Accelerated Solvent Extraction of Extractables from Polymeric Components Used in Precision Drug Delivery Devices

Introduction

Many regulatory authorities require the routine monitoring of extractables from polymeric drug delivery device components. Extractables are defined as compounds that can be extracted from polymeric drug delivery device components using a strong solvent. Routine extractables testing is performed on device components to control leachables within the final product. Leachables are compounds extracted from polymeric drug delivery device components by and into the drug product during the shelf life of the device. Leachables can present safety concerns and may influence the effectiveness of the drug product.

Traditionally, routine extractables testing has been performed using Soxhlet and reflux extraction. These techniques have disadvantages associated with the handling and disposal of significant volumes of potentially flammable and hazardous organic solvents. Extractions usually proceed for 24 h and therefore must be left unattended. Arrays of extraction apparatus consume valuable bench space.

Accelerated solvent extraction is an an established technique and an improvement over these traditional extraction techniques. Accelerated solvent extraction is a powerful technique to reliably extract compounds from polymer materials. Accelerated solvent extraction uses organic solvents at temperatures above their atmospheric pressure boiling points to deliver extractions equivalent to traditional techniques, but in a shorter amount of time, with reduced solvent use, and with automation of the extraction process.

This Application Note outlines the use of accelerated solvent extraction in the routine extractables analysis of a typical elastomeric device component.

Equipment

- Thermo Scientific™ Dionex™ ASE™ 200 Accelerated Solvent Extractor* system equipped with 11 mL extraction cells
- Thermo Scientific Dionex ASE Solvent Controller (optional)
- Thermo Scientific™ Dionex™ AutoASE™ Software (optional)
- Analytical Balance
- Filter Disk, Cellulose, for 11 mL Cell (P/N 049458)
- Thermo Scientific Dionex SE 400 or SE 500 Solvent Evaporator
- Gas Chromatograph (GC) with Quadrupole Mass Spectrometer (MS)
- 30 m × 0.25 mm × 0.25 µm Capillary Column
- Thimbles, Cellulose, 11 mL

*Dionex ASE 150 and 350 Accelerated Solvent Extractor systems can be used for equivalent results.

Solvents

- Acetone (glass-distilled grade)

Extraction Procedure

The following procedure provides high extraction efficiencies for a number of elastomer extractables such as cross-linking agent residues and by-products of the cross-linking process.

However, each elastomer formulation is unique, so the procedure may need modifications to optimize extraction speed and efficiency. Exercise caution to ensure that artifacts are not created by extreme extraction conditions that may destabilize the elastomer.

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Cell Preparation

Insert a cellulose filter disk into the cell.

Sample Preparation

Cut up the elastomeric components to increase the surface area for extraction. Weigh approximately 1.0 g of sample and mix it with enough sand to fill the extraction thimble. Some materials can be extracted more reproducibly without the addition of Ottowa Sand (Fisher Scientific); this attribute should be evaluated in method development. Quantitatively transfer the elastomer/sand mixture to the extraction thimble in the cell and place a cell cap on the inlet end of the cell. Place the cell in the upper carousel of the Dionex ASE 200 Accelerated Solvent Extractor system and place the appropriate number of vials in the lower carousel.

Extraction Conditions

Enter the following conditions on the Dionex ASE 200 Accelerated Solvent Extractor system and initiate the run.

Parameter	Value
Pressure:	1000 psi (6.89 MPa)
Oven Temperature:	80 °C
Preheat:	0 min
Purge During Preheat:	Off
Heat Time:	5 min
Static Time:	10 min
Flush Volume:	60% of cell volume
Purge Time:	60 s
Static Cycles:	5
Solvent:	Acetone
Rinse Between Samples:	On

Postextraction

Transfer the collection vial to a Dionex SE 400 or SE 500 Solvent Evaporator (or other appropriate evaporation device) and reduce the extract volume to 4 mL.

N-tetradecane is employed as an internal standard.

Extractables Analysis

Cross-linking agent residues and by-products were extracted from the elastomer using the procedure described above. These compounds were determined by GC/MS using the following conditions:

Carrier Gas:	Helium (high purity)
Flow Rate:	1 mL/min (constant flow)
Injection Mode:	Automated cool on column in oven-track mode
Injection Volume:	1 µL
Capillary Column:	30 m × 0.25 mm × 0.25 µm (or equivalent)
Initial Oven Temperature:	40 °C for 1 min
Temperature Ramp:	9.8 °C/min
Final Oven Temperature:	280 °C
Final Temperature Hold Time:	2.5 min
Interface Temperature:	280 °C
MSD Mode:	Full scan

Results and Discussion

The identities of the compounds extracted are proprietary. A direct comparison with Soxhlet extraction is not possible since this accelerated solvent extraction method was developed for a new elastomer grade. However, the data in Table 1 demonstrates precision of the analysis.

The accelerated solvent extraction method was developed as part of the routine extractables method for an elastomeric device component resulted in a total extraction time of approximately 1 h per sample. A significant reduction in sample preparation time is achieved with the accelerated solvent extraction method as compared with the typical 24-h Soxhlet extractions.

The precision of the method was acceptable, considering the low concentrations of compounds A and B.

Accelerated solvent extraction reduced organic solvent usage by ~70% compared to Soxhlet. Manual handling of solvents was reduced significantly and unattended operation overnight was considered more reliable and productive than traditional extraction techniques.

Table 1. Precision of accelerated solvent extraction of elastomer extractables (µg/g) of component.

Replicate	1	2	3	4	5	6	Mean	Standard Deviation	%RSD
Compound A	25	21	25	23	27	26	25	2.2	8.8
Compound B	10	10	11	11	13	11	11	1.1	10.0
Compound C	208	209	217	202	217	215	211	6.0	2.8
Compound D	114	122	118	115	115	120	117	3.2	2.7

Conclusion

This Application Note provides a general principle for the use of accelerated solvent extraction for extractables from elastomeric drug delivery device components.

Supplier

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