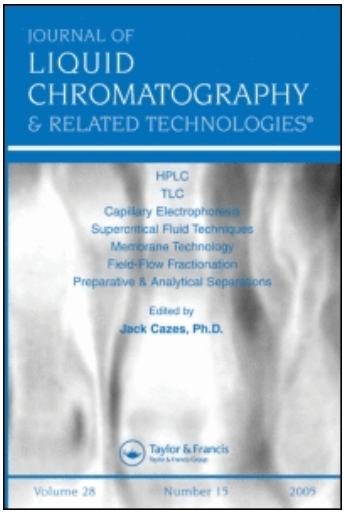

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Organic Extractables from Packaging Materials: Chromatographic Methods Used for Identification and Quantification[#]

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ABSTRACT

A review is provided, related to the chromatographic methods used to assess the accumulation of leachable substances from packaging materials used for pharmaceutical products. The review considers methods used to identify and/or quantify such leachables in actual products or product simulating solvent systems.

Key Words: Organic extractables; Packaging materials; Plastics; Leachables; Pharmaceuticals.

[#]Reprinted from the *Encyclopedia of Chromatography*, Jack Cazes, Ed., Marcel Dekker, Inc. (© 2003); URL: http://www.dekker.com/servlet/product/productid/E-ECHR.

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DISCUSSION

Plastic materials are widely used in medical items, such as solution containers, transfusion sets, transfer tubing, devices, and packaging systems. The physiochemical nature of these materials provides medical products with their necessary, desirable performance characteristics. While an important performance characteristic of plastics used in medical application is chemical inertness, interactions between a plastic material and a contacted pharmaceutical product are well documented. Such interactions may include sorption, the uptake of product components by the plastic material, or leaching, i.e., the release of plastic material components into the product. In the case of leaching, both the identities of the leached substances and their accumulation levels may impact the ultimate utility of the product.

Assessment of the impact of the accumulation of leached substances in pharmaceutical products contacted by a plastic material during their manufacture, storage, and/or use is a multi-faceted undertaking involving disciplines within the applied physical, chemical, and biological sciences. While numerous strategies can be envisioned, and have been utilized to perform such an assessment, considerations include the identification of the leached substances and the measurement of the actual or probable accumulation levels of the identified substances. The identification process is an extensive investigation that utilizes sensitive and information-rich scouting analytical methods for the dual purposes of first revealing the leachables and then providing relevant information (e.g., formula and structure), that leads to their identification. In the worst case scenario, such an analytical investigation is conducted blind; i.e., the analytical team is faced with the unenviable challenge of finding an unknown number of unknown compounds, many of which accumulate in the product at levels much lower than its other constituents. These constituents may include both additives and non-material related contaminants, such as ingredient impurities and degradation products. This search for material-derived leachables in pharmaceutical products is greatly facilitated if it is conducted with information-rich analytical methodologies that exhibit a comprehensive ability to respond to a large population of analytes in both a universal, but very specific, manner. The dual performance requirements of universality and specificity are the primary reasons why chromatographic methods are almost exclusively used in investigations associated specifically with organic leachables.

Given the variety of packaging materials used in pharmaceutical applications, the population of potential primary and secondary organic leachables is large and compositionally diverse. While an analytical chemist has a multitude of chromatographic tools with which to perform a leachables assessment, some guidance in terms of successfully applied strategies and methods can

Table 1. Examples of HPLC methods used to identify and/or quantify packaging system extractables.

Material	Sample matrix	Sample preparation	Column	Mobile phase	λ (nm)	Others	Extractables	Refs.
PVC	Saline extracts	Extraction into hexane	Shandon ODS C_{18}, 200 × 4.6 mm, 200 × 2.1 mm	ACN/MeOH (9/1)	270	20 µL, 0.8 or 0.17 mL min^{-1}	Di-ethylhexyl-phthalate	[1][a]
PVC, PE, PS	Organic solvents	Direct injection	Spherisorb C_{18} ODS2, 250 × 4.6 mm, 5 µm	MeOH/ phosphate buffer (pH 5.5), 1/1	225	20 µL, 1 mL min^{-1}	Monomers, capro-lactam, amino-caproic acid	[2]
PVC, PE, PS	Organic solvents	Direct injection	Spherisorb C_{18} ODS2, 250 × 4.6 mm, 5 µm	ACN/THF (95/5)	280	20 µL, 1 mL min^{-1}	Antioxidants (BHT, Irganox 1010, Irganox 1076)	[2]
PET	Oils	Solvent partitioning (ACN/ hexane) with evaporative concentration	Microsorb C8, 250 × 4.6 mm, 5 µm	A = water/ACN (85/15)[b] B = ACN/water (85/15)	254	20 µL, 1.5 mL min^{-1}	PET oligomers (trimer–octamer), plasticizers (diethylene glycol dibenzoate)	[3]
PET	Oils	Solvent partitioning (ACN/ hexane) with evaporative concentration	Microsorb C8, 250 × 4.6 mm, 5 µm	A = water/ MeOH/AA (85/15/0.25)[c] B = ACN/water (85/15)	254	20 µL, 1.5 mL min^{-1}	PET oligomers, terephthalic acid, dimethyltereph-thalate, bis(2-hydroxyethyl) terephthalate	[4][a]
PP	Solvent extracts (hexane, ethyl acetate, diethyl ether)	Solvent evapora-tion, reconsti-tuted in chloroform/ MeOH	Spherisorb ODS-1 50 × 4.6 mm, 5 µm	15–40% ethyl acetate gradient in 75/25 MeOH/water	271	35°C, 2 mL min^{-1}	Antioxidants (BHT, Irganox 1010, Irganox 1076, Irgafos 168)	[5][a]

(*continued*)

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Table 1. Continued.

Material	Sample matrix	Sample preparation	Column	Mobile phase	λ (nm)	Others	Extractables	Refs.
HDPE	Dissolution with mobile phase	Direct injection	Spherisorb C_{18} ODS-2, 150 × 4.6 mm, 3 μm	MeOH/water/AA(66.5/32.5/1)	280	20 μL, 1 mL min^{-1}	Phenolic antioxidants[d], propyl *p*-hydroxybenzoate	[6][a]
Laminated polyolefin	Drug product	SPE concentration, residue reconstituted in ethanol	LiChrosorb C18 ODS-2, 250 × 4.6 mm, 5 μm	MeOH/water (70/30)	280	20 μL	Caprolactam butylhydroxytoluene, phthalic acid derivative	[7]
Filter cartridges	Water or ethanol extracts	Direct injection or after evaporative concentration	Nucleosil 100-5 RP18, 250 cm	MeOH/water (90/40)	220	20 μL, 1 mL min^{-1}	Phthalates, fatty acids, phenols, siloxanes, acrylates, aliphatics, amides[h]	[8][e]
PC	Methylene chloride extract	Direct injection after polymer ppt with methanol	Shandon Hypercarb S, 150 × 4.6 mm, 7 μm[f]	MeOH/Water/ACN 25.0/26.2/48.8	[j]	20 μL, 0.5 mL min^{-1}	Bisphenol A	[9]
PET, PVC	Solvent extraction	Solvent evaporation reconstituted in IPA	Spherisorb ODS-2[f]	Various binary mixtures	254	Various flow rates	Erucamide PET oligomers	[10]
Polyolefin	Pharmaceutical products	Extract with chloroform, reconst. in 2-propanol	Spherisorb LC-SI, 250 × 4.6 mm, 5 μm	*n*-hexane/2-propanol (9/1)	210	25 μL, 1.5 mL min^{-1}	Caprolactam	[11]
PVC	Pharmaceutical products	Direct injection	Nucleosil ODS, 200 × 4.6 mm, 5 μm	ACN/water (pH 2.7)[g]	[i]	1 mL	Phthalic acid, phenol, cyclohexanone, phthalide, benzoic acid, benzaldehyde,	[12]

								bispenol A, butyl hydroxyanisol, mono-(2-ethyl-hexyl) phthalate, dibutyl phthalate, di(2-ethylhexyl) phthalate	
PVC	Leaching of administration sets	Direct injection	Econosphere C18 150 × 4.6 mm 5 μm	A = 1% acetic acid B = ACN 50% B for 3.5 min, change to 65% B	254	1 mL min^{-1}, 50 μL 35°C		Phthalide, mono-butyl phthalate, mono-(ethyl-hexyl) phthalate	[13][a]
Adhesives	Extraction with water, 50°C, 3 days	Direct injection	NovaPak C18, 150 × 2.1 mm	40 min gradient from 5% to 85% ACN in 0.1% acetic acid	220[k]	0.25 mL min^{-1}		1,3-benzenedicarboxylic acid, mono(7,12-dioxo-3,6,13,16-tetraoxaoctadec-17-en-1-yl) ester, hexanedioic acid, 2-[2-[(5-carboxy-1-oxopentyl)oxy] ethoxy], ethyl 2-(ethenyloxy) ethyl ester, 1,3-benzenecarboxylic acid, 2-[2-[(carboxy benzoyl)oxy]ethoxy], ethyl 2-(ethyloxy) ethyl ester	[14]

(*continued*)

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Table 1. Continued.

Material	Sample matrix	Sample preparation	Column	Mobile phase	λ (nm)	Others	Extractables	Refs.
PP	Extraction with acetonitrile	Direct injection after filtration	Waters Symmetry C8, 150 × 3.9 mm	Start at ACN/water, (30/70), to 100% ACN at 10 min, to 30% ACN at 30 min, hold at 30% ACN for 10 min	MS, EI & APCI, UV	0.4 mL min^{-1} 10 μL	Naugard XL, Irganox 1076, 1-octadecanol, NC-4, 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propanoic acid, 7,9-di-*tert*-butyl-1-oxaspiro-[4,5deca-6,9-diene-2,8-dione]	[35]

Note: PP, polypropylene; PVC, poly(vinyl chloride); HDPE, high density polyethylene; PC, polycarbonate; PS, polystyrene; PET, polyethylene terephthalate; MeOH, methanol; CAN, acetonitrile; AA, acetic acid.

[a]Method performance data provided in this reference.

[b]Gradient was as follows: 0.0 min, 70% A; 18.0 min, 0% A; 22.0 min, 0% A; 23.0 min, 70% A.

[c]Gradient was as follows: 0.0 min, 95% A; 8.0 min, 40% A; 16.0 min, 30% A; 17.0 min, 0% A; 21.0 min, 0% A; 22.0 min, 95% A.

[d]Specific compounds detected included propyl-3,4,5 trihydroxy benzoate, 2-tertbutyl-4-methoxy phenol, 2-tertbutylphenol, 2-tertbutyl-4-methylphenol, and octyl-3,4,5-trihydroxybenzoate.

[e]FTIR analysis of collected peaks used to confirm analyte identification.

[f]Various column sizes used.

[g]Gradient was as follows: 5% ACN for 2 min, 5–50% ACN in 28 min, 50–98% ACN in 15 min.

[h]This cited reference documents numerous compounds in these and other general compound classes.

[i]Multiple wavelengths used.

[j]Fluorescence detection.

[k]Compound identification performed via MS and MS/MS using both APCI and ESI in the positive ion mode.

Table 2. Examples of GC methods used to identify and/or quantify packaging system extractables.

Material	Sample matrix	Sample preparation	Column	Oven program	Detection	Others	Extractables	Refs.
Rubber	Water extract, 121°C, 2 hr	Evaporative concentration	Cross-linked methyl silicone 25 m × 0.3 mm i.d. and DB-Wax-30N, 0.25 mm i.d.	30°C for 1 min, ramp at 8°C min^{-1} to 250°C and 34°C for 1 min, ramp at 6°C min^{-1} to 200°C	FID 325°C[a]	Splitless injection $T = 250$°C	2-Butoxyethanol, cyclohexanone, diphenylamine, 9,10-dihydro-9,9-dimethyl-acridine, dibutylformamide, 1,1,2,2-tetrachloroethane, acetophenone, 2-phenyl-2-propanol, benzothiazole, 2,2,5,5-tetramethyl-tetrahydrofuran	[15]
PET	Solvent extracts, 40°C, 10 days	Evaporative concentration	HP1, 50 mm × 0.25 mm	200–280°C at 8°C min^{-1}	FID 280°C	Split injection $T = 250$°C	Isophthalic acid, terephthalic acid, PET oligomers	[16]
PVC	Water extract	Evaporative concentration	J&W DB-5, 15 m × 0.53 mm, 15 μm film	32°C, 1.5 min; to 75°C at 6°C min^{-1}, to 250°C at 30°C min^{-1}, hold for 2 min	FID 350°	3 μL (splitless) $T = 210$°C	Cyclohexanone	[17]
PVC	Products	Acidification, solvent extraction, evaporative concentration	J&W DB-5, 30 m × 0.32 mm, 0.25 μm film	30°C for 0.5 min, to 225°C at 6°C min^{-1}	FID 350°C	Cold on-column injection	Di-(ethylhexyl) phthalate, dibutyl phthalate, cyclohexanone, phthalide, 2-ethyl-1-hexanol, 2,6-di-*tert*-butyl-*p*-cresol	[18][b]
Filter cartridges	Water or ethanol extracts	SPE with evaporative concentration	J&W DB-5, 60 m	60°C for 2 min, to 280°C at 10°C min^{-1}, hold	MS	1 mL, split $T = 250$°	Phthalates, fatty acids, phenols, siloxanes, acrylates, aliphatics, amides[c]	[8]

(*continued*)

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Table 2. Continued.

Material	Sample matrix	Sample preparation	Column	Oven program	Detection	Others	Extractables	Refs.
PC	Methylene chloride extract	Direct injection after polymer ppt with methanol	Restek RTx-5 FSOT, 30 m × 0.25 mm, 1.0 µm film	100–280°C at 10°C min^{-1}, hold for 3 min	MS m/z 213 T = 290°C	2 µL, split T = 280°C	Bisphenol A	[9]
PVC	Pharmaceutical products	Solvent extraction, evaporative concentration	3% QF-1 or 3% SE-30 on supelcoport	120°C for 1 min, to 225°C at 4°C min^{-1}	MS EI+ T = 230°C	T = 230°C	9,10-Epoxystearate ester	[20]
Rubber stoppers	Methylene chloride extracts	Direct injection	J&W DB-5MS, 30 m × 0.25 mm, 0.25 µm film	50°C for 5 min, to 275°C at 10°C min^{-1}, hold for 20 min	MS EI+ T = 200°C 50–650 amu	1 µL, splitless, 200°C	Tributoxyethylphosphate, BHT, diphenylamine, 4-(2,2,3,3-tetramethylbutyl) phenol, 2,2′-methylene-bis[6,(1,1 dimethylethyl)-4-ethyl] phenol	[19]
Laminated polyolefin[d]	Soxhlet and *n*-heptane extracts	Evaporative concentration with and without silylation	J&W DB-5, 30 m × 0.32 mm, 0.25 µL film	From 100°C to 280°C at 10°C min^{-1}	MS[f]	T = 220°C	Penta to octa-decane, phthalic acid esters, mono to hepta-cosane, 13-diocosenoic acid, alkyl esters of nonanoic acid	[21, 22][e]
PET	Soxhlet extraction	Evaporative Concentration, with and without silylation	J&W DB-1, 15 m × 0.53 mm, 1 µm film	50°C, hold for 10 min, to 280°C at 10°C min^{-1}	MS SIM mode, also FID	T = 280°C	Ethylene glycol, BHT, phthalic acid esters, palmitic, stearic, oleic acid, terephthalic acid, alkyl terephthalic acid, esters, 2,6-bis-(1,1methylethyl)-4-ethyl phenol, pyrogallol	[23][e]

Polyolefin	Solvent extraction	Evaporative concentration	TRB-5, 60 m × 0.25 mm, 0.5 μm film	40°C for 1 min, to 300°C at 20°C min^{-1}, hold for 26 min	MS EI+	1 μL, splitless $T = 300$°C	Aliphatic hydrocarbons, straight-chained, branched and cyclic[e,g]	[24][h]
PE[i]	Solvent extraction	Direct injection	DB-1, 30 m × 0.25 mm, 0.32 μm film	50°C for 2 min, to 340°C at 5°C min^{-1}, hold for 10 min	MS EI+, 40–700 daltons, $T = 270$°C	Splitless $T = 250$°C	1,3- Di-*tert*-butyl benzene, oligomers, 2,4-di-*tert*-butylphenol, oxidized antioxidants, butanoic acid vinylester	[25][e,j]
Rubber[k]	Water extraction	Evaporative concentration	3% OV17 on Cas-Chrom Q, 1.5 m × 2 mm	140–200°C at 10°C min^{-1}	MS EI+ $T = 250$°C	2 μL $T = 250$°C	Benzothiazole derivatives[l]	[26]

Note: PP, polypropylene; PVC, poly(vinyl chloride); HDPE, high density polyethylene; PC, polycarbonate; PS, polystyrene; PET, polyethylene terephthalate.

[a]MS used in compound identification.

[b]Method performance data provided in this reference.

[c]This reference documents numerous extracted compounds in these general categories.

[d]Laminated film consisting of glycol-modified polyethylene terephthalate (PETG), polyvinylidene chloride (PVDG), and polyethylene (PE) with a polyurethane adhesive.

[e]These cited references document numerous compounds in these and other general compound classes.

[f]GC/IR was also used under differing operating parameters to aid in compound identification.

[g]Straight chained = C_{12}—C_{25}; branched = C_{19}—C_{30}; cyclic = C_{24}—C_{35}.

[h]Similar methods were used to identify compounds from polystyrene (styrene, styrene derivatives, glycolic esters of C16—C25 fatty acids, *trans*-1,2-diphenylcyclobutane).

[i]Material was gamma irradiated prior to analysis.

[j]A similar method was used to identify compounds from PP, PVC, PS, PET, and polyamide.

[k]Components of disposable syringes.

[l]Compounds identified include 2-hydroxybenzothiazole, 2-mercaptobenzothiazole, 2-(methylmercapto)benzothiazole, 2-(2-hydroxyethoxy) benzothiazole, and 2-(2-hydroxyethylmercapto)benzothiazole.

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Table 3. Examples of GC methods used to identify and/or quantify volatile packaging system extractables.

Material	Sample matrix	Sample preparation	Column	Oven program	Detection	Others	Extractables	Refs.
Paper and board	Extracts in water, ethanol, or chloroform	2.5 g sample per vial; 70°C for 30–60 min	Chrompack CP-Sil 8 CB, 50 m × 0.32 mm, 1.2 μm film	70°C for 2 min, ramp at 5°C min^{-1} to 110°C	MS	Also used diffusion trapping	Butanal, pentanal, hexanal, heptanal, 2-heptanal, ethyl acetate, chloroform, methyl acetate, nonanal, *o*-and *p*-xylene, benzene, benzaldehyde, others	[27]
PVC bags	Portions of bags from actual products	1–5 mg sample per vial, 120°C for 5–20 min	SE-54, 20 m × 0.2 mm	30°C for 2 min, ramp at 10°C min^{-1} to 280°C	MS	Evolved gas trapped in trap cooled with liquid nitrogen	Ethanol, pentane, acetic and formic acids, cyclohexanal, xylene, cyclohexanone, pentanal, heptanal, nonanal, phthalates, BHT, tetradecanoic acid, hexadecanoic acid	[12]
Polyolefin packaging material	7 cm^2 portion of material	Investigated effect of temperature from 30° to 125°C with a 3 min desorption	2% OV-7 on Aue 2 m × 2 mm	Start at 0°C, ramp at 10°C min^{-1} to 150°C	FID and MS	Also used purge and trap	Methanol, 1-propanol, *t*-butanol, toluene, 2-methyl-2-propanol, 1-ethoxy-2-propanol, methyl ethyl ketone, 2-(2-hydroxypropoxy-1) propanol	[28]

Drinking water in plastic bottles	Water solution	1 L of water stripped with N_2 at 600 mL min^{-1} for 8 hr, trapped on activated carbon	HP Ultra 2, 30 m × 0.53 mm, 1.5 μm film	40°C for 2 min, ramp at 10°C min^{-1} to 120°C, hold for 3 min.	MS	Analyte desorbed with CS_2 from activated carbon	2-ethyl-1-hexanol, di-2-ethylhexyl phthalate	[29]
Irradiated polyethylene film	Pieces of film	Gas evolved at 80°C, transferred through trap with 3 L of N_2 at 50 mL min; trapped volatiles desorbed at 200°C into N_2	Porapak Q, 3.1 m × 3.2 mm[a] or Ucon Oil HB2000 LB550X, 80 m × 0.2 mm[b]	60°C for 8 min, ramp to 230°C at 4°C min^{-1} [a] or 60°C for 16 min, ramp to 140°C at 4°C min^{-1} [b]	FID and MS	Tenax-GC 18 cm × 5 mm (60/80 mesh) rap used	Acetic acid, butyric acid, ethanol, isopropanol, *n*-propanol, *n*-butane, 2-pentanaone, 2-hexanone, 3-hexanone, 3-heptanone, toluene, butanal, acetaldehyde, propane, propionic acid	[30]

[a]Used for low boiling compounds.
[b]Used for high boiling compounds.

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Table 4. Examples of miscellaneous chromatographic methods used to identify or quantify material extractables.

Material	Test sample	Method description	Extractables	Refs.
Polypropylene	Aqueous food simulating solvents	Capillary SFC. Column: 10 m × 50 mm i.d. SB-Biphenyl-30, 0.25 μm film. Mobile phase = CO_2, linear flow rate ≈ 3 cm sec^{-1}. Pressure program, 100 to 400 bar; temperature program, 55–100°C. One micro liter injection using solvent venting with gas purging. Retention gap was 1.8 m × 100 μm deactivated fused silica. Detection by FID and MS	Pentaerythrityl-tetrakis((3-(3,5-di-*tert*-butyl-4-hydroxy-phenyl) propionate), (*N*,*N*′-bis-(2-hydroxyethyl)-C12.C14-amine), *tris*-2,4-di-*tert*-butylphenyl)-phosphite	[31]
Polyolefins; polypropylene, polyethylene	Soxhlet extracts	Capillary SFC. Coulmn: 10 m × 50 μm i.d. fused silica capillary coated with cross-linked 5% phenyl-methylpolysiloxane (0.4 μm film). Mobile phase = CO_2. Various temperature and pressure gradients used. Detection = FID at 300°C	Stearic acid, Irganox 1010, Irganox PS802, Atmos 150, mono- and di-glycerides, alkenes, cycloalkanes	[32]
Polypropylene	Soxhlet extracts	Capillary SFC. Column: 10 m × 50 μm i.d. fused silica capillary coated with cross-linked methylpolysiloxane (SB-Methyl-100) or 50% octyl substituted methylpolysiloxane (SB-Octyl-50), 0.25 μm film. Mobile phase = CO_2. Pressure program, 129–350 atm at 3 atm min^{-1}; temperature = 110°C. Detection = FID	Additives including Topanol, Irgafos 168, Irganox 1076, Irganox 1330, Irganox 1010, ethylbenzoate, ethyl stearate	[33]
Polyolefin laminate	Drug product stored in plastic bags, SPE prep	HPTLC. Plate = 10 × 20 cm silica gel. Mobile phase: acetone–chloroform–concentrated sodium hydroxide (20/80/0.2). Photodensitometric detection, at 200 and 234 nm before derivitization, 388 nm after derivitization with ninhydrin and 580 nm after derivitization with Bratton/Marshall reagent	ε-Caprolactam, Irganox 1010, butylhydroxytoluene, 4,4′-methylene dianiline	[7]
Polyethylene	Organic and water extracts	HPTLC. Plate = 10 × 10 cm Fertigplatten Kiselgel 40. Mobile phase: Chloroform/cyclohexane (12/1). Densitometric detection	Irganox 1076, 3,5-di-*tert*-butyl-4-hydroxy-phenyl propionic acid	[34]

greatly facilitate the assessment. Thus, this article contains a general compilation of published chromatographic methods and strategies that have been successfully applied to the identification and quantification of packaging material leachables. Examples are provided for each major separation strategy (e.g., HPLC, GC, TLC, SFC) and for most commonly employed detection methods (e.g., UV, MS, FID). While the compilation in Tables 1–4 is by no means exhaustive, it is sufficiently broad in scope to provide the investigator with a general overview of the ways in which chromatography has been applied to meet the objectives of a leachables investigation.

Tables 1–4 provide general method details, such as column type, elution and detection conditions, and other operating conditions. The materials investigated, as well as the specific leachables examined, are also indicated. General comments are provided in terms of sample preparation. Given the number of methods cited, it is not possible, here, to provide detailed chromatographic profiles, which are readily available in the cited references.

While not a chromatographic issue per se, pre-injection sample preparation, nevertheless, is an important consideration in the successful application of a complete analytical process. Nerin et al.[36] reviewed sample treatment techniques applicable to polymer extract analysis, including headspace methods, supercritical fluid extraction, and solid phase micro-extraction.

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