Establishing Extractables Testing from Plastic Packaging Materials and Systems for Pharmaceutical Use by TOC Analysis According to USP <661>

Introduction
The USP chapter <661> (formerly known as “Container-Plastics”) was revised under the title “Plastic Packaging Systems and their Materials of Construction”. The two new sub chapters of the new monograph describe TOC testing approaches of water-based extracts addressing “Plastic Materials of Construction” <USP 661.1> and “Plastic Packaging Systems for Pharmaceutical Use” <USP 661.2>.

The whole chapter aims at further improving product safety of pharmaceutical products by using only well-characterized materials for packaging. Besides TOC testing these materials and systems should be characterized with regard to their identity, biocompatibility (biological reactivity), physicochemical properties (like UV/Vis absorbance, alkalinity or acidity), plastic additives and extractable metals.

According to USP <661.1> and <661.2> the TOC methods used need to provide a linear dynamic range of 0.2–20 mg/l TOC with a detection limit of max. 0.2 mg/l. The TOC limit value in plastic materials of construction used in packaging systems is NMT (not more than) 5 mg/l (USP 661.1) and in plastic packaging systems for pharmaceutical use it is NMT 8 mg/l (USP 661.2).
Materials and Methods

Samples and Reagents
A sample of a plastic packaging system for pharmaceutical use and several samples from plastic materials of construction used in such packaging systems were prepared and analyzed according to USP guidelines:

Plastic materials of construction used in packaging system:
- Polyethylene, cyclic olefins and polypropylene
- Polyethylene terephthalate and polyethylene terephthalate G
- Plasticized Polyvinyl chloride

Sample Preparation
The samples were extracted as per USP guidelines. The details of sample preparation are given for each type of material.

Polyethylene, cyclic olefins and polypropylene
25 g of the test material are placed in a borosilicate glass flask and boiled under reflux conditions with 500 ml of purified water for 5 hours. The cooled extracting solution is to be filtered through a sintered-glass filter. The filtrate is collected in a 500 ml volumetric flask and made up to volume with purified water. This solution has to be used within 4 hours of preparation for TOC measurement.

Polyethylene terephthalate and polyethylene terephthalate G
10 g of the test material are placed in a borosilicate glass flask and heat at 50 °C with 200 ml of purified water for 5 hours. After cooling, the solution is decanted into a 200 ml volumetric flask and made up to volume with purified water. This solution has to be used within 4 hours of preparation for TOC measurement.

Plasticized Polyvinyl chloride
25 g of the test material are placed in a borosilicate glass flask, 500 ml of purified water added and the flask’s neck covered with aluminum foil or a borosilicate beaker. The flask is heated in an autoclave at 121 ± 2 °C for 20 minutes. After cooling, the solution is decanted into a 500 ml volumetric flask and made up to volume with purified water. This solution has to be used within 4 hours of preparation for TOC measurement.

Plastic packaging systems for pharmaceutical use
The packaging system is filled to its normal capacity with purified water and closed by using the normal means of closure or otherwise with an inert closure. The packaging system is heated in an autoclave at 121 ± 2 °C for 30 minutes. If heating at 121 °C leads to the deterioration of the container, heat treatment at 100 ± 2 °C for 2 hours or at 70 ± 2 °C for 24 ± 2 hours can be applied. After cooling the filled packaging system, its content is emptied and used within 4 hours of preparation for TOC measurement. For this testing method a blank standard has to be prepared by heating purified water in a borosilicate glass flask closed with an inert closure, under the same temperature and time conditions as for sample preparation.
Calibration
The analyzers of the multi N/C pharma series were calibrated for NPOC in the range from 0.1 to 20 mg/L with standard solutions prepared from a 1000 mg/L sucrose stock solution. A multi-point calibration type was used. The calibration curve and its characteristics are presented in Figure 1.

An outstanding linearity could be demonstrated throughout the whole calibration range from 0.1 to 20 mg/L for all three analyzer models of the multi N/C pharma series.

Instrumentation
The analysis was performed on the multi N/C pharma UV, the multi N/C pharma HT and the multi N/C 3100 pharma. The following method settings were used to determine the TOC content:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>multi N/C pharma UV</th>
<th>multi N/C pharma HT, multi N/C 3100 pharma¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPOC</td>
<td>NPOC</td>
<td>NPOC</td>
</tr>
<tr>
<td>Digestion</td>
<td>UV radiation assisted by Na₂S₂O₈</td>
<td>high-temperature oxidation using Pt catalyst at 800 °C</td>
</tr>
<tr>
<td>Number of repetitions</td>
<td>min. 3, max. 4</td>
<td>min. 3, max. 4</td>
</tr>
<tr>
<td>NPOC purge time</td>
<td>300 s</td>
<td>300 s</td>
</tr>
<tr>
<td>Rinse with sample before injection</td>
<td>3 times</td>
<td>3 times</td>
</tr>
<tr>
<td>Injection volume</td>
<td>5 mL</td>
<td>2 mL, 1 mL¹</td>
</tr>
</tbody>
</table>

Results
Three customer provided readymade extracts from plastic materials used in packaging systems were measured alongside with a QC check standard after system calibration as described above. Results are displayed in the table below.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>NPOC Average [mg/L]</th>
<th>RSD [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>2.48</td>
<td>0.9</td>
</tr>
<tr>
<td>Sample 2</td>
<td>0.984</td>
<td>1.3</td>
</tr>
<tr>
<td>Sample 3</td>
<td>8.72</td>
<td>0.5</td>
</tr>
<tr>
<td>QC check (2.0 mg/L)</td>
<td>2.04</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Conclusion

This application note clearly demonstrates that the applied TOC analyzers of the multi N/C pharma series provide the required performance characteristics to comply with the USP standards for TOC testing in plastic packaging systems for pharmaceutical use and their materials of construction. With their high oxidation power, the FR-NDIR detector and a sophisticated design the instruments even exceed the required specifications providing a linear dynamic range of 0.1–20 mg/L.

With TOC analyzers from the multi N/C pharma series you are making your lab fit for the new challenges on pharmaceutical TOC testing.

References

Bletzinger, B.; Êtes-vous prêt à relever les exigences du TOC des nouvelles méthodes USP? La Gazette, September 2016
Bletzinger, B.; Are you fit for the TOC challenges according to new USP regulations? GIT Labor-Fachzeitschrift, October 2016