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A Study On The Detection And Quantification Of Foreign Particles Using Filtration-Based Analytical Techniques In Drug Substances

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Abstract
The Active Pharmaceutical Ingredient (API) is the pivotal element in pharmaceutical formulations, responsible for delivering the intended therapeutic outcomes. The contamination of drug substances with foreign particles presents considerable health risks to patients, the long-term ramifications of which remain largely undefined. This necessitates comprehensive studies on particulate contamination. This research quantitatively analyzes foreign particulates in commercially sourced APIs, employing samples from various manufacturers under controlled laboratory conditions. The methodology involved weighing of APIs, subsequent dissolution in appropriate solvents, and filtration through 0.45 µm membrane filters, examining particulates obtained on filter paper. Acceptance criteria were delineated based on thresholds informed by expert consensus and pharmaceutical industry standards and category: - Category 1 (Soft Particles): Maximum of 2 particles per gram (up to 1 mm). - Category 2 (Hard Particles): Maximum of 5 particles per 50 grams (up to 0.5 mm). - Category 3 (Other Hazards): Zero tolerance for hazards such as insect fragments, human tissue, hair, glass, wood, and paint chips. Sampling from two pharmaceutical manufacturers yielded a total of four extraneous particles across five samples, all of which adhered to the defined acceptance criteria. While the ideal condition would be to have drug substances free from any foreign particulate contamination, the findings of this study demonstrate that complete absence is not achievable. Though particles were present in almost samples, they were characterized as non-harmful to patient health. This underscores the inherent challenges of particulate contamination in pharmaceuticals and reinforces that while absolute elimination may be unrealistic, the detected contaminants do not compromise patient safety. Continuous monitoring and further research are imperative to uphold the integrity and safety of pharmaceutical products. The results of this study reveal significant compliance gaps within pharmaceutical manufacturing processes, offering manufacturers an opportunity to enhance their quality management systems and mitigate foreign particle contamination. Given the limited sample size, there is a compelling case for broader investigations involving larger cohorts. The promotion of such research on a global scale is warranted, and regulatory bodies should prioritize these studies to safeguard patient health.
Keywords: *Contamination, Foreign Particles, Active Pharmaceutical Ingredient*

INTRODUCTION

Foreign substances in pharmaceutical products compromise the integrity of the product. No one knows what effect the unknown foreign particles found in medicine will have on the patient's body.

No prescriber/doctor wants pharmaceutical products with foreign particles. The patient, who is entirely unaware of the drug information and is already suffering from the disease, should be kept away from the contaminated drug.

The medicine given to patients in various forms is made from many ingredients. The main ingredient is Active Pharmaceutical Ingredients, which are mandatory. (Nusim, 2010) The pharmaceutical industry tries to remove foreign particles from medicine through various techniques. However, it is not technically possible for any external substance or foreign particles to not be in the Active Pharmaceutical Ingredients. No API manufacturer can completely eliminate the presence of foreign matter in the API. However, the mindset of any Drug Regulatory Authority Investigator or any other officer is that the API is entirely free from external substances. In this situation, it is tough to satisfy all regulatory investigators completely. As a result, regulatory investigators, customers, and other authorized persons make comments, complaints, and other statutory actions for the API manufacturer.

The presence of foreign matter in the API is also very harmful from the point of view of the health of the consumer/patient. Therefore, in this case, the right decision is to work towards reducing the presence of

foreign matter in the API. The world's health authorities (USFDA, EMA, and others) and Pharmacopoeias (USP, EP, and Others) are rarely mentioned in identifying external substances and guidelines for their elimination. The foreign material should be found and eradicated at the time of API and its manufacturing, and a proper format should be prepared for it. It is necessary to work in this context because it is related to the risk of life of common and patients.

In the above topic, APIC (ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE) has developed a guidance document. The Guidance on Handling of Insoluble Matter and Foreign Particles in APIs document offers best industry practices and guidance for appropriate controls for the unavoidable presence of minute amounts of particles in APIs. The guideline highlights potential factors to minimize patient risk within reasonable limits. (APIC A. P., 2015)

Many companies manufacture Active Pharmaceutical Ingredients and follow GMP regulations. However, for some reason or other factors, some foreign particles remain in the Active Pharmaceutical Ingredient. This research aims to identify and quantify these foreign particles in drug substances.

To achieve this objective, research was initiated focusing on the active pharmaceutical ingredient. First, it was understood the process of becoming an active pharmaceutical ingredient. Subsequent to that, a request was dispatched to several API manufacturing companies seeking samples for the purpose of empirically assessing the presence of foreign particle contamination in commercially available APIs. A formal request form was circulated among the companies, leading to the acquisition of various API samples for analytical study. The evaluation was conducted utilizing filtration-based methodologies at the university's laboratory. This investigation aims to ascertain the existence of foreign particle contamination within the commercial APIs and to quantify the levels of such contamination.

MATERIALS AND METHODS

❖ Materials And Equipment

- Laminar airflow cabinet (pre-sterilized and fully operational)
- API sample (5–100 Gms, single API batch)
- Pharmaceutical-grade solvent (i.e., Methanol, Acetone, 80% ethanol in Water, Purified Water)
- Precision analytical balance
- Glass beaker or flask (capacity suited to solvent volume, e.g., 100–2000 mL)
- Glass stirring rod or magnetic stirrer
- Filtration system:
  - Funnel (Büchner for vacuum filtration or standard for gravity filtration)
  - Filter paper (0.45 µm pore size default; adjustable per pre-test or other suitable filter paper)
  - Filter flask (for vacuum filtration)
- Vacuum pump
- Drying oven or air-drying station (within the cabinet) if required
- Sterile tweezers (for filter handling)
- Magnet
- Microscope or magnifying lens (10x magnification)

❖ Method

The analysis of API samples was performed one by one.

- Laminar Airflow Cabinet Preparation
  - Activated the laminar airflow cabinet and operated it for a minimum of 15 minutes to establish a sterile, particle-free environment.
  - Cleaned interior surfaces with 70% ethanol, ensuring complete evaporation before use.
  - Transferred all required equipment and materials into the cabinet prior to commencing the procedure.
- Solvent Purity Verification and Blank Trial (Control Assessment)
  - Filtered each selected solvent through a 0.45 µm filter paper using the designated filtration system as per the samples sequence.
  - No foreign particles were observed on 0.45 µm filter papers.
  - Preparation of API Samples
  - Accurately weighed API samples using the analytical balance, recording mass.
  - Placed the sample into a separate clean beaker.
- Dissolution of APIs
  - Added solvent to API sample at a ratio of 10 mL per 1 gms (e.g., 50 mL for 5 gms), or dissolved based on solubility.

- Stirred gently using a clean glass rod or magnetic stirrer until the API was fully dissolved, confirming that no undissolved API remained (excluding potential particulate matter).

➢ Filtration Process

- Configured the filtration system within the cabinet: Vacuum Filtration: Secured a 0.45 µm filter paper in a Büchner funnel, connected to a filter flask, and attached the vacuum pump.
- The slowly added API solution was passed through its respective filter, after which the beaker was washed with 5-10 mL of solvent to ensure complete transfer of particles.
- Carefully removed filter paper using sterile tweezers to prevent contamination or particle loss.
- Filter paper was used for further assessment.

➢ Visual Identification and Quantitative Analysis

- Positioned the dried filters (Blank and API) on a clean, illuminated surface within the cabinet.
- Inspected each filter visually for particulate matter, recording presence, color, and approximate quantity.
- Evaluated and identified particles using a microscope.
- Compared API filters against the blank filters to confirm particulates were sample-specific.
- To identify metal particles, bring a magnet close to the filter paper and observed if any particles were attracted to the magnet or if they moved in response to it.

➢ Precautions:

- Equipment cleaning: Ensured all equipment was thoroughly cleaned and completely dry before use.
- Solvent Purity: Pre-verification eliminated false positives; only pharmaceutical-grade solvents were used.
- Filter Selection: Defaulted to 0.45 µm pore size filter papers were used.
- Safety Precautions: Wore PPE (gloves, goggles, and an Apron) per laboratory requirements.
- Contamination Prevention: Pre-sterilized all materials and (or sterile materials were used) maintained aseptic conditions within the cabinet, following GMP-like practices.

➢ Acceptance Criteria

- Solvent Purity: No particulate matter is visible on the 0.45 µm filter or appropriate filter paper from solvent verification under illumination.
- Blank Trial: The 0.45 µm blank filter or appropriate filter paper shows no particulate matter when examined with a microscope.
- Dissolution: The API sample achieves complete dissolution, with no undissolved API residue (excluding particulates) in the beaker.
- Filtration Integrity: The filtration system functions without leaks or blockages, retaining all particulates on the filter.
- Documentation Completeness: All required data are accurately recorded.
- Foreign Particles Limit on Filter Paper: APIs are utilized across various drug product dosage forms, and the particle limits may also depend on the route of administration. For particles smaller than 1 mm in size, the limit should be established based on typical process performance, which should be defined by the individual API manufacturer using historical data. Additionally, analytical samples must not contain any particles larger than 1 mm (APIC A. P., 2015). The following are established thresholds informed by expert consensus and pharmaceutical industry standards, intended for academic application.

Category Properties	**Criteria**
Soft particles encompass materials such as fiber, cotton, nylon, rubber, cellulose, Polypropylene, Paper, Polyester, Teflon, and Charcoal, among others.	1. A maximum of 2 particles per gram (Size: up to 1 mm in dimension). 2. Particles exceeding a dimension of 1 millimeter are prohibited.
Hard particles encompass materials such as metals, Stainless Steel, Plastics, PVC, Stone, and various other rigid substances.	1. Maximum of 5 particles per 50 grams (Size: up to 0.5 mm in dimension). 2. Maximum of 3 particles per 25 grams (Size: up to 0.5 mm in dimension). 3. Maximum of 1 particle per 25 grams (Size: between 0.5 mm to 1.0 mm in dimension).

	4. Particles exceeding a dimension of 1 millimeter are prohibited.
Other Materials (Hazards) such as insect fragments, human tissue or body parts, hair, glass, wood, and paint chips.	No particles allowed.

Table 1: Establish criteria for obtaining foreign particles in API Samples

➢ Limitations

▪ This study utilizes samples sourced from two pharmaceutical companies, encompassing five distinct drug substances, to facilitate robust statistical analysis. The research is anchored within the Indian pharmaceutical sector, offering a valuable foundation for further exploration by other researchers in the field.

RESULTS

Five Active Pharmaceutical Ingredients (APIs) were evaluated for particulate contamination: Atenolol, Chlorthalidone, Furosemide, and Losartan Potassium sourced from Ipca Laboratories Limited, Ratlam (India), along with Lamotrigine from UNICHEM Laboratories, Dhar (India).

Each API sample underwent dissolution, followed by filtration, and was subsequently assessed for particulate matter through visual inspection and microscopy on filter paper.

❖ API Sample-1 Results:

Name of Active Pharmaceutical Ingredient	Atenolol IP
API Batch Number	24350A2BRII
Manufacturing Date	September 2024
Expiry Date	August 2029
Quantity	50 Gms
Manufacturer	Ipca Laboratories Limited, Sejavata, Ratlam, 457001, Madhya Pradesh, India

Table 2: Sample Details for Atenolol IP

Number of Foreign Particles identified: Detected 1 particle
Type of foreign particle: Carbon/Charcoal
Size: 100 to 200 microns
Color: Black
Texture: Soft & Crumbly
Nature: Soft in Nature

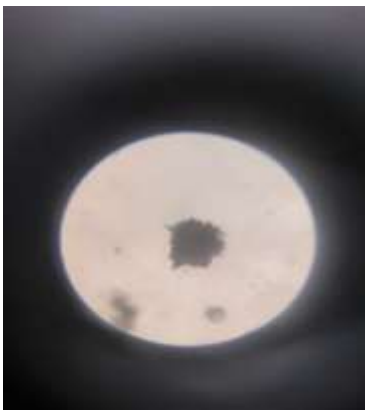

Image-1: Microscopic View of a foreign particle obtained from an Atenolol Sample

Shape: Slightly Spherical

Metallic or Non-metallic Composition: Non-metallic.

❖ API Sample-2 Results:

Name of Active Pharmaceutical Ingredient	Chlorthalidone Ph. Eur.
API Batch Number	24014CT6RII

Manufacturing Date	April 2024
Expiry Date	March 2029
Quantity	50 Gms
Manufacturer	Ipca Laboratories Limited, Sejavata, Ratlam, 457001, Madhya Pradesh, India

Table 3: Sample Details for Chlorthalidone Ph. Eur.

Number of Foreign Particles identified: Detected 1 particle
Type of foreign particle: Fiber
Size: 300 to 400 microns
Color: White
Texture: Smooth & Crisp
Nature: Soft in Nature

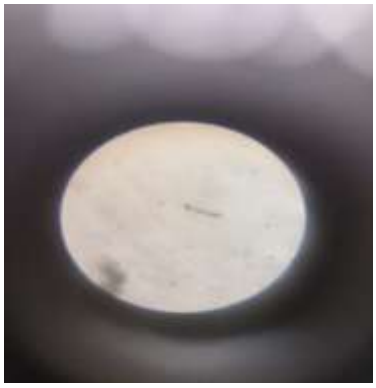

Image 2: Microscopic View of a foreign particle obtained from the Chlorthalidone Sample

Shape: Straight Fiber

Metallic or Non-metallic Composition: Non-metallic.

❖ API Sample-3 Results:

Name of Active Pharmaceutical Ingredient	Furosemide Ph. Eur.
API Batch Number	24009H1BRII
Manufacturing Date	January 2025
Expiry Date	December 2029
Quantity	50 Gms
Manufacturer	Ipca Laboratoris Limited, Sejavata, Ratlam, 457001, Madhya Pradesh, India

Table 4: Sample Details for Furosemide Ph. Eur.

Number of Foreign Particles identified: Detected 1 particle
Type of foreign particle: Stone or Granite Stone
Size: 300 to 400 microns
Color: A Combination of grey, white, and black
Texture: Coarse-grained texture, known as phaneritic texture
Nature: Hard Particle

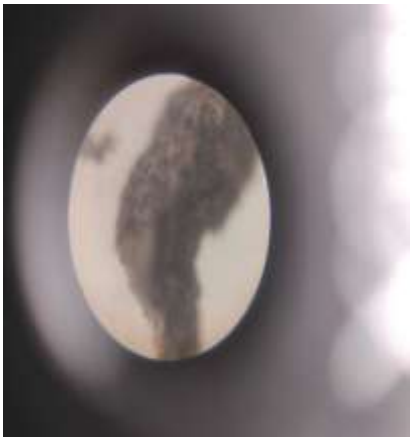

Image 3: Microscopic View of a foreign particle obtained from the Furosemide Sample.

Shape: Irregular, Fragments with edges and crevices

Metallic or Non-metallic Composition: Non-metallic.

❖ API Sample-4 Results:

Name of Active Pharmaceutical Ingredient	Lamotrigine USP
API Batch Number	PLGP210140
Manufacturing Date	December 2021
Expiry Date	November 2026
Quantity	20 Gms
Manufacturer	UNICHEM Laboratories Limited, Plot No. 197, Sector-1 Industrial Area, Pithampur, District-Dhar 454775, Madhya Pradesh, India

Table 5: Sample Details for Lamotrigine USP

Number of Foreign Particles identified: No Particles Detected

❖ API Sample-5 Results:

Name of Active Pharmaceutical Ingredient	Losartan Potassium USP
API Batch Number	24010LB5MRI
Manufacturing Date	July 2024
Expiry Date	June 2029
Quantity	50 Gms
Manufacturer	Ipca Laboratories Limited, Sejavata, Ratlam, 457001, Madhya Pradesh, India

Table 6: Sample Details for Losartan Potassium USP

Number of Foreign Particles identified: Detected 1 particle
Type of foreign particle: Cotton or Looks like Cloth Cotton
Size: 100 to 200 microns
Color: Red
Texture: Soft, Smooth, and Pleasant against the skin
Nature: Soft Particle

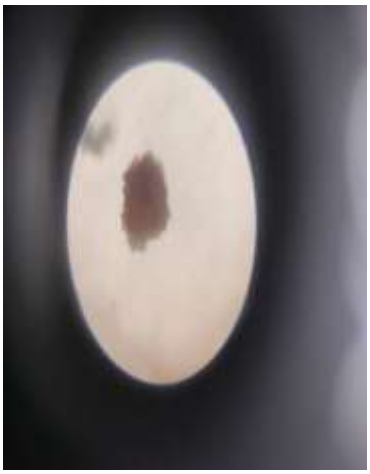

Image 4: Microscopic View of a foreign particle obtained from the Losartan Potassium Sample

Shape: Slightly Spherical

Metallic or Non-metallic Composition: Non-metallic

In total, four particles were identified across all samples. All APIs conformed to the established acceptance criteria across the three categories evaluated.

Formulators and drug regulatory bodies maintain that drug substances should ideally be devoid of any foreign particulate contamination. However, this experiment reveals that the complete absence of such contaminants is unattainable. The findings indicate that extraneous particles mix with the drug substance. All samples analyzed in this study exhibited the presence of some foreign particles; nonetheless, these particulates are determined to be non-harmful to patients. This research underscores the presence of foreign particulate contamination in pharmaceuticals, while also reassuring that the identified contaminants do not pose a risk to patient safety.

The evaluation of particulate contamination in the selected Active Pharmaceutical Ingredients underscores an important aspect of pharmaceutical quality control. Despite rigorous testing methods employed, the presence of foreign particles was inevitable in all samples analyzed. The identified contaminants were classified according to their nature, with all particles falling within established acceptance criteria, indicating compliance with safety standards. This study highlights the reality that while a complete absence of particulate contamination may not be achievable, the detected particles are non-harmful and do not compromise patient safety. Ongoing vigilance in monitoring and mitigating particulate contamination remains essential to ensure the integrity and safety of pharmaceutical products, emphasizing the need for continued research and development in this area.

DISCUSSION

This research highlights the pharmaceutical manufacturing system's significant gaps and noncompliance activity. This presents a valuable opportunity for all stakeholders and pharmaceutical companies involved in the production of active pharmaceutical ingredients to assess and enhance their quality management systems and build up a robust elimination process in order to avoid foreign particles. This research has been conducted with a limited number of samples. If any researcher wants to, they can further continue with a larger number of samples. There is a great need to promote such research globally, and regulatory agencies should place greater emphasis on this type of investigation to ensure patient safety.

CONCLUSION

Foreign substances in pharmaceutical products can compromise their integrity and pose risks to patients. Prescribers and patients expect medications to be free from contaminants, but Active Pharmaceutical Ingredients (APIs) can never be entirely free of foreign particles. Despite industry efforts, the presence of these contaminants remains an issue, leading to compliance challenges as regulatory authorities require APIs to be contaminant-free. To address this, the Active Pharmaceutical Ingredients Committee (APIC) has provided guidelines for managing foreign particles and enhancing patient safety. This research quantifies foreign particles in commercially available APIs by analyzing samples from multiple manufacturers in a controlled laboratory. The methodology involved weighing APIs, dissolving them in solvents, and filtering through 0.45 µm filter papers, with examinations for particulates. The study defined acceptance criteria based on particle size and category: - Category 1 (Soft Particles): Max 2 particles per gram (up to 1 mm); no particles over 1 mm. - Category 2 (Hard Particles): Max 5 particles per 50 grams (up to 0.5 mm); others follow stricter limits. - Category 3 (Other Hazards): Zero tolerance for contaminants like insect fragments, hair, or glass. Sampling from two pharmaceutical companies revealed four extraneous particles in a total of five samples, all within acceptable criteria. While the ideal is the absence of contamination, the findings show that minor non-harmful particles can occur, emphasizing the need for ongoing monitoring and research to ensure product safety. This limited sample study highlights gaps in pharmaceutical manufacturing and suggests that regulatory authorities prioritize further investigation for improved quality management in the industry. There's a critical need for global promotion of such research, and regulatory agencies should prioritize these studies to ensure patient safety.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

DISCLAIMER

The contents of this publication are solely the responsibility of the authors, and this research is not intended to focus on or obtain information about any company. The purpose of this research is to improve the entire pharmaceutical company. Along with this, the only objective is to reduce the contamination of foreign particles in the products made by the pharmaceutical company. The purpose of the research is only related to "patient safety."

ABBREVIATIONS

APIs: Active Pharmaceutical Ingredients
µm: Micrometer (micron)
mm: Millimeter
USFDA: United States Food and Drug Administration
Gms: Grams
i.e.: that is
mL: Milliliter
°C: ° centigrade

PPE: Personal Protective Equipment
IP: Indian Pharmacopoeia
GMP: Good Manufacturing Practices
APIC: Active Pharmaceutical Ingredients Committee
Max: Maximum
USP: United States Pharmacopoeia
EP/ Ph. Eur.: European Pharmacopoeia
EMA: European Medicines Agency
PVC: Polyvinyl Chloride

APPENDIX

Protocol and Research Report

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