 ppm TOC value would be a L4 limit that could easily be considered in a protocol using TOC as the analytical method. On the other hand, if the L3 value were as low as 0.2 $\mu g/cm^2$, the corresponding L4 values would be 0.15 ppm (150 ppb) TOC. Considering that as a practical matter, the quantitation limit for TOC in cleaning validation protocol would be on the order of 100 ppb (remember that I am subtracting out the blank value to arrive at the net TOC due to residues on the swabbed surface), I might not want to perform a protocol where the quantitation limit is that close to my calculated L4. To continue the analogy, the L4 value for the HPLC method in this case (assuming again a SDA of 4 mL) would be about 1.25 ppm. Of course, the suitability of using HPLC will depend on the quantitation limit for the HPLC procedure.

$$L4 = \frac{(M)\,(SA)}{(SDA)}$$

Note that the purpose of the Cleaning Memo is not to discourage the use of TOC as an analytical technique for cleaning validation protocols. It certainly has value, which is why it is widely used. However, as with any analytical method, understanding the advantages and disadvantages can help avoid situations where an inappropriate analytical method is used.