Water Technologies & Solutions
application note

USP <661.1> Plastic Packaging Materials of Construction Screening with Sievers M9 Total Organic Carbon (TOC) Analyzers

introduction

Pharmaceutical manufacturers of therapeutic products require packaging systems to deliver their products to market. Such packaging systems are frequently constructed from plastic materials and their components and include, but are not limited to, IV bags, blister packs, bottles, and pre-filled syringes.

The plastic materials used in these packaging systems are composed of not only the intended polymer, but may also contain additives such as antioxidants, stabilizers, lubricants, plasticizers, and colorants. When therapeutic products come into direct contact with the plastic packaging system and its components, an interaction between the therapeutic product and the plastic packaging system may occur. To ensure product integrity, efficacy, and patient safety, the United States Pharmacopeia (USP) has issued regulatory requirements for plastic packing systems and their individual components for therapeutic drug products.

Introduced in May 2016, USP General Chapter <661> provides robust characterization of individual plastic materials and the complete packaging systems[1]. Subsequently, this chapter was revised May 1, 2017[2]. The revisions effectively accomplish two things. First, they allow for a three-year implementation period with a final effective date of May 1, 2020[2]. Second, they remove the "grandfathered in" packaging systems previously approved and on the market. The scope of the regulation now universally affects every pharmaceutical manufacturer of any product on the market now or in the future.

USP <661>

USP <661> addresses Plastic Packaging Systems and their Materials of Construction. USP <661> is divided into two subchapters: USP <661.1> Materials of Construction[3] and USP <661.2> Plastic Packaging Systems for Pharmaceutical Use[4]. This application note focuses on USP <661.1> and demonstrates the materials and methods required for compliance.

USP <661.1> prescribes a series of tests to characterize and screen specific plastic materials to ensure suitability for their intended use. These characteristics include identity, biological reactivity, general physiochemical properties, and composition testing for probable extractables and potential leachables[3]. Of the physicochemical tests, Total Organic Carbon (TOC) analysis is one of the compendia tests required. The specifications for a suitable TOC instrument and method are[3]:

"...the method used to perform the TOC analyses should have a limit of detection of 0.2 mg/L (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg/L..."

Furthermore, the material screening acceptance criteria for TOC testing are stated[3] (**Table 1**).

Table 1: USP <661.1> TOC Acceptance Criteria

Group	Plastics	TOC Specification
1	Polyethylene, Cyclic Olefins and Polypropylene	≤ 5 mg/L
2	PET and PETG	≤ 5 mg/L
3	Plasticized Polyvinyl Chloride	≤ 5 mg/L

The extraction and test methods for each group of plastics in **Table 1** are specified within USP <661.1>. These methods represent a worst-case controlled study to determine the extent to which probable extractables may become potential leachables.

USP <661.1> testing methods

Group 1 - Polyethylene, cyclic olefins, and polypropylene[3]: *Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 mL of Purified Water (PW), and boil under reflux conditions for 5 h. Allow to cool, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500-mL volumetric flask and dilute with PW to volume. Use within 4 hours of preparation.*

Group 2 - Polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG)[3]**:** *Place 10 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 200 mL of PW, and heat at 50° for 5 h. Allow to cool, decant the solution into a 200-mL volumetric flask, and dilute with PW to volume. Use within 4 hours of preparation.*

Group 3 - Plasticized polyvinyl chloride (PVC)[3]: *Place 25 g of the test material into a borosilicate glass flask. Add 500 mL of PW, cover the flask's neck with aluminum foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2° for 20 min. Allow solution to cool and solids to settle, decant the solution into a 500-mL volumetric flask, and dilute with PW to volume.*

results

The suitability of the Sievers* M9 TOC Analyzer for USP <661.1> Materials of Construction screening was demonstrated by testing standards for each plastic classification specified in USP <661.1>. The test methods specified in USP <661.1> were followed. Blanks for each group were also prepared and analyzed. The blank subtracted TOC results of the plastics tested are shown in **Table 2** and **Figure 1**.

Table 2: USP <661.1> TOC lab testing results

Material	TOC (ppm)	RSD (%)
Cyclic olefins	0.097	5.83
Polyethylene	0.886	1.48
Polypropylene	0.895	0.24
PETG	1.147	0.23
PET	2.267	0.91
PVC	4.036	0.12

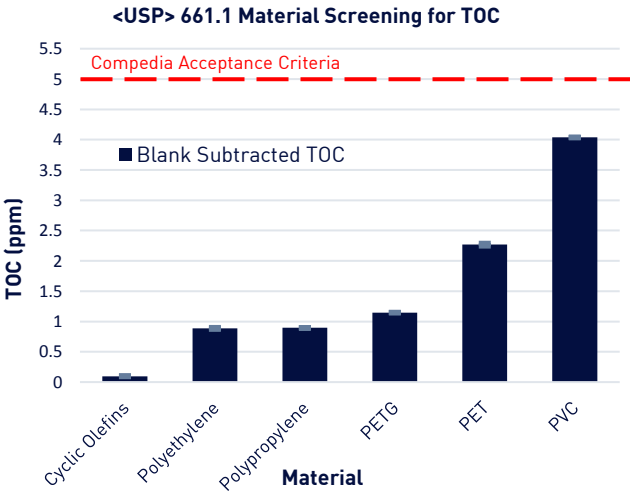

Figure 1: USP <661.1> TOC lab testing results

discussion

The TOC analyzer and method criteria set forth by USP <661.1> have a limit of detection of 0.2 mg/L (ppm) and a linear dynamic range from 0.2 to 20 mg/L (ppm)[3]. Sievers M9 TOC Analyzers have a limit of detection of 0.03 µg/mL (ppb) and a linear dynamic range from 0.03 µg/mL (ppb) to 50 mg/L (ppm). Meeting and exceeding the specifications set forth by USP <661.1> qualifies the Sievers M9 for compendial screening of TOC in plastics for compliance with USP <661.1>.

The USP <661.1> screening results show that even on controlled, standard plastics, there is a wide range of leachables and extractables measured depending upon the type of plastic. These results demonstrate the importance of proper packaging selection through robust material screening and testing.

conclusion

Sievers M9 TOC Analyzers are qualified for compliance testing of plastic packaging materials of construction per USP <661.1> regulations. Furthermore, Sievers offers additional application support for USP <661.1> through its standards and documentation. The following certified reference materials, accredited to ISO Guide 34 and ISO/IEC 17025, are available from Sievers to support the Sievers M9 for USP <661.1> compliance[1]:

- Accuracy/Precision, 8 ppm (STD 77013)
- Accuracy/Precision Set, 5 ppm (STD 99011)
- USP <661> Linearity Set (STD 99012)

A linearity protocol and spreadsheet for reference can be provided upon request.

These standards, combined with the Sievers investigative Failure Analysis Report (FAR), provide traceability and enable expedited Out of Specification investigations. As demonstrated in this application note, a wide range of TOC can be measured in the plastics specified within USP <661.1> using the Sievers M9 TOC Analyzer. Together with traceable standards and FARs, Sievers offers full application support for USP <661.1> compliance.

References

1. USP <661> Compliance for TOC Analysis, 300 00347, 2017. Retrieved Dec. 20, 2017, from https://geinstruments.com/down-media?f_id=39418.
2. <661> Plastic Packaging Systems and Their Materials of Construction, 2017. Retrieved Dec. 20, 2017, from http://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/661_rb_notice.pdf.
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4. <661.2> Plastic Packaging Systems for Pharmaceutical Use, 2017. Retrieved Dec. 20, 2017, from http://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/661.2_rb_notice.pdf.