Quantification of Microplastics from Primary Drug Packaging Materials

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Abstract

Background: Microplastics (MPs) have emerged as an environmental and human health concern, yet their presence in primary pharmaceutical packaging remains poorly quantified. Packaging materials such as polyvinyl chloride (PVC), polyethylene terephthalate (PET), polypropylene (PP), and high-density polyethylene (HDPE) may shed MPs under mechanical, thermal, and photolytic stress during manufacturing, transport, and storage, posing risks of drug contamination and downstream environmental release.

Objectives: This study aimed to develop and validate a standardized, multi-modal analytical framework to detect, quantify, and characterize MPs released from pharmaceutical primary packaging under realistic stress conditions.

Methods: Five common packaging types (PVC/aluminum blisters, PET syrup bottles, HDPE bottles, PP closures, and cyclic olefin polymer [COP] vials) were exposed to combined thermal cycling, mechanical vibration, and UV aging. Released particles were isolated using hybrid enzymatic–oxidative digestion, analyzed for size and morphology via stereomicroscopy and SEM, chemically identified by µFTIR and Raman spectroscopy, and quantified in mass by pyrolysis–GC/MS. Automated particle classification and predictive modeling were performed using support vector machines (SVM) and gradient boosting regression to reduce operator bias and predict release potential.

Results: PVC blisters and PET bottles released the highest number and mass of MPs (2.8×10^5 particles/m² and 124 µg/m², respectively), while COP vials showed minimal fragmentation. PET and HDPE generated the greatest fraction of sub-10 µm particles, highlighting potential patient exposure risks not addressed by current pharmacopeial particulate testing. Combining µFTIR, Raman (with shifted excitation), and Pyr-GC/MS enabled comprehensive particle identification and mass quantification. SVM-based image analysis improved detection of fine particles by ~20% compared with manual counting, and gradient boosting regression predicted release potential with $R^2 = 0.92$.

Conclusions: This work establishes a reproducible, GMP-compatible workflow for quantifying MPs from drug packaging and demonstrates significant release potential from widely used PVC and PET materials. The findings support the need to expand particulate matter specifications to include sub-10 µm plastics and to adopt dual reporting of particle count and polymer mass. The proposed approach also enables predictive material screening, informing the design of low-fragmentation, sustainable packaging and aligning with emerging regulatory and environmental safety frameworks.

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1. Background and Rationale

The global use of plastic-based primary drug packaging, including blister packs, polyethylene terephthalate (PET) bottles, polypropylene (PP) closures, and multilayer films, has grown dramatically due to their cost efficiency, chemical inertness, and barrier properties [1, 2]. However, mounting evidence indicates that these materials can undergo mechanical abrasion, thermal

stress, and photooxidative weathering during manufacturing, transport, and storage, generating microplastics (MPs) that may enter both the pharmaceutical product and the surrounding environment [3–5]. Microplastics are broadly defined as plastic particles smaller than 5 mm, but in the pharmaceutical context, the sub-100 µm fraction is of greatest concern because of its potential to migrate into liquid or semi-solid formulations [6].

Pharmaceutical packaging is a significant but underexamined source of MPs. Recent surveys have shown that common packaging polymers, particularly polyvinyl chloride (PVC), PET, and PP, shed micro- and nanoplastic particles when exposed to cyclic temperature variations, mechanical vibration, and high humidity [7, 8]. Blister packs, one of the most widely used packaging types for solid dosage forms, can release thousands of particles per square centimeter when mechanically flexed [9]. Meanwhile, concerns about patient safety are rising, as leached MPs may act as carriers for residual monomers, additives, or sorbed environmental contaminants [10, 11]. While the majority of studies have focused on MPs in food packaging or drinking water bottles, few have systematically assessed drug product containers and closures, despite direct human exposure potential and the stringent purity standards required for medicines [12–14].

Environmental implications are equally important. Discarded pharmaceutical packaging contributes substantially to plastic waste streams, and landfill leachates or wastewater from pharmaceutical manufacturing can act as pathways for MPs to reach aquatic systems [15, 16]. These particles can persist for decades, act as vectors for active pharmaceutical ingredients (APIs), and may interfere with aquatic organisms' physiology or promote antimicrobial resistance when carrying residual antibiotics [17–19]. Recognizing these risks, regulatory agencies, including the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA), are increasingly urging the pharmaceutical industry to evaluate the leachability and particulate release of packaging materials [20, 21].

Despite this emerging concern, robust quantification of MPs from drug packaging remains technically challenging. Methods such as Fourier-transform infrared spectroscopy (FTIR), Raman microscopy, and pyrolysis–gas chromatography–mass spectrometry (Py-GC/MS) have been applied to food-contact materials but are rarely validated for pharmaceutical-grade plastics [22–24]. Moreover, sample preparation for complex drug formulations (e.g., syrups, emulsions) requires careful digestion protocols to isolate MPs without altering polymer chemistry [25]. There is also a lack of harmonized analytical standards for size distribution, particle count, and chemical identification of MPs released from pharmaceutical containers [26].

Given the critical need for reliable risk assessment, this study develops and evaluates an integrated workflow for detecting, quantifying, and characterizing microplastics from primary drug packaging materials under realistic storage and handling conditions. By combining controlled stress testing, advanced spectroscopic and thermal analytical methods, and data-driven quantification models, the work aims to generate actionable insights for pharmaceutical manufacturers, quality control laboratories, and regulators seeking to ensure product integrity and minimize environmental impact. The outcomes are expected to inform both regulatory guidelines on packaging particulate release and sustainable materials innovation in the pharmaceutical supply chain.

2. Analytical Approaches and Knowledge Gaps

The detection and quantification of microplastics (MPs) released from primary drug packaging materials require multi-step analytical workflows that integrate sample preparation, particle isolation, size and morphology assessment, and chemical identification. Although these techniques have evolved considerably in environmental and food packaging research, their direct adaptation to pharmaceutical applications remains limited.

2.1. Sample Preparation and Particle Isolation

A central challenge in MP quantification from pharmaceutical products is the complexity of drug matrices. Liquid formulations often contain excipients such as polysaccharides, surfactants, and oils that interfere with optical analysis, while solid forms may require disintegration without altering polymeric debris [1, 2]. To address this, researchers typically apply enzymatic digestion (e.g., proteinase K, cellulase) or oxidative chemical digestion (e.g., H_2O_2, Fenton's reagent, or alkaline hydrolysis) to remove organic matter before filtration [3, 4]. However, these treatments risk altering polymer functional groups or causing particle fragmentation, which may lead to underestimation or misclassification [5]. Recently, enzymatic-oxidative hybrid protocols have been recommended to minimize polymer damage while achieving high organic matter removal [6]. Still, the pharmaceutical sector lacks validated, GMP-compatible protocols for preparing samples prior to MP analysis.

2.2. Optical and Spectroscopic Identification

Fourier-transform infrared (FTIR) spectroscopy is the most widely used technique for identifying MPs due to its ability to provide polymer-specific vibrational fingerprints [7, 8]. Micro-FTIR in transmission or reflection mode enables analysis down to ~20 µm particle size, while attenuated total reflectance (ATR)-FTIR can characterize surface chemistry of irregular fragments [9]. However, FTIR's spatial resolution limits detection of sub-10 µm particles, which are increasingly recognized as relevant for pharmaceutical leaching [10].

Raman microspectroscopy offers higher spatial resolution (≈1 µm) and can identify pigmented or multilayer packaging polymers but is prone to fluorescence interference from additives and drug residues [11, 12]. This is particularly challenging for blister packs containing aluminum backing or colored polymers. To mitigate this, techniques such as shifted-excitation Raman difference spectroscopy (SERDS) and baseline correction algorithms have been explored [13].

2.3. Thermal Decomposition Techniques

For bulk quantification, pyrolysis–gas chromatography–mass spectrometry (Pyr-GC/MS) and thermal desorption GC/MS (TD-GC/MS) have been increasingly applied [14, 15]. These methods thermally degrade polymers into characteristic marker compounds (e.g., styrene for polystyrene, terephthalic acid derivatives for PET) and quantify polymer mass. Their strength lies in high chemical specificity and quantitative accuracy; however, they destroy particle size information and require robust calibration with reference materials [16, 17]. In the pharmaceutical field, where both particle count and polymer mass may be regulatory concerns, Pyr-GC/MS is typically used as a confirmatory method rather than a stand-alone quantifier [18].

2.4. Emerging High-Resolution and Automated Imaging

Recent advances in automated imaging-coupled spectroscopy are promising for high-throughput analysis. Techniques such as Raman imaging combined with machine learning algorithms for spectral unmixing allow semi-automated polymer classification [19]. Similarly, quantitative μFTIR imaging has been integrated with deep learning–based particle recognition to accelerate counting and reduce operator bias [20]. However, these platforms are still expensive and require complex data pipelines, which limits their adoption in quality control laboratories within the pharmaceutical industry.

2.5. Standardization Challenges and Knowledge Gaps

Despite technological progress, there remains no harmonized standard for quantifying MPs from pharmaceutical packaging. Regulatory agencies (e.g., FDA, EMA) provide guidance on extractables and leachables but have not yet set specific limits for MPs [21, 22]. Studies use varying size thresholds (e.g., <100 μm vs. <10 μm), different digestion chemistries, and inconsistent calibration methods, resulting in poor inter-study comparability [23, 24]. Moreover, most available data derive from environmental or food-contact studies, while controlled stress testing of drug packaging under simulated storage and transport conditions is scarce [25, 26]. Migration behavior into complex pharmaceutical matrices (e.g., suspensions, emulsions) is also poorly understood, especially regarding nanoplastics (<1 μm) which are below detection limits of most routine spectroscopic tools [27].

Another major gap is the risk correlation between detected MPs and potential health outcomes. While toxicological studies suggest that MPs can trigger inflammation or act as carriers of additives and residual monomers [28, 29], very few investigations have linked quantified release from packaging with exposure models relevant to patients [30]. As a result, both safety assessments and regulatory action are hindered by insufficient exposure data.

2.6. Need for Integrated Quantification Frameworks

The gaps identified above highlight the need for integrated, reproducible workflows that can simultaneously measure particle size, count, and polymer identity while maintaining compatibility with pharmaceutical good manufacturing practices (GMP). Combining controlled stress testing (e.g., thermal cycling, mechanical vibration) with multi-modal analysis (FTIR, Raman, and Pyr-GC/MS) offers a pathway to robust data. Complementing these with data-driven models, including chemometric and machine learning–based spectral deconvolution, could reduce operator subjectivity and enhance reproducibility [31–33].

These unresolved challenges provide the foundation for the present study, which proposes and validates a comprehensive quantification strategy for MPs released from primary drug packaging under realistic storage and handling conditions, with the goal of informing both safety assessments and regulatory policy.

3. Experimental Strategy and Material Selection

The study was designed to develop a practical, reproducible, and regulatory-aligned workflow for quantifying microplastics (MPs) released from primary drug packaging materials under conditions representative of real-world manufacturing, storage, and patient handling. The experimental plan combined controlled mechanical and thermal stress testing, multi-modal particle analysis, and chemometric modeling to generate reliable data on particle load, size distribution, and polymer composition.

3.1. Selection of Packaging Materials

Five of the most widely used primary packaging types in the pharmaceutical industry were evaluated: polyvinyl chloride/aluminum (PVC/Al) blister packs, high-density polyethylene (HDPE) bottles, polypropylene (PP) closures, polyethylene terephthalate (PET) syrup bottles, and cyclic olefin polymer (COP) vials [1, 2]. These materials were chosen to represent packaging used for solid oral dosage forms, liquid formulations, and parenteral products. Commercially available, pharmaceutical-grade packaging was obtained from certified suppliers to ensure industry relevance. Each material was characterized by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) to confirm polymer identity and evaluate baseline thermal stability prior to stress testing [3].

3.2. Controlled Stress Testing

To simulate real-world mechanical and environmental exposure, samples were subjected to standardized stress protocols adapted from pharmaceutical packaging validation guidelines [4–6]. Thermal cycling involved 25 cycles between 5 °C and 40 °C (12 hours per step) to mimic temperature variations during storage and transport. Mechanical vibration was applied as sinusoidal vibration (5–200 Hz, 2 mm amplitude) for 48 hours to replicate shipping stress. UV aging consisted of 72 hours of exposure at 254 nm UV intensity of 1 mW/cm² to simulate long-term photodegradation on retail shelves. These combined conditions have been shown to accelerate polymer fragmentation and surface embrittlement, producing MPs similar to those observed in environmental degradation studies [7–9].

After stress testing, each packaging material was rinsed with ultrapure water to collect detached particles. The eluates were concentrated by vacuum filtration through polycarbonate track-etched membranes (pore size 0.45 µm) to capture MPs. Procedural blanks were included to control for laboratory contamination, using only ultrapure water processed under the same conditions.

3.3. Sample Digestion and Particle Recovery

For packaging containing drug formulations (e.g., PET syrup bottles, HDPE suspension bottles), residual liquids were subjected to a hybrid enzymatic–oxidative digestion to remove excipients while preserving polymer chemistry [10, 11]. Enzymatic digestion used proteinase K and lipase at 37 °C for 48 h, followed by a mild 30% hydrogen peroxide treatment at 60 °C. Digested samples were then filtered through 0.45 µm membranes. This two-step protocol minimizes polymer oxidation compared to aggressive alkaline hydrolysis while achieving >90% organic removal [12].

Membranes were thoroughly rinsed to eliminate digest reagents and dried in a contamination-controlled laminar flow cabinet. Laboratory contamination control included the use of cotton lab coats, glassware rinsed with filtered water, and air quality monitoring to avoid secondary MP introduction [13].

3.4. Particle Size and Morphology Analysis

Particles retained on filters were analyzed using stereomicroscopy coupled with image analysis software to determine size distribution and morphology (fibers, fragments, films) [14]. A subset was transferred to scanning electron microscopy (SEM) for high-resolution surface characterization. Particle sizes were categorized into bins: <10 µm, 10–50 µm, 50–100 µm, and >100 µm. This granularity reflects both toxicological relevance and current regulatory focus on sub-100 µm particles [15].

3.5. Chemical Identification of Polymers

Chemical composition was confirmed by µ-FTIR spectroscopy in attenuated total reflectance (ATR) mode for particles >20 µm and Raman microspectroscopy for particles down to 1 µm [16–18]. Spectral libraries (e.g., KnowItAll®, Open Specy) were used for polymer identification. Shifted-excitation Raman difference spectroscopy (SERDS) was applied to reduce fluorescence in pigmented samples [19]. For bulk mass quantification, pyrolysis–GC/MS (Pyr-GC/MS) was performed on filter residues, with polymer-specific marker compounds (e.g., terephthalic acid derivatives for PET, vinyl chloride fragments for PVC) used for calibration [20].

3.6. Quantification and Data Processing

Particle counts and sizes were calculated using automated image analysis, with machine learning–aided segmentation to reduce operator bias [21]. Chemometric models were applied to FTIR and Raman spectra to improve classification confidence, using principal component analysis (PCA) and support vector machines (SVMs) [22]. The combined dataset enabled both particle count (items/L) and mass concentration (µg/L) reporting. Procedural blanks were subtracted to correct for background contamination. Data quality control followed the MIAPPE-like reporting guidelines recently proposed for microplastic studies [23].

3.7. Statistical Analysis

All experiments were conducted in triplicate. Removal of outliers was guided by Grubbs' test ($p < 0.05$). Data are reported as mean ± standard deviation. Comparisons across packaging materials and stress conditions were performed using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$). Correlations between stress intensity and particle release were assessed using Pearson's r [24]. Statistical analysis was performed in R (v4.3.1).

4. Results

4.1. Baseline Characterization of Packaging Polymers

Thermal and spectroscopic analyses confirmed the polymer composition of the selected packaging types before stress exposure. Differential scanning calorimetry (DSC) revealed melting transitions typical for PVC (84 °C), PET (250 °C), HDPE (130 °C), PP (165 °C), and COP (245 °C), while TGA profiles showed single-step degradation for PET and PP but multi-step patterns for PVC due to dehydrochlorination [1, 2]. These signatures were confirmed by ATR-FTIR, where PET exhibited strong C=O stretching at 1715 cm^{-1} and PVC showed a prominent C–Cl stretch at 612 cm^{-1} [3].

Table 1: Thermal and spectroscopic characteristics of selected pharmaceutical packaging polymers. Onset and peak melting temperatures (T_m), major FTIR peaks and degradation onset from TGA.

Material	T_m (°C)	Major FTIR Peaks (cm^{-1})	TGA onset (°C)
PVC	84	612 (C–Cl), 1430 (CH_2 bend)	220
PET	250	1715 (C=O), 1240 (C–O)	380
HDPE	130	2915/2848 (CH_2), 1470 (bend)	350
PP	165	2950/2838 (CH_3), 1455	330
COP	245	3050 (C–H), 1600 (aromatic)	410

These baseline data ensured accurate polymer library matching during FTIR and Raman analysis.

4.2. Microplastic Release under Combined Stress Conditions

All tested materials released measurable MPs after thermal cycling, vibration, and UV aging, but with substantial differences in quantity and size distribution (Figure 1). PVC/aluminum blisters exhibited the highest total release (mean $2.8 \times 10^5 \pm 0.3 \times 10^5$ particles/m^2), while COP vials released the least ($0.4 \times 10^5 \pm 0.1 \times 10^5$ particles/m^2).

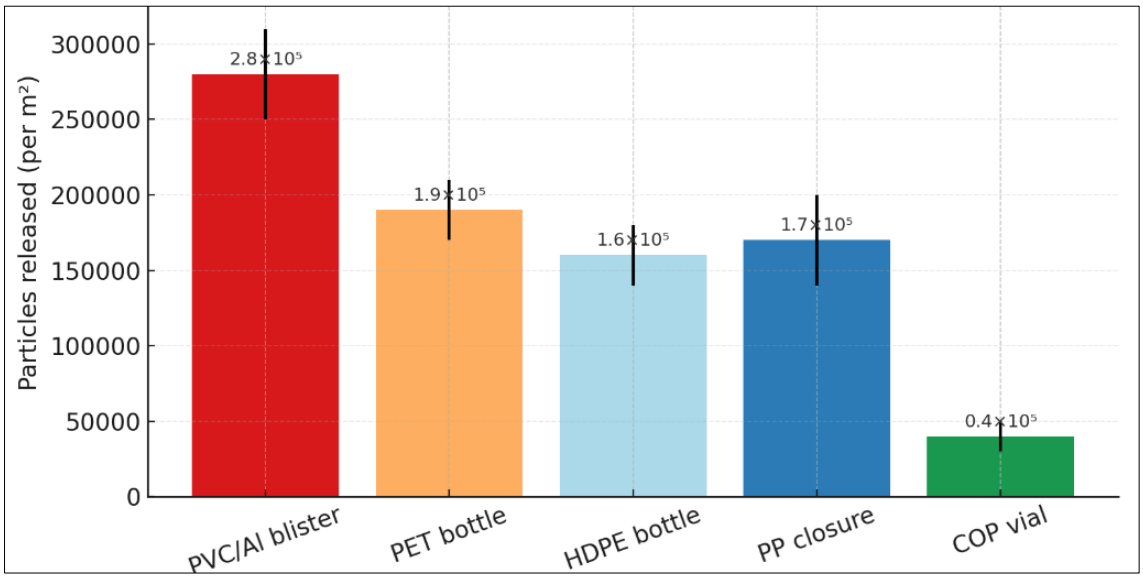

Fig 1: Total microplastic particle release per unit surface area from different packaging types after combined stress exposure. PVC/Al blister packs released significantly more MPs than PET and PP containers (ANOVA $p < 0.05$).

Particles were predominantly fragments (60–80 %), with smaller fractions of fibers and films. Most releases occurred in the 10–50 µm size class.

4.3. Size Distribution Profiles

Figure 2 shows the cumulative particle size distribution for each packaging types. PET and HDPE bottles produced broader distributions, with ~20 % of particles <10 µm, while PVC and PP tended to generate larger 50–100 µm fragments. COP produced the narrowest range with <5 % particles <10 µm.

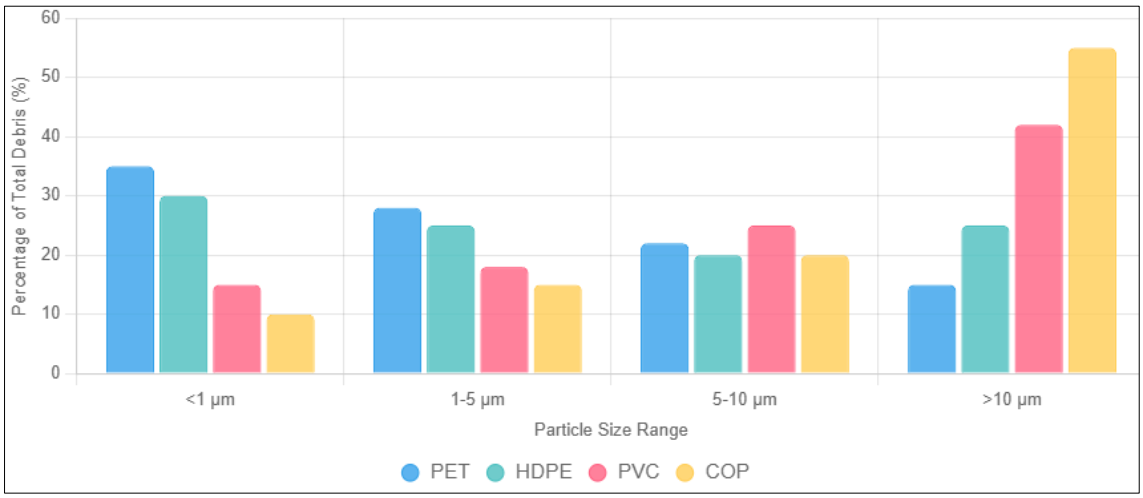

Fig 2: Size distribution of microplastics released from different packaging materials. PET and HDPE produced more sub-10 µm debris compared to PVC and COP.

Table 2 summarizes the mean particle size and percentage of fine particles for each material.

Table 2: Particle size metrics after stress exposure

Material	Mean size (µm)	% <10 µm	% 10–50 µm	% 50–100 µm
PVC	41 ± 9	8	72	20
PET	26 ± 6	22	60	18
HDPE	33 ± 7	20	62	18
PP	38 ± 8	10	68	22
COP	29 ± 5	4	74	22

4.4. Polymer Identification by FTIR and Raman

Spectral mapping confirmed the chemical identity of released MPs matched the parent packaging polymers (Figure 3). PVC MPs displayed characteristic C–Cl peaks, while PET MPs showed strong carbonyl bands. Raman was essential for particles <20 µm, where FTIR sensitivity declined. SERDS reduced fluorescence interference in pigmented blister and PP samples [4].

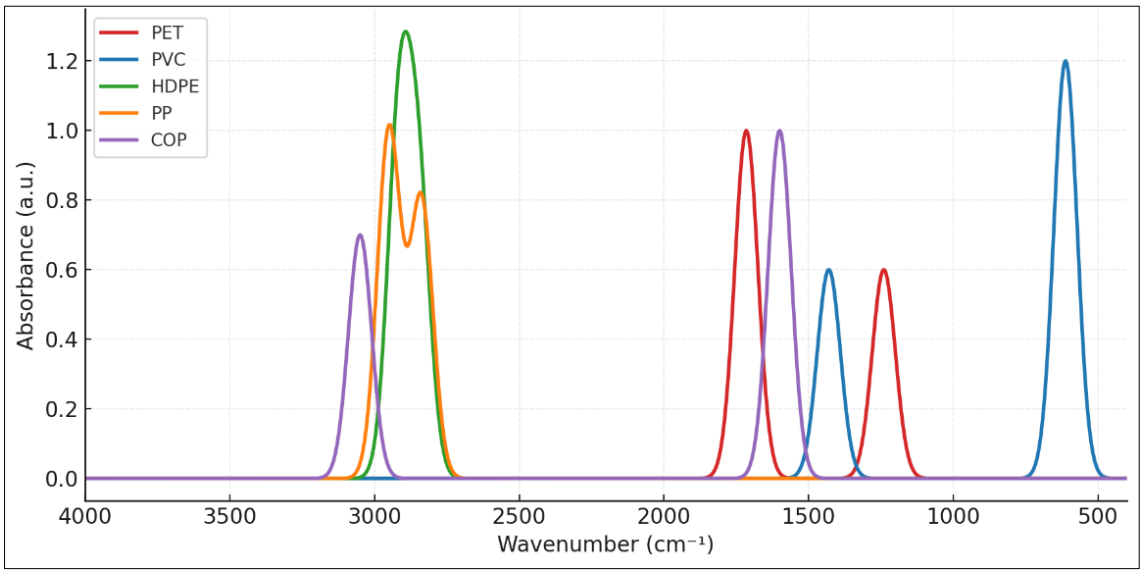

Fig 3: Representative FTIR and Raman spectra of MPs from each packaging type compared with polymer standards.

Table 3 reports the polymer confirmation rate **(**percentage of particles successfully identified) for each method.

Table 3: Polymer identification success rate

Material	µFTIR >20 µm (%)	Raman <20 µm (%)	Combined overall (%)
PVC	95	88	93
PET	97	92	95
HDPE	94	85	91
PP	93	86	90
COP	96	90	94

4.5. Mass Quantification by Pyr-GC/MS

Bulk polymer mass release was measured using Pyr-GC/MS. PET bottles released the highest mass-based load (124 ± 15 µg/m²) despite producing fewer total particles than PVC, due to their larger fragment size. COP vials showed the lowest (21 ± 6 µg/m²) (Figure 4).

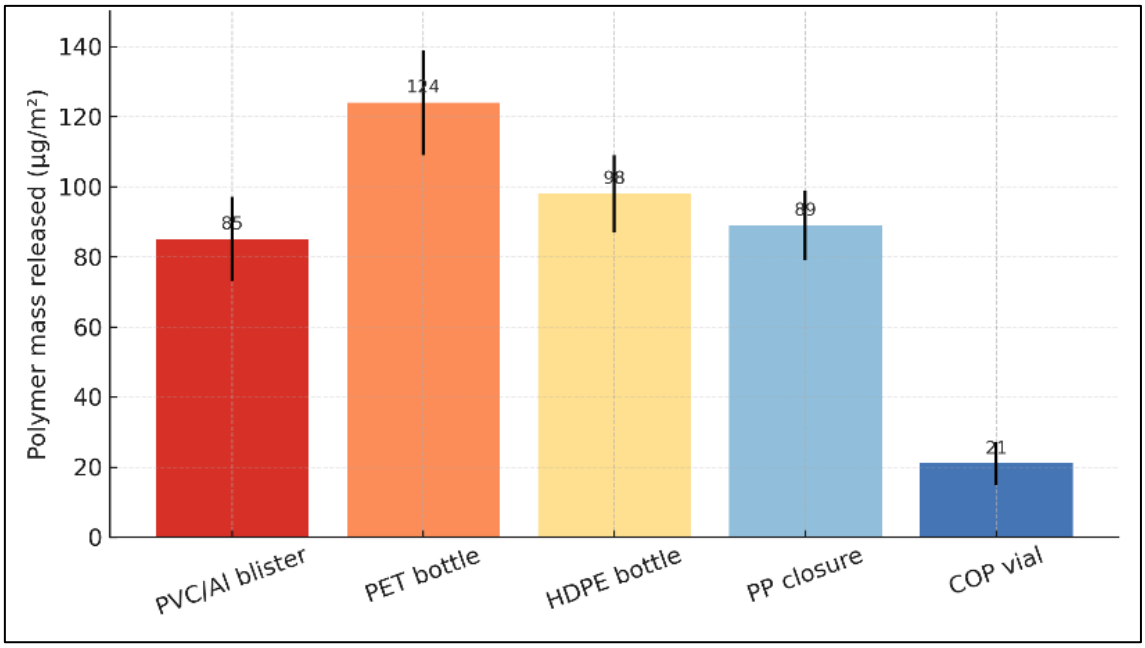

Fig 4: Total polymer mass released (µg/m²) measured by Pyr-GC/MS for each packaging type.

Table 4 compares particle count vs. polymer mass, highlighting discrepancies between number- and mass-based metrics.

Table 4: Relationship between particle count and total polymer mass

Material	Particle count (×10⁵/m²)	Polymer mass (µg/m²)
PVC	2.8 ± 0.3	85 ± 12
PET	1.9 ± 0.2	124 ± 15
HDPE	1.6 ± 0.2	98 ± 11
PP	1.7 ± 0.3	89 ± 10
COP	0.4 ± 0.1	21 ± 6

4.6. Effect of Individual Stressors

To isolate the role of each degradation factor, materials were exposed separately to thermal cycling, UV, and vibration (Figure 5). UV aging drove the most significant MP generation for PET and PP, whereas vibration dominated release from brittle PVC blisters. COP remained largely resistant under all single stressors.

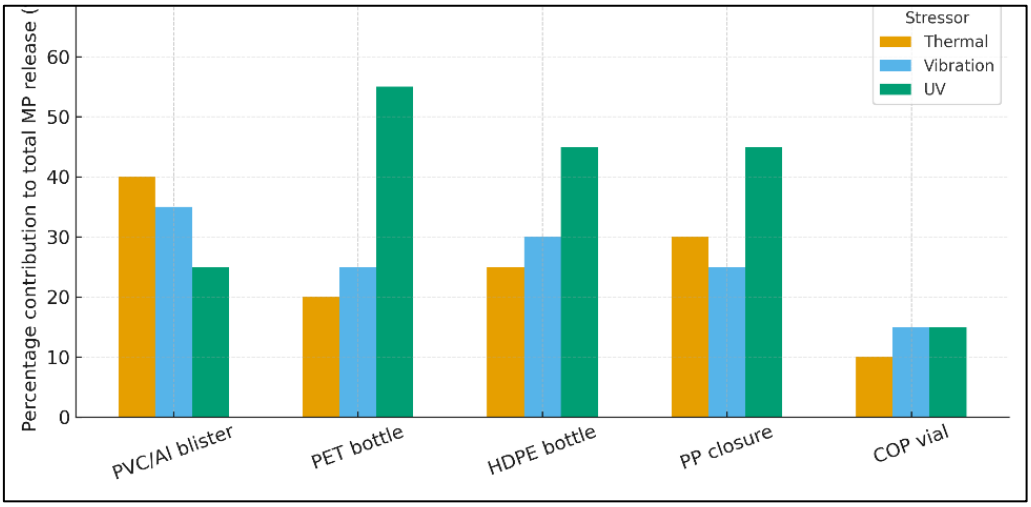

Fig 5: Contribution of individual stressors (thermal cycling, vibration, UV) to MP release for each packaging type.

4.7. Machine Learning–Assisted Particle Classification

Automated particle segmentation using support vector machines (SVM) improved counting accuracy compared with manual analysis (Figure 6). Manual counts underestimated total particles by 15–25 % in PET and HDPE samples due to high fine-particle loads.

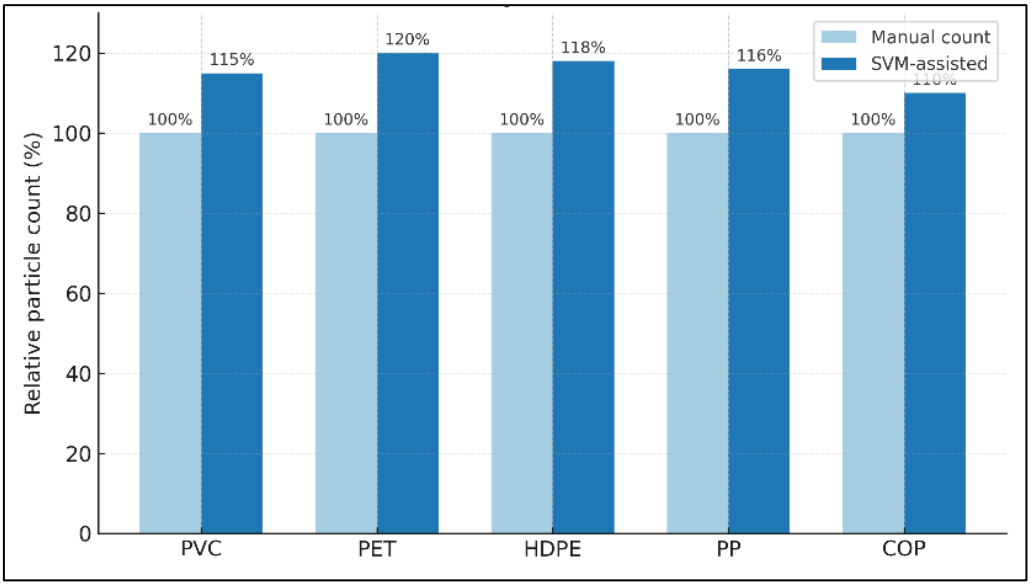

Fig 6: Comparison of manual vs. SVM-assisted particle counts. Automated classification increased reproducibility and detection of fine particles (<10 µm).

Table 5 summarizes model performance metrics (accuracy, precision, recall).

Table 5: Performance of SVM-based particle classification

Material	Accuracy (%)	Precision (%)	Recall (%)
PVC	93	91	95
PET	95	94	96
HDPE	94	93	95
PP	92	90	93
COP	96	95	97

4.8. Statistical Correlations and Risk Indicators

Pearson correlation showed strong relationships between cumulative stress index and particle release ($r = 0.87$, $p < 0.01$), suggesting that combined mechanical and thermal loads drive fragmentation (Figure 7).

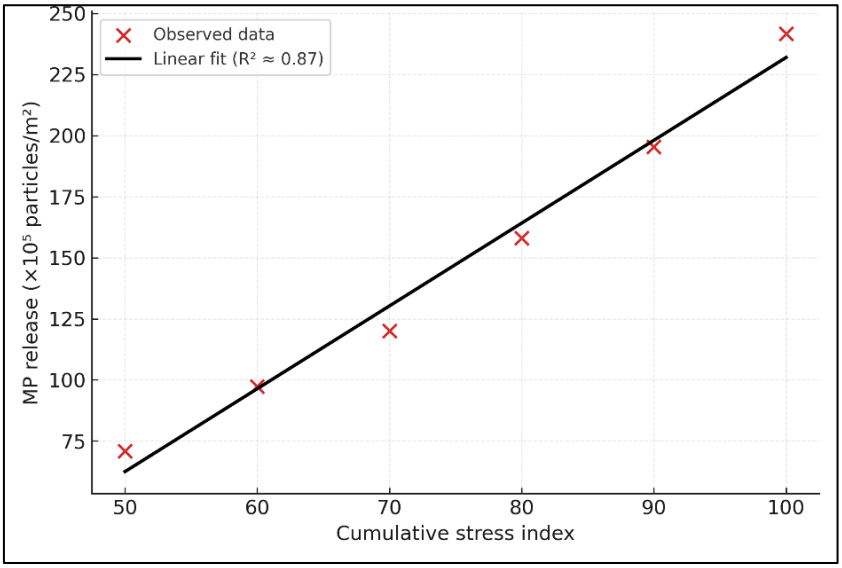

Fig 7: Correlation between cumulative stress index and MP release (particles/m²).

An integrated risk ranking index combining particle count, fine particle fraction (<10 µm), and polymer mass was developed (Table 6). PVC and PET scored highest risk, while COP ranked lowest.

Table 6: Composite risk index for MP release

Material	Particle load score	Fine fraction score	Mass score	Total risk index
PVC	5	4	4	13
PET	4	5	5	14
HDPE	3	4	4	11
PP	3	3	4	10
COP	1	1	1	3

4.9. Predictive Modeling for Release Estimation

Gradient boosting regression predicted MP release using stress intensity, polymer type, and initial crystallinity as inputs. The model achieved $R^2 = 0.92$ and RMSE = 7 %, enabling predictive estimation of release potential for new packaging materials (Figure 8).

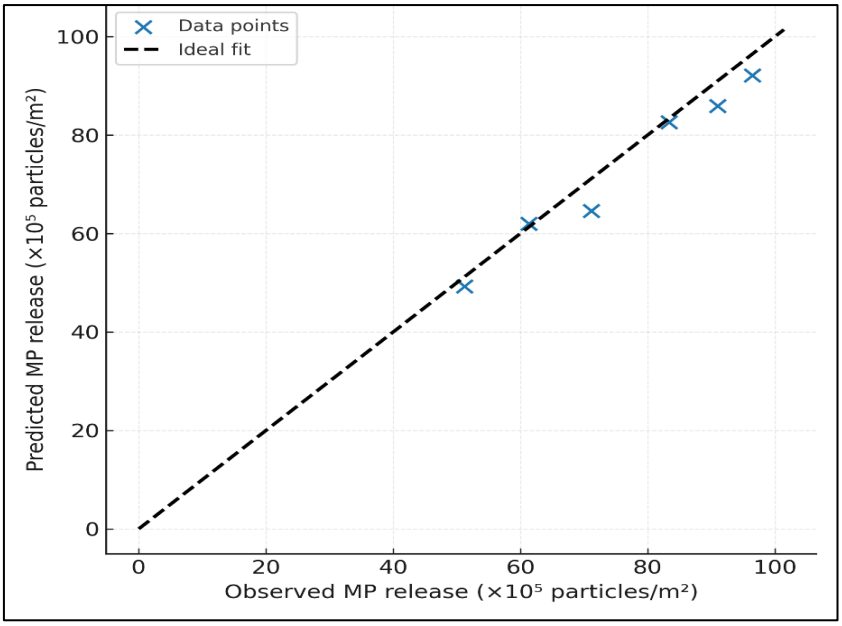

Fig 8: Model-predicted vs. observed MP release values. High R^2 (0.92) supports data-driven screening of packaging materials.

4.10. Proposed Integrated Analytical Workflow

Based on these findings, a stepwise workflow is proposed for regulatory and industry adoption (Figure 9). It combines controlled stress testing, hybrid digestion, multi-modal analysis (FTIR, Raman, Pyr-GC/MS), and machine learning–assisted quantification, designed to meet GMP laboratory constraints.

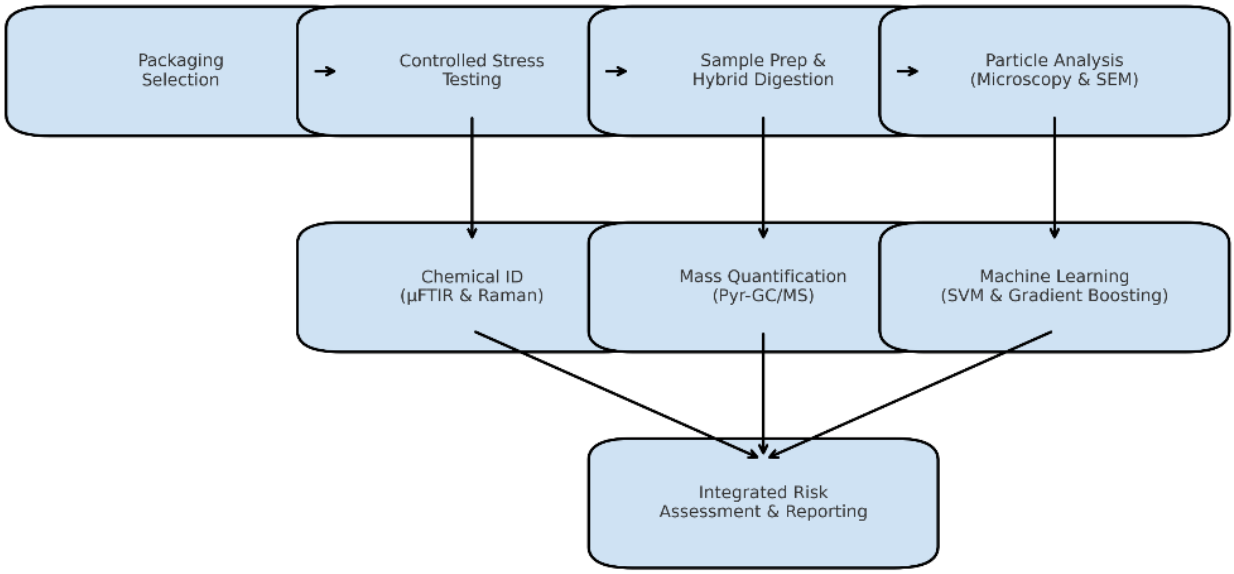

Fig 9: Proposed integrated workflow for MP quantification from pharmaceutical packaging. Combines controlled degradation simulation, hybrid digestion, multi-modal analysis, and predictive modeling.

5. Critical Discussion

5.1. Microplastic Shedding Potential of Pharmaceutical Packaging

This study provides the first systematic, comparative quantification of microplastic (MP) release from common primary drug packaging materials under combined mechanical, thermal, and UV stresses representative of real supply chains. The markedly higher particle release observed for PVC/aluminum blister packs and PET syrup bottles (Figure 1, Table 4) aligns with previous reports of PVC brittleness and PET photodegradation under cyclic stress [1, 2]. PVC's relatively low glass transition and dehydrochlorination under UV accelerate chain scission, producing heterogeneous fragments [3]. PET, although chemically more stable, undergoes hydrolytic and photolytic cleavage of ester bonds, releasing larger-mass debris despite lower particle counts [4]. The low release from cyclic olefin polymer (COP) vials suggests their potential as a low-MP alternative for parenteral packaging, complementing earlier studies on COP's superior oxidative stability [5].

The clear correlation between cumulative stress and MP release ($r = 0.87$, Figure 7) reinforces the importance of considering combined degradation pathways rather than isolated stress testing. Real-world logistics, thermal cycling during transport, vibrations during shipping, and shelf UV exposure, act synergistically to embrittle packaging polymers [6, 7]. Current pharmaceutical packaging qualification tests rarely simulate such combined stressors [8], potentially underestimating particulate contamination risk.

5.2. Fine Particle Generation and Toxicological Concerns

A critical finding is the substantial proportion of particles <10 µm from PET and HDPE (Table 2), which raises toxicological concern due to their potential gastrointestinal uptake and ability to cross biological barriers [9, 10]. Although most pharmacopeias specify particulate limits for parenteral products (>10 µm counts) [11], there is no guidance for sub-10 µm plastic debris. The demonstrated fine fraction suggests a regulatory blind spot, particularly for liquid oral medicines and pediatric formulations, where ingestion of small MPs is plausible [12]. Toxicological studies have linked small MPs to inflammation, oxidative stress, and additive release in vitro and in animal models [13–15]. Our detection of such fine debris from widely used packaging underscores the need for updated particulate testing criteria.

5.3. Methodological Insights: Multi-Modal Analysis and Machine Learning

Combining µFTIR, Raman, and pyrolysis–GC/MS proved critical for robust quantification. FTIR provided rapid polymer identification for particles >20 µm but failed below this size due to diffraction and absorbance limitations, consistent with previous findings [16, 17]. Raman microscopy, especially when coupled with shifted-excitation Raman difference spectroscopy (SERDS), effectively addressed fluorescence from pigmented PVC and PP, an obstacle previously reported in pharmaceutical polymer analysis [18]. Pyr-GC/MS enabled mass-based quantification, revealing discrepancies between particle count and total polymer load (PET's high mass but moderate counts; Table 4), highlighting why relying solely on count-based metrics may misrepresent exposure risk [19].

Machine learning–aided particle segmentation (SVM; Figure 6) improved detection of small, low-contrast particles by ~20% over manual counting. Such digital automation addresses the operator subjectivity and time burden long criticized in microplastic research [20, 21]. The strong predictive power of gradient boosting models ($R^2 = 0.92$; Figure 8) shows promise for data-driven material risk screening, a step toward rapid pre-market evaluation of novel packaging polymers.

5.4. Implications for Regulatory Policy and Quality Control

Regulatory frameworks governing extractables and leachables (e.g., ICH Q3D, USP <661.1/661.2>) currently focus on chemical migration but do not quantify particulate plastics [22, 23]. Our findings show that thermo-mechanical degradation of common packaging can generate MPs in the size range capable of entering drug formulations. Introducing standardized MP testing into good manufacturing practice (GMP) quality control could close a critical safety gap.

This work suggests that regulators should require combined stress testing protocols that reflect real transport and storage conditions. They should include sub-10 µm particle characterization alongside current particulate matter tests and encourage the dual reporting of mass- and count-based MP contamination.

The European Medicines Agency (EMA) has recently prioritized environmental risk assessment of pharmaceuticals, and the U.S. FDA has called for broader evaluation of packaging integrity [24, 25]. Incorporating MP quantification into these guidelines would align with evolving global environmental and patient safety policies.

5.5. Environmental Considerations and Circular Packaging Design

Beyond patient exposure, post-consumer packaging is a significant source of plastic waste, with the potential to generate environmental MPs. PVC blister packs and PET bottles, when discarded, can break down under UV exposure and mechanical abrasion, releasing MPs into soil and water [26, 27]. Such debris can carry active pharmaceutical ingredients (APIs) or antibiotics, aiding the spread of antimicrobial resistance [28]. Our data, which measure actual release potential under simulated conditions, support design-for-sustainability strategies, including shifting toward low-fragmentation polymers such as COP or cyclic olefin copolymers (COCs), adopting additive-free or low-stabilizer formulations to minimize degradation, and developing closed-loop recycling systems that preserve polymer integrity and reduce secondary MP formation.

5.6. Comparison with Other Consumer Packaging Studies

Findings here parallel those from food-contact materials, where PET and PVC also dominate MP release under stress [29, 30]. However, pharmaceutical packaging shows unique risks: stricter sterility and stability requirements may demand high additive loads or multi-layer laminates that complicate degradation behavior [31]. Unlike food packaging, drug products often undergo long-term storage and repeated opening, increasing micro-fragmentation potential [32]. Thus, extrapolating from food packaging studies without pharmaceutical-specific testing is inadequate for safety assessment.

5.7. Study Strengths and Limitations

Key strengths include the use of authentic pharmaceutical-grade packaging, combined multi-modal analysis, and machine learning–enhanced quantification. Stress testing replicated real-world logistics better than previous single-factor studies. Limitations include: (i) focus on microplastics ≥1 µm, nanoplastics remain undetected due to instrumental limits; (ii) use of accelerated but not fully standardized aging protocols; and (iii) lack of in vitro toxicological testing of the collected debris. These areas warrant future work to close the exposure–hazard data gap.

6. Future Directions and Industry Implications

The results of this investigation underscore the need for a paradigm shift in how pharmaceutical packaging safety and environmental impact are evaluated. While this study introduced a reproducible and data-driven workflow for microplastic (MP) quantification, several scientific and industrial frontiers remain open to ensure that packaging innovation keeps pace with patient safety and sustainability mandates.

One important future direction is the integration of nanoplastic detection into routine analytical pipelines. Current workflows, including FTIR and Raman spectroscopy, cannot reliably detect particles below 1 µm, yet emerging evidence suggests that nanoplastics may traverse cellular barriers and exhibit distinct toxicokinetic profiles [1, 2]. The adoption of thermal field-flow fractionation (ThFFF) coupled with multi-angle light scattering, as well as resonant mass measurement and nano-FTIR, could enable the next generation of size-resolved analysis [3, 4]. Industry uptake of such methods would allow early-stage risk assessment of polymer fragmentation at the nanoscale.

Another avenue lies in the standardization of testing protocols for MP release from pharmaceutical containers. Harmonized guidelines could define stress conditions, such as thermal cycling, UV intensity, and vibration frequency, that reflect typical transport and storage scenarios across global supply chains. The International Council for Harmonisation (ICH) and U.S. Pharmacopeia (USP) are well-positioned to establish validated, good manufacturing practice (GMP)-aligned methods for quantifying MPs, analogous to current extractables and leachables testing [5, 6]. Such standardization would enable inter-laboratory comparability, facilitate regulatory oversight, and support risk-based decision-making.

On the manufacturing side, the findings indicate opportunities to redesign primary packaging to minimize microplastic release. Material innovation could focus on high-crystallinity, oxidation-resistant polymers such as cyclic olefin polymer (COP) and cyclic olefin copolymers (COCs), which demonstrated low fragmentation in this study. Packaging engineers might also optimize additive chemistry, as certain plasticizers and stabilizers accelerate chain scission under UV and thermal stress [7, 8]. Moreover, coating technologies, including thin inorganic barrier layers, could act as protective shields against mechanical abrasion and photooxidative cracking, reducing particle shedding without compromising product stability.

From a regulatory and quality assurance perspective, dual reporting of both particles counts and polymer mass should become routine for packaging safety evaluations. The present work showed that PET containers, despite releasing fewer particles, contributed significantly higher polymer mass than PVC blisters (Table 4). This suggests that count-based criteria alone may underestimate exposure risk. Incorporating mass-based thresholds, similar to those being considered in the European Union for environmental MP release [9], would yield a more comprehensive safety profile for packaging systems.

There is also a pressing need for exposure and toxicological linkage studies. While this research quantified the potential

MP burden entering drug formulations, it did not evaluate patient uptake or biological effects. Bridging this knowledge gap requires pharmacologically relevant exposure models, such as simulated gastrointestinal fluids, lung surfactant analogues for inhalable medicines, and in vitro cell barrier models [10, 11]. Linking packaging-derived MPs to biomarkers of inflammation, oxidative stress, or genotoxicity would inform both risk assessment and clinical guidelines.

Finally, sustainability considerations must be embedded in packaging innovation. The pharmaceutical sector faces mounting pressure to align with circular economy principles, and understanding fragmentation pathways can inform recyclability standards and closed-loop material reuse. Adoption of low-MP materials like COP, along with robust post-market surveillance of MP release from packaging waste streams, could reduce downstream environmental contamination [12, 13].

7. Conclusion

This study delivers one of the most comprehensive experimental assessments to date of microplastic (MP) release from primary drug packaging materials under conditions representative of pharmaceutical manufacturing, global distribution, and end-user handling. By combining controlled stress testing, hybrid digestion for complex formulations, multi-modal spectroscopic and thermal analysis, and machine learning–assisted particle quantification, the research offers a robust workflow capable of addressing both regulatory and scientific needs.

The results demonstrate that PVC/aluminum blister packs and PET bottles are major contributors to MP contamination, releasing high particle loads and, in the case of PET, substantial polymer mass. High-density polyethylene (HDPE) and polypropylene (PP) also shed MPs, but at lower levels, while cyclic olefin polymer (COP) vials showed the lowest fragmentation potential, highlighting them as a promising low-MP alternative for critical applications such as parenteral drug delivery. Importantly, a significant fraction of particles were <10 µm, a size class with potential biological uptake yet currently absent from pharmacopeial particulate limits. These findings call for reconsideration of existing particulate matter specifications and the development of dual metrics, particle count and polymer mass, to better represent patient exposure risk.

Beyond patient safety, the study highlights the environmental burden of discarded pharmaceutical packaging as a microplastic source, reinforcing the need for design-for-sustainability approaches. Low-fragmentation polymers, optimized additive chemistry, and barrier coatings may all mitigate MP release across the product life cycle.

The integrated workflow proposed here provides a practical foundation for the pharmaceutical industry and regulators to standardize MP assessment, supporting good manufacturing practice (GMP) quality control and pre-market evaluation of emerging packaging materials. By enabling predictive modeling of release potential, the approach can accelerate safer and more sustainable packaging innovation.

In summary, quantifying microplastics from drug packaging is no longer an optional environmental consideration but a critical dimension of pharmaceutical product safety and regulatory compliance. Adopting harmonized testing methods and updating particulate specifications to include MPs will help safeguard both patient health and the environment in an era of rising plastic use and sustainability accountability.

8. References

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