Challenge
According to USP <661.1> and <661.2>, TOC methods need to demonstrate a limit of detection of 0.2 mg/L and a linear dynamic range of 0.2 to 20 mg/L

Solution
A calibration strategy to cover a TOC working range from 0.1 mg/L to 20 mg/L and successful demonstration of an equivalent linear dynamic range

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". Two sub chapters have been added, describing 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).

For the analysis, purified water extractions from polymer packaging materials have to be prepared under described conditions and to be tested for TOC within four hours after preparation according to USP <643>. It represents the general method for TOC testing in pharmaceutical applications and provides guidance on how to qualify the analytical technique for use as well as guidance on how to interpret instrument results for use as a limit test (e.g., the 500 ppb limit for WFI – water for injection).
This application note describes the procedure for TOC analysis according to USP <661.1> and <661.2> on the TOC analyzers multi N/C 4300 UV, multi N/C 3300 HS and the multi N/C 3300 and proves their performance for these test methods.

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 four 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 five 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 four hours of preparation for TOC measurement.

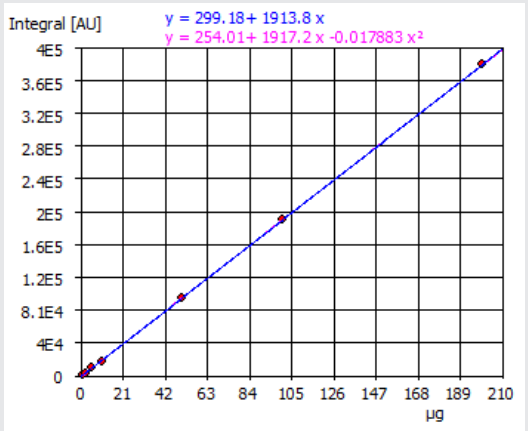
Plastic packaging systems for pharmaceutical use

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 two hours or at 70 ± 2 °C for 24 ± two hours can be applied. After cooling the filled packaging system, its content is emptied and used within four 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 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 used analyzer models of the multi N/C x300 series.



Residual SD:	353.06AU	Linearity:	OK
Method SD:	18.45µg/l	Variance homogeneity:	OK
Method VC:	0.35091%	Detection limit:	27.80µg/l
Qual. of rep.:	0.99999	Identification limit:	55.60µg/l
Correl. coeff.:	1	Quantification limit:	106.2µg/l

Figure 1: NPOC – calibration curve and characteristics

Instrumentation

The analysis was performed on the multi N/C 4300 UV, the multi N/C 3300 HS, and the multi N/C 3300. The following method settings were used to determine the TOC content:

Table 1: Method settings

	multi N/C 4300 UV	multi N/C 3300 HS, multi N/C 3300[1]
Parameter	NPOC	NPOC
Digestion	UV radiation assisted by $Na_2S_2O_8$	high-temperature oxidation using Pt catalyst at 800 °C
Number of repetitions	min. 3, max. 4	min. 3, max. 4
NPOC purge time	300 s	300 s
Rinse with sample before injection	3 times	3 times
Injection volume	5 mL	2 mL, 1 mL[1)]

Results and Discussion

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 2: Results

Sample ID	NPOC Average [mg/L]	RSD [%]
Sample 1	2.48	0.9
Sample 2	0.984	1.3
Sample 3	8.72	0.5
QC check (2.0 mg/L)	2.04	0.7

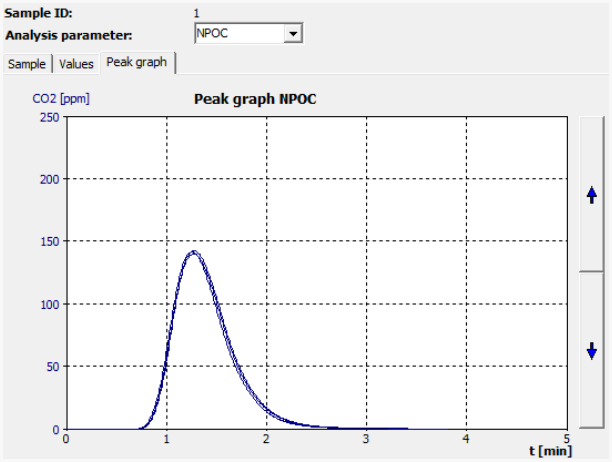


Figure 2: TOC peak graph for sample 1.

Summary

This application note clearly demonstrates that the applied TOC analyzers of the multi N/C 3300 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 Focus Radiation 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 x300 series you are making your lab fit for the new challenges on pharmaceutical TOC testing.

Figure 3: multi N/C 3300 HS with AS vario

References

[1] IBletzinger, B.; Are you fit for the TOC challenges according to new USP regulations? GIT Labor-Fachzeitschrift, October 2016

[2] Bletzinger, B.; Êtes-vous prêt à relever les exigences du TOC des nouvelles méthodes USP? La Gazette, September 2016

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