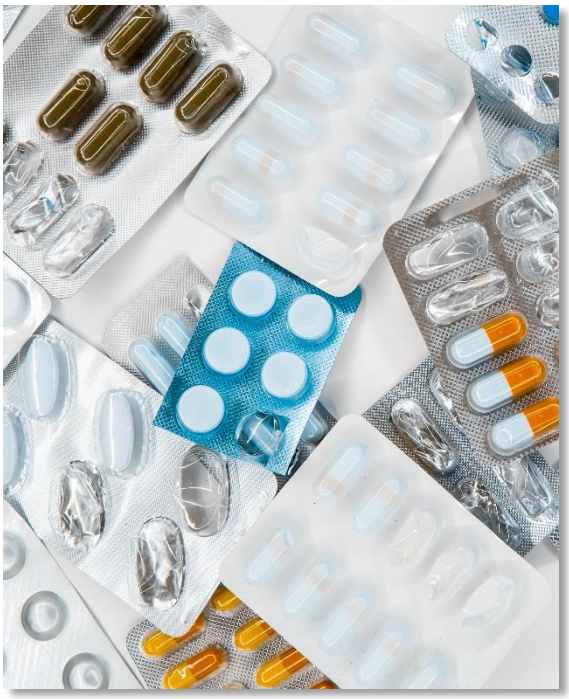
SCIENT™ **GMP-Authorized Laboratory**
(ANMDM Romania, Certificate No: 045/2024/RO)

PerkinElmer®

APPLICATION NOTE

Analysis of Extractable & Leachable Compounds from Drug Formulations using Perkin Elmer GC-MS Systems



The purpose of Extractible & Leachables analysis is to identify and quantify possible harmful compounds that can migrate (Leachables) from primary packaging systems and medical devices into pharmaceuticals and other finished products. The E&L analysis is mandatory to be carried out based on a toxicological risk assessment following regulatory requirements.

Identification of potentially toxic chemicals leaching from a great variety of polymers and plastics destined for pharmaceutical packaging products has received an important attention, but remains a quite challenging analysis for testing laboratories.

Most common additives used in pharmaceutical primary packaging systems are:

- Plasticizers;
- Flame retardants;
- Impact modifiers;
- Antioxidants;
- Antimicrobials;
- UV Stabilizers;
- Colorants;
- Lubricants and processing aids.

Extractables and Leachables studies using gas chromatography-mass spectrometry (GC/MS) are designed to detect volatile and some semi-volatile compounds from medical devices and closure systems. For the semi-volatiles analysis, direct liquid injection is preferred, while for the volatiles the headspace technique is most advantageous.

Extractables testing involves exposing the primary packaging system and its components to organic solvents / water at different pH, high temperatures, or an extended period of time to simulate a leachable profile. This is called the worst-case scenario and it must give information (qualitative and quantitative) about all the compounds that can leach into drug formulation.

In Figure 1. a LDPE dropper system was used in an Extractable study with organic solvents (IPA and n-Hexane) and water at acidic and alkaline pH in a reflux system for 6 hours. The chromatograms were recorded with a Perkin Elmer GC-MS Clarus 680 / Clarus SQ 8T.

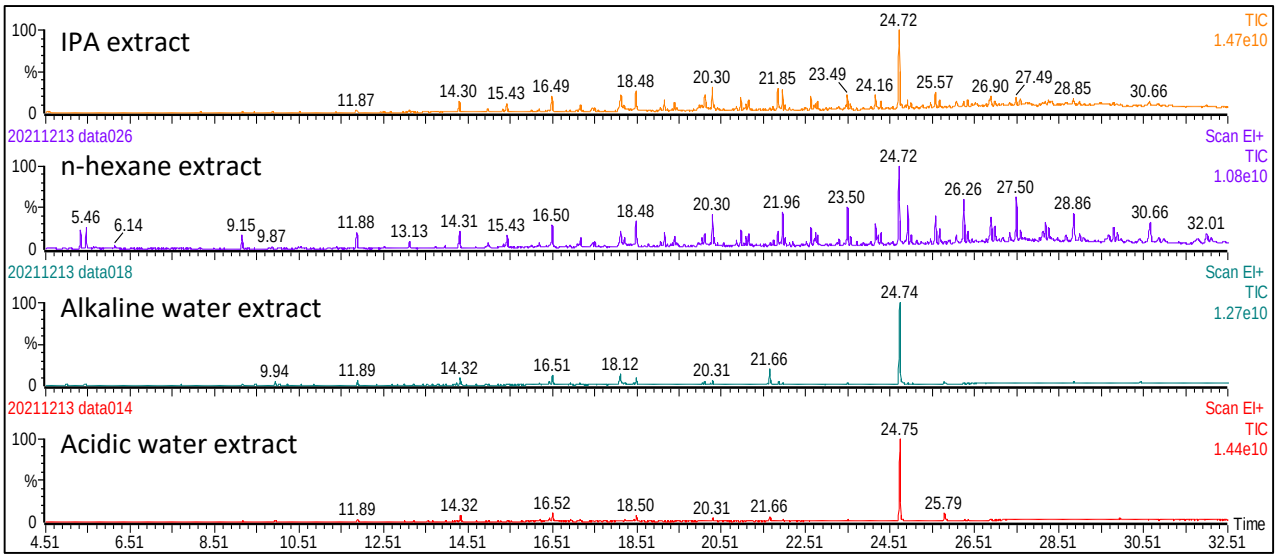


Figure 1. GC-MS total ion chromatogram obtained in the Extractables study of a LDPE system with IPA, n-hexane and water as extraction solvents.

Table 1. Compounds detected in LDPE system extracted with IPA and n-hexane using GC-MS (liquid injection and Headspace)

#	Name	CAS	Match	Common uses
1	Dodecane	112-40-3	936	Plasticizer
2	Tetradecane	629-59-4	942	Plasticizer
3	Hexadecane	544-76-3	918	Plasticizer
4	Heptadecane	629-78-7	924	Plasticizer
5	1-Octadecanol	112-92-5	878	Lubricant
6	Octadecane	593-45-3	918	Plasticizer
7	Eicosane	112-95-8	937	LDPE degradation product
8	1-Eicosanol	629-96-9	883	
9	3-Heptadecanone	84534-29-2	753	
10	Hexadecanamide	629-54-9	860	
11	Heneicosane	629-94-7	907	LDPE degradation product
12	1-Docosanol, methyl ether	-	878	
13	3-Pentadecanone	18787-66-1	749	
14	Octadecanamide	124-26-5	829	
15	n-Tetracosanol-1	506-51-4	893	
16	Pentacosane	629-99-2	889	LDPE degradation product
17	1-Cyclopentyleicosane	-	885	
18	Octacosane	630-02-4	913	LDPE degradation product
19	Octacosyl pentyl ether	-	875	
20	Tetratetracontane	7098-22-8	909	LDPE degradation product
21	Pentyl triacontyl ether	-	858	
22	Hentriacontane	630-04-6	911	LDPE degradation product
23	Dotriacontyl methyl ether	-	831	
24	Tetratetracontane	7098-22-8	901	LDPE degradation product
25	Tetratriacontyl pentafluoropropionate	-	842	
26	Hentriacontane	630-04-6	899	LDPE degradation product
27	Hexatriacontyl pentafluoropropionate	-	849	

Extractables

Leachables Volatiles

Leachables Semi-volatiles

Results reporting

Leachables studies are performed on the actual drug formulation under normal or accelerated storage conditions.
Leachable compounds are typically part of the extractables because of the direct contact of drug formulation with the packaging material.

For the analysis of volatile leachables, we developed, optimized and validated a HeadSpace – GC – MS method able to identify and quantify the possible harmful compounds at low limits of detection.

The quantification of leachables is based on the relative response factor approach calculated from a calibration solution that contains ethanol, methyl-isobutyl-ketone, toluene, 1-propanol, n-decane. 1,4-Dioxane is the internal standard.

Table 2. HS-GC-MS analytical parameters used for E&L studies

Perkin Elmer TurboMatrix S40	
Oven temperature (°C)	80
Needle temperature (°C)	120
Loop temperature (°C)	125
Incubation time (min)	60
Pressurization time (min)	3.0
Vial pressure (psi)	20.0

Perkin Elmer GC Clarus 680	
Column	Elite-Volatile 30m x 0.25mm x 1.40µm
Injector temperature (°C)	200
Injection time (min)	0.10
Injection mode	split injection @ split ratio 20:1
Carrier gas, Mode/Flow	He, constant flow @ 2.00 mL/min
GC oven temperature program	
Temperature 1 (°C)	35
Hold time 1 (min)	7
Temperature 2 (°C)	40
Rate (°C/min)	1
Hold time 2 (min)	15
Temperature 3 (°C)	100
Rate (°C/min)	10
Temperature 4 (°C)	240
Rate (°C/min)	25
Hold time 3 (min)	5

Perkin Elmer MS SQ8T	
Inlet temperature (°C)	180
Source temperature (°C)	150
Acqusition mode	EI+ @ 70eV, scan range 25-200

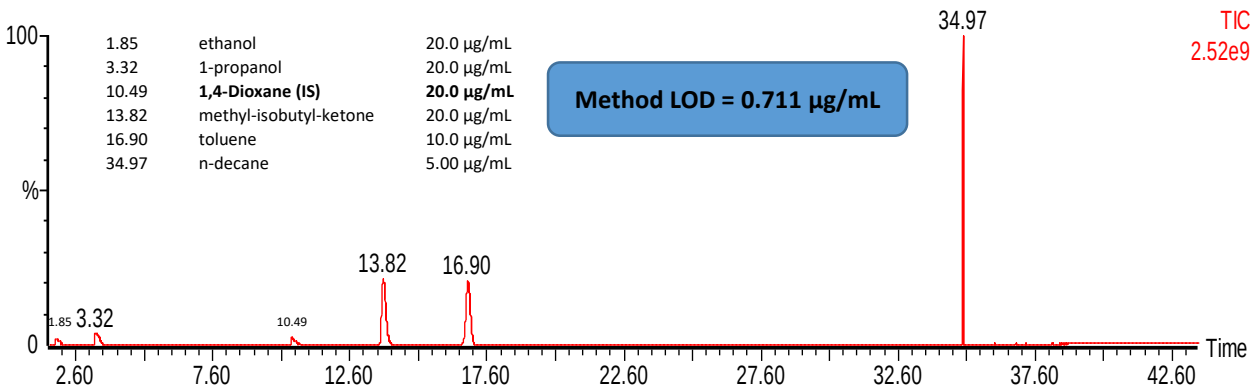


Figure 2. System Suitability Solution for HeadSpace-GC-MS

For the analysis of semi-volatile leachables, a direct liquid injection GC – MS method is used to identify and quantify the compounds at sub-ppm limits of detection.

The quantification of leachables is based on the relative response factor approach calculated from a calibration solution prepared from Grob Test Mix (Restek, P/N 35000). Irganox 415 is the internal standard.

For System Suitability the acceptance criteria is:

- Resolution between n-undecane and n-nonanal must be not less than 1.0
- Signal-to-noise ratio for 1-octanol peak must be not less than 3:1

Table 3. Liquid injection- GC-MS analytical parameters used for E&L studies

Perkin Elmer Liquid Autosampler	
Syringe capacity volume (µL)	5.0
Injection speed	Normal
Viscosity delay (s)	3
Pre-injection solvent wash	2
Pre-injection sample wash	1
Post-injection solvent wash	5

Perkin Elmer GC Clarus 680	
Column	Elite-5MS 30m x 0.25mm x 0.25 µm
Injector temperature (°C)	300
Injection volume (µL)	1.0
Injection mode	split injection @ split ratio 10:1
Carrier gas, Mode/Flow	He, constant flow @ 1.20 mL/min
GC oven temperature program	
Temperature 1 (°C)	50
Hold time 1 (min)	1
Temperature 2 (°C)	8
Rate (°C/min)	315
Hold time 2 (°C)	5

Perkin Elmer MS SQ8T	
Inlet temperature (°C)	315
Source temperature (°C)	230
Acqusition mode	EI+ @ 70eV, scan range 30 - 620

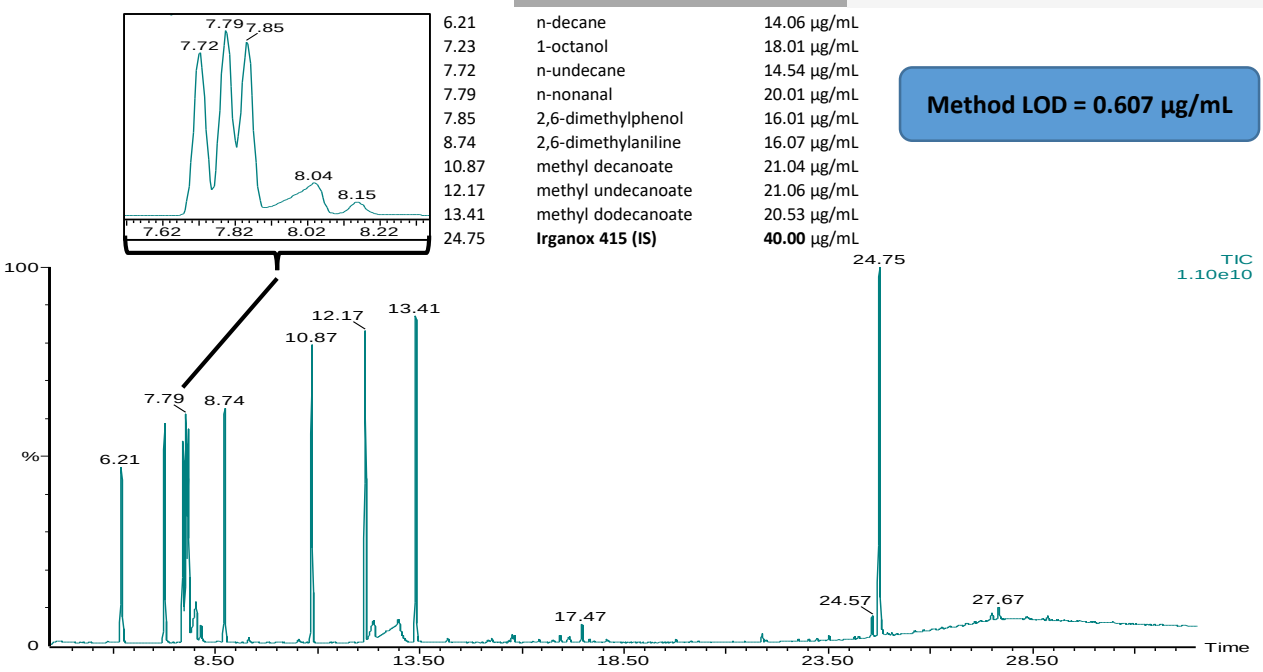


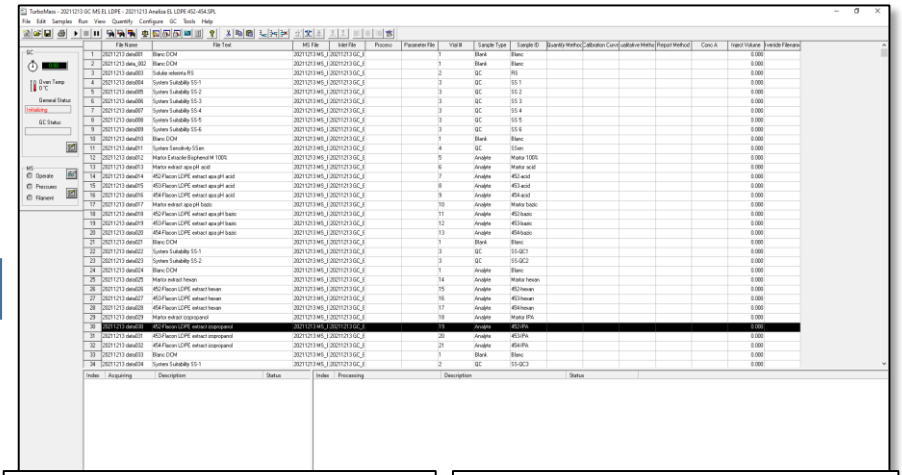
Figure 3. System Suitability Solution (prepared as 20x dilution from Grob Test Mix, RESTEK PN 35000)

Compound identification

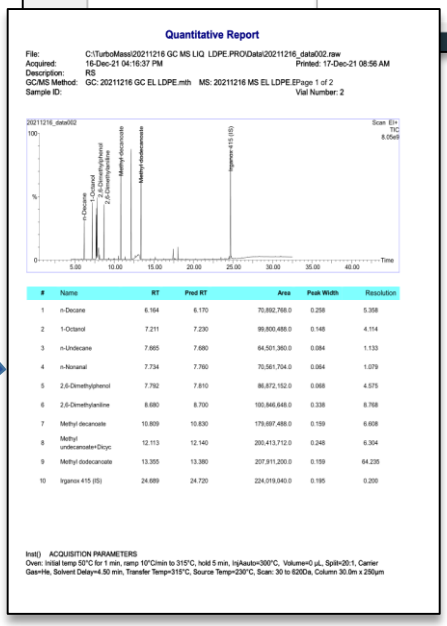
Compounds were characterized using the Perkin Elmer TurboMass software (version 6.1.2) and Communique software to generate the reports.

Mass spectra of all compounds were matched with the NIST Library 2.2 and Wiley9 Library. Compounds with a mass spectral match of at least 700 were considered, and the top match was used in the result reporting.

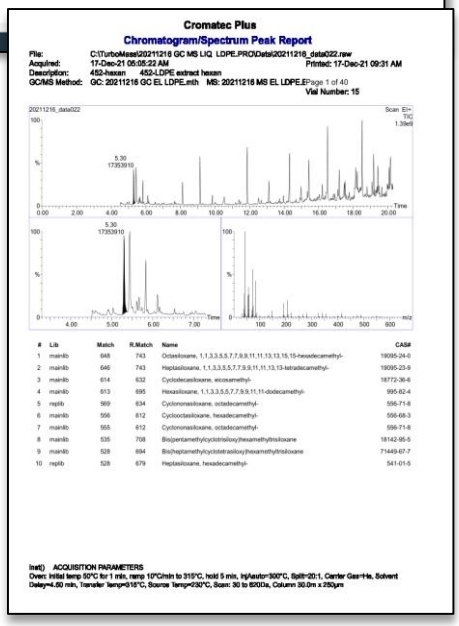
Perkin Elmer TurboMass Software (ver. 6.1.2)



Communique™



System Suitability Report using Communique – peak area + resolution



Qualitative Report using Communique – NIST, Wiley libraries integrated