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COMPREHENSIVE EXTRACTABLES PROFILING OF LOW-DENSITY POLYETHYLENE (LDPE) PHARMACEUTICAL PACKAGING MATERIAL USING MULTI-SOLVENT EXTRACTION AND ORTHOGONAL ANALYTICAL TECHNIQUES

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ABSTRACT

Polymeric containers are widely used for the primary packaging of pharmaceutical products; however, chemical species can migrate from such packaging into the drug product, giving rise to extractables and leachables (E&L) that may compromise patient safety, product stability, and regulatory acceptance. The present study reports a comprehensive extractables profiling of low-density polyethylene (LDPE, Purell PE 1840H grade) pharmaceutical packaging material using a multi-solvent, multi-technique controlled extraction protocol. The test article was subjected to four independent extraction procedures - neat headspace enrichment, reflux extraction in Water for Injection (WFI), reflux extraction in dichloromethane (DCM), and microwave-assisted acid digestion - to capture volatile, semi-volatile, non-volatile organic, and inorganic (elemental) extractables. The resulting extracts were characterized using four orthogonal analytical platforms: Headspace Gas Chromatography/Mass Spectrometry (HS-GC/MS) for volatiles, Gas Chromatography/Mass Spectrometry (GC/MS) for semi-volatiles, Liquid Chromatography/Mass Spectrometry with diode array detection (LC-PDA-MS) for non-volatile organics, Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) for elemental impurities, and Ion Chromatography (IC) for anions. Screening identified 10 volatile compounds above the 0.5 mg/kg reporting limit in the neat sample, 2 semi-volatile compounds in the WFI extract and 15 in the DCM extract, and 3 non-volatile organic compounds in positive-ionization LC/MS mode from the WFI extract; no metals or anions were detected above their respective reporting limits. Compounds were assigned identification confidence levels (Identified, Most Probable, Tentatively Identified, or Unidentified) based on NIST mass-spectral library matching and comparison with authentic reference standards. The resulting extractables inventory provides the scientific foundation for an Analytical Evaluation Threshold (AET)-based, risk-proportionate triage of compounds requiring confirmatory leachables monitoring in the finished drug product, in alignment with USP <1663>/<1664> and ICH Q3D expectations. The approach demonstrates a cost-effective, regulation-aligned strategy for qualifying LDPE packaging systems and strengthens indigenous analytical capability for pharmaceutical packaging safety assessment.

INTRODUCTION

Pharmaceutical packaging materials are never entirely chemically inert. Polymeric containers, closures, and delivery-system components can interact with the formulations they hold, potentially releasing chemical entities - extractables under exaggerated laboratory conditions, and leachables under normal conditions of storage and use - into the drug product. Such packaging-derived impurities may compromise drug safety, alter product stability, or affect efficacy, and their control has therefore become a central concern of pharmaceutical quality-by-design and regulatory review.

Low-density polyethylene (LDPE) is among the most widely used polymers for primary pharmaceutical packaging, including bottles, bags, tubing, and liners,

owing to its chemical resistance, flexibility, moisture-barrier properties, and processability. Despite these favourable properties, LDPE resins may contain residual monomers, polymerization catalysts, antioxidants, slip agents, processing aids, and degradation products that are capable of migrating into a packaged drug product over its shelf life.

Regulatory guidance - including USP General Chapters <1663> (Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems) and <1664> (Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems), together with ICH Q3D (Guideline for Elemental Impurities) - recommends a systematic, risk-based extractables and leachables (E&L) evaluation for packaging systems in contact with drug products. A scientifically defensible extractables profile requires (i) extraction under conditions that exaggerate, but remain relevant to, the intended clinical use of the packaging system, (ii) analysis by multiple complementary analytical techniques capable of detecting compounds across a wide range of polarity, volatility, and molecular weight, and (iii) a risk-based Analytical Evaluation Threshold (AET) to focus subsequent confirmatory leachables testing only on extractables of potential toxicological significance.

Building on this framework, the present study describes a controlled extractables investigation of an LDPE (Purell PE 1840H) pharmaceutical packaging test article. Four extraction procedures - headspace enrichment of the neat resin, WFI reflux extraction, DCM reflux extraction, and microwave-assisted acid digestion - were combined with liquid/liquid extraction clean-up and analyzed using four orthogonal analytical techniques (HS-GC/MS, GC/MS, LC-PDA-MS, and ICP-OES/IC) to generate a comprehensive extractables inventory. The study aims to demonstrate how such an integrated, multi-technique extractables profile can be used to support an AET-based, risk-proportionate approach to leachables qualification, consistent with current compendial and international regulatory expectations.

MATERIALS AND METHODS

All analytical instruments used in this study were subject to documented, periodic performance qualification. The overall workflow proceeded from controlled extraction of the LDPE test article, through complementary analytical characterization, to AET-informed selection of extractables of interest for leachables monitoring.

Sample preparation and extraction

Four independent extraction procedures were applied to the LDPE (Purell PE 1840H) test article to capture compounds across a broad range of volatility and polarity:

(i) Headspace enrichment of the neat resin: approximately 2.00 g of test material was placed in a 20 mL headspace vial and spiked with a toluene-d8 internal standard (corresponding to 10.2 µg/sample) for subsequent HS-GC/MS analysis of volatile organic compounds.

(ii) Reflux extraction in Water for Injection (WFI): approximately 30.00 g of test material was refluxed with WFI at a weight/solvent ratio of 1 g/10 mL for 8 hours under constant stirring to simulate aqueous-contact extraction conditions.

(iii) Reflux extraction in dichloromethane (DCM): approximately 5.0 g of test material was refluxed with DCM at a weight/solvent ratio of 1 g/10 mL for 8 hours to capture organic-soluble semi-volatile and non-volatile extractables.

(iv) Microwave-assisted acid digestion: approximately 0.2 g of test material was digested in concentrated nitric acid under microwave-assisted, pressure-monitored conditions and diluted with WFI for subsequent elemental analysis.

A liquid/liquid extraction clean-up was additionally performed on the WFI reflux sample using DCM at unadjusted pH (~5.5), acidic pH (<3), and alkaline pH (>12) to transfer organic extractables into a low-boiling solvent suited to GC/MS and LC/MS analysis. Extracts were concentrated under nitrogen flow and reconstituted for analysis.

Analytical characterization

Volatile organic compounds were screened by Headspace Gas Chromatography/Mass Spectrometry (HS-GC/MS) on the neat sample preparation, using a DB-624 capillary column with scan-mode mass spectrometric detection. Semi-volatile organic compounds were screened by Gas Chromatography/Mass Spectrometry (GC/MS) on the WFI (post liquid/liquid extraction) and DCM reflux extracts, using an HP-5MS capillary column with 2-fluorobiphenyl as internal standard. Non-volatile organic compounds were screened by Liquid Chromatography/Mass Spectrometry with photodiode array detection (LC-PDA-MS), operated in both positive (APCI+) and negative (APCI-) atmospheric pressure chemical ionization modes with full-wavelength UV-VIS (190-400 nm) diode array detection, using Tinuvin 327 and palmitic acid-d4 as internal standards. Elemental extractables (20 target elements, including Al, Ba, Cd, Ca, Cr, Co, Cu, Fe, Pb, Li, Mg, Mn, Ni, Pt, K, Si, Ag, Sr, Ti, and Zn) were quantified in the acid-digested extract by Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) using external calibration. Formate and acetate anions were screened in the WFI extract by Ion Chromatography (IC) using a hydroxide-eluent gradient with conductivity detection.

Compound identification and semi-quantitation

Detected compounds were classified into one of four identification-confidence categories: Identified Compound (IC) - confirmed by library match and consistency with an authentic reference standard; Most

Probable Compound (MPC) - excellent library or literature spectral match, but no reference standard available for confirmation; Tentatively Identified Compound (TIC) - consistent with a chemical class but not assignable to an individual compound; and Unidentified (U) - not classifiable in the above categories. Semi-quantitative concentrations were estimated by comparison of analyte peak area to that of the relevant internal standard, normalized for sample mass, extraction solvent volume, and concentration factor. Reporting limits were set at 5% of the internal standard response for each screening method.

RESULTS AND DISCUSSION

All results are expressed in mg/kg, representing the mass of extractable compound per unit mass of extracted polymer, in accordance with standard extractables reporting conventions.

Volatile organic compounds (HS-GC/MS)

Headspace GC/MS screening of the neat LDPE sample, at a reporting limit of 0.5 mg/kg, revealed 10 volatile organic compounds above the reporting limit. These compounds are typical of residual monomers, low-molecular-weight polymer degradation products, and process-related solvent residues associated with polyethylene manufacture. As thermal desorption efficiency is temperature-dependent, and headspace temperature was restricted to 150 °C to avoid thermal degradation of the polymer, the reported concentrations should be regarded as approximate, semi-quantitative estimates rather than absolute values.

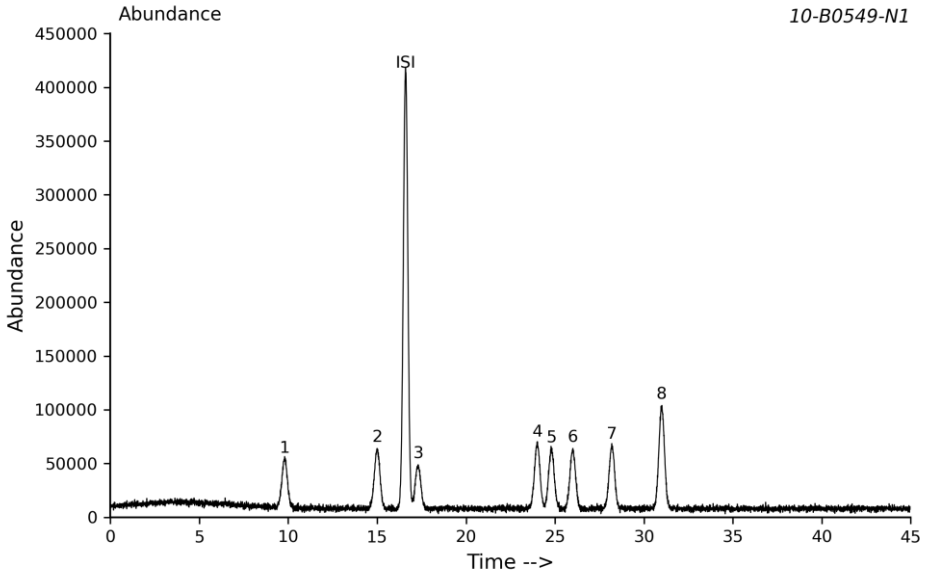

Figure 1: Chromatogram of the HS-GC/MS analysis for volatiles in the neat LDPE (Purell PE 1840H) test sample. ISI denotes the internal standard for injection; numbered peaks (1-8) correspond to reported volatile compounds.

Semi-volatile organic compounds (GC/MS)

GC/MS screening of the WFI reflux extract (after liquid/liquid extraction into DCM), at a reporting limit of 0.05 mg/kg, identified 2 semi-volatile compounds above the threshold, reflecting the relatively low extraction efficiency of semi-polar organic species into the aqueous vehicle. In contrast, the DCM reflux extract, analyzed at a reporting limit of 5.0 mg/kg, revealed a substantially higher number of semi-volatile extractables - 15 compounds - consistent with the greater affinity of process lubricants, plasticizers, antioxidants, and polymer degradation products for a non-polar organic extraction medium relative to an aqueous one.

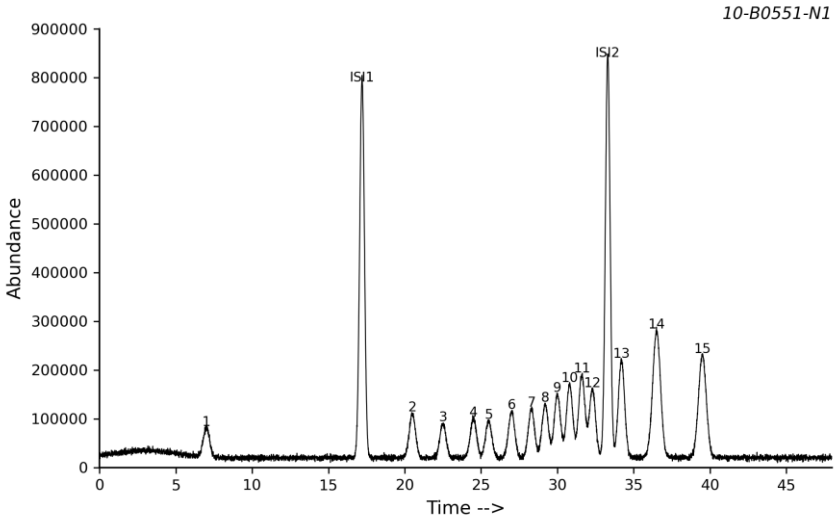

Figure 2: Chromatogram of the GC/MS analysis for semi-volatile extractables in the DCM reflux extract of the LDPE test sample. ISI1 (2-fluorobiphenyl) and ISI2 (Tinuvin 327) are internal standards; numbered peaks (1-15) correspond to reported semi-volatile compounds.

Non-volatile organic compounds (LC-PDA-MS)

LC/MS screening of the WFI extract in positive ionization mode (APCI+) revealed 3 non-volatile organic compounds above the 0.1 mg/kg reporting limit; no compounds were detected in the DCM extract above its 5 mg/kg reporting limit. The relatively limited number of non-volatile extractables observed is consistent with the comparatively simple additive package typically used in LDPE formulations intended for pharmaceutical-grade applications.

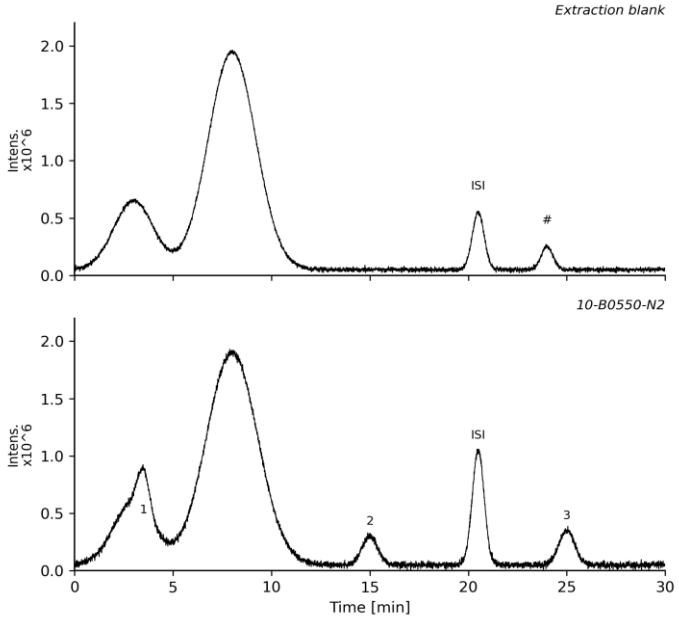

Figure 3: Total ion chromatograms of the LC/MS screening analysis (APCI+) for non-volatile extractables in the WFI reflux extract (post liquid-liquid extraction in DCM) of the LDPE test sample, compared against the extraction blank. ISI: internal standard (Tinuvin 327); numbered peaks (1-3) correspond to reported non-volatile compounds.

Elemental impurities (ICP-OES) and anions (IC)

No metals among the 20 targeted elements were detected above their respective reporting limits in the acid-digested extract, and no formate or acetate anions were detected in the WFI extract by ion chromatography. These findings indicate a low elemental-impurity and anionic-extractable burden for this LDPE grade, consistent with its intended use as a pharmaceutical-contact packaging material and supportive of compliance with ICH Q3D expectations for elemental impurities arising from container/closure systems.

Risk-based interpretation using the Analytical Evaluation Threshold (AET)

Consistent with the PQRI/USP AET framework, the extractables identified above their respective reporting limits were evaluated against a compound-specific Analytical Evaluation Threshold derived from the maximum daily dose of the packaged drug product and an appropriate safety concern threshold. This risk-based triage step is essential to focus subsequent, more resource-intensive confirmatory leachables studies only on those extractables of genuine toxicological relevance, rather than performing exhaustive leachables testing on every detected extractable irrespective of its concentration or hazard potential.

Relevance to Sustainable Development and National Priorities

Beyond its immediate analytical and regulatory relevance, this extractables profiling approach for LDPE pharmaceutical packaging aligns with several Sustainable Development Goals (SDGs) and national policy priorities of India:

- SDG 3 (Good Health and Well-Being): Ensures drug product safety by systematically screening for packaging-derived extractables and leachables before they reach the patient.
- SDG 9 (Industry, Innovation and Infrastructure): Builds indigenous analytical infrastructure and expertise in LC-PDA-MS, ICP-OES/ICP-MS, and GC/MS-based extractables testing.
- SDG 12 (Responsible Consumption and Production): Verifies the safety of packaging materials, thereby reducing product recalls, rejections, and associated material waste.
- Make in India / Atmanirbhar Bharat: Supports indigenous packaging qualification capability, reducing dependence on overseas testing laboratories.
- Production Linked Incentive (PLI) Scheme for Pharmaceuticals: Supports Indian manufacturers in meeting global quality standards required for export markets.
- National Health Mission / Jan Aushadhi: Strengthens public trust in the safety and quality of affordable generic medicines packaged in polymeric containers.

Novelty of the Study

- An integrated protocol combining aqueous (WFI) and organic (DCM) reflux extraction, headspace enrichment, and microwave-assisted acid digestion within a single, coherent extractables workflow.
- Use of four orthogonal analytical techniques (HS-GC/MS, GC/MS, LC-PDA-MS, and ICP-OES/IC) to achieve comprehensive coverage of volatile, semi-volatile, non-volatile organic, and inorganic extractables.
- Application of an AET-based risk triage strategy for cost-effective, science-driven selection of extractables warranting confirmatory leachables monitoring.
- Contribution toward indigenous extractables and leachables (E&L) testing capability for polyolefin-based pharmaceutical packaging in India.
- An end-to-end analytical pipeline extending from extractables screening of the packaging material to targeted leachables monitoring of the finished drug product.

Future Perspective

- Application of AI/ML-based predictive modelling to prioritize testing toward high-risk extractables.
- Development of indigenous AET reference databases for various polymer types used in Indian pharmaceutical packaging.
- Indigenization of advanced analytical instrumentation (e.g., ICP-MS) to reduce dependence on imported equipment and associated costs.
- Alignment of packaging material selection with green and sustainable packaging principles.
- Establishment of regional centres of excellence for E&L testing to strengthen the competitiveness of Indian pharmaceutical exports.

CONCLUSION

The integrated, multi-solvent extraction and multi-technique analytical protocol applied in this study provided a comprehensive extractables profile of an LDPE pharmaceutical packaging material, identifying 10 volatile, 17 semi-volatile (combined WFI and DCM extracts), and 3 non-volatile organic extractables, while confirming the absence of detectable metal and anionic extractables. These findings demonstrate that a scientifically robust, AET-guided extractables and leachables assessment strategy can effectively support the safety qualification of polyolefin-based pharmaceutical packaging while remaining cost-effective and aligned with USP <1663>/<1664> and ICH Q3D expectations. The approach further contributes to building indigenous analytical testing capability, supporting India's broader goals of self-reliance in pharmaceutical quality infrastructure and global regulatory competitiveness.

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Conflict of interests

The authors declare that they have no competing intrests.

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