ejpmr, 2023, 10(12), 348-354

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON EXTRACTABLES AND LEACHABLES OF DIFFERENT PACKAGING MATERIALS

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Article Received on 12/10/2023 **Article Revised on 02/11/2023** **Article Accepted on 22/11/2023**

ABSTRACT

Extractable and leachable (E&L) impurity testing is crucial for toxicological risk assessment in pharmaceuticals, bioprocess manufacturing systems, and medical devices. Challenges include complex matrices, low analyte evaluation thresholds, and high-resolution chromatography instruments. Obtaining consistent, high-quality data requires multiple systems.

KEYWORDS: Leachables, Extractables, GC, LC.

INTRODUCTION

Leachables and Extractables

Extractables and leachables are pollutants that are giving biopharmaceutical firms grief since they can result in impurities of extremely valuable therapeutic products.

The FDA provides the following definitions for the two terms:

Extractables

In the presence of a solvent, extractables are substances that can be removed from container closure systems.

Extractables are substances or compounds that can be removed from a primary container, component material, delivery system, or manufacturing surfaces when laboratory manipulation takes place (solvent or heat exposure), resulting in contamination of pharmaceutical products.

The majority of extractables are produced when a drug product interacts with its packaging, which may be made up of single-use consumables or other biopharmaceutical packaging elements, like a single-use bioprocess container. Excessive circumstances, such as the presence of potent solvents or high temperatures, are typically the cause of extractables. The breakdown of the packing material or primary container, which is primarily made of polymers, can also result in extractables after gamma-irradiation.

Leachables

Leachables are substances that enter the drug product formulation from the container closure system as a result of direct interaction with the formulation.

Leachables are substances that leak into the drug product through the container closure system, whether they come from coating materials, elastomeric, polymeric, or other plastic components.

The main cause of leaching is direct contact with the formulation. Leachables are frequently a subset of extractables, although, unlike extractables, they can happen in usual usage circumstances. Leachables can be caused by coatings, comparable inorganic compounds, release agents, or additives.

Although the terms "extractables" and "leachables" both refer to foreign substances that may contaminate extremely valuable therapeutic products, it is crucial to comprehend both their definitions.

Properties of Extractables and Leachables

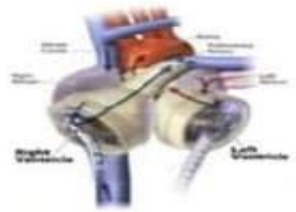
Leachables are a subset of extractables, as was already mentioned. Both of these are brought on by poor manufacturing processes or an inability to regulate the additives or agents utilized in the basic materials.

Leachables, on the other hand, can happen even in normal settings, whereas extractables are brought on by exceptional circumstances. To emphasize the distinction, it should be noted that extractables may only be present after gamma irradiation has been used to sterilize containers made in a clean room, but leachables may always be present in a low-quality sample storage container.

Sources of Extractables and Leachables in various Departments[1]

Pharmaceutical Packaging

Examples :
Parental
Ophthalmic
Oral Inhaled Products



Biomedical devices

Examples:
Blood glucose monitoring devices
Brain activity sensors
Cardiac pacemakers
Implantable defibrillators
Cochlear implants
Contact lenses
Stents
Cannulas

Food Packaging

Examples:
Plastic
Paper
Glass
Alloys

Source of Contamination
Packing material
Any individual component of a container closing system is considered a packaging component. A primary packaging component is one that directly contacts the dosage form, either directly or indirectly. A packaging element that is not and will not come into contact with the dosage form directly is referred to as a secondary packaging component.

Targets for the study of extractable and leachable
- Volatile organic compounds
- Semi-volatile organic compounds
- Elastomers
- Plasticizers
- Nitrosamine's
- Poly aromatic hydrocarbons
- Anti-Oxidants
- Trace elements
- Phthalates
- 2-mercapto benzothiazole and anions such as chloride, fluoride, and Bromide.

Extractables and Leachables in containers and closures[5]
Material used in Container closure systems:
Ingredients, impurities, contaminants, and degradants are all present in the primary package components and have the potential to build up in the product. Typically, these components are referred to as extractables or leachables.

They might also consist of substances found on the packaging's surface that merely solubilize the product.

Understanding the components of the container-closure system that can be extracted from pharmaceutical products and those that can leak into the product formulation.

Chemical species that have the potential to harm a pharmaceutical product are known as extractables.

They are chemical species that are liberated from a primary container or component material.

Depending on the solvent and temperature circumstances, interactions between products and their packaging over time usually result in extractables.

The therapeutic product's organic chemical components. Fortunately, information on suspected leachables can be found by looking at the known components of rubber and plastic materials as well as the valve's manufacturing method.

Example: Thiurams.

Plastic containers

Sources of extractable are plastic and elastomeric components (monomers, polymeric initiators, plasticizers, etc.) ink and adhesives (label), and degradation products (processing, storage, sterilization) polybutylene terephthalate (PBT) is a popular polyester plastic. In medical devices and MDI valve components, The valve components made from this substance can also leach PBT oligomers and other residues or degradation products.

Plastic packaging, closures, and films typically consume less material, are less expensive to manufacture, and weigh less, which lowers the cost of handling and shipping.

Chemicals can be found in plastic parts

Polythene, polypropylene, polystyrene, polyvinylchloride, polyamide, polycarbonate, polytetrafluoroethylene (PTFE), phenol-formaldehyde, urea-formaldehyde, and melamine-formaldehyde are some of the polymers now in use.

Along with elastomers, coatings, vulcanizing agents, accelerants, antioxidants, inks, and colors.

Phthalates are one example in particular.

To make plastics more flexible, these carcinogens are added, and they are present during the production process as well as in packaging materials.

Chemicals can be found in rubber-derived carcinogens such as nitrosamines and polynuclear aromatic hydrocarbons (PAHs).

Dithiocarbamates, and Ercaptobenzothiazoles are frequently used sulfur-containing curing agents in rubber manufacturing and could therefore leach into drug products that employ sulfur-cured rubber.

Glass containers and closures

Glass ‗ If the glass is coated (with silicone), a study may need to look specifically for extractables that are coming from the coating. Needs to be determined based on the drug product formulation and the potential for it to interact with the coating.

When it comes to parenteral/liquid products, they have typically been thought to be far less reactive than plastic. Leachables and extractables are present at much lower concentrations.

Glass has many benefits over other packing materials, although the issue with alkali and flake release is primarily limited to lime-soda glass.

The glass containers discharge soluble alkali. So that the Liquid preparations may be buffered.

Although borosilicate glass is extremely pricey, it releases very little alkali. Insoluble flakes have occasionally been observed to appear in solutions kept in glass containers.

In borosilicate glass, flake production happens at temperatures significantly higher than those employed in autoclaving, although it can happen in non-borosilicate glass right away after autoclaving.

The inertness of pure glass manufactured just from silicon dioxide is well known, but its high melting point and high cost exclude its usage in packaging. Many businesses produce glass containers in various sizes.

Three natural components silica sand, soda ash, and limestone are used to make glass containers. The components are combined with "cullet," or recycled glass. The primary component of O-I's glass bottles and containers is the cullet.

Metal container and closures

Additionally, some metals are employed as the main containers or closures for pharmaceutical items.

Metallic collapsible tubes can be used to efficiently package a variety of semisolid items including paste, gel, cream, or ointment.

Tin, plastic-coated tin, tin-coated lead, aluminum, coated aluminum for collapsible tubes, and aluminum- and tin-plated steel are among the frequently used metals.

These substances are quantified using relative reference standards, and the analytical evaluation threshold (AET), above which an extractable or a leachable must be submitted for toxicological assessment, is determined by a certified toxicologist. Customers can use analytical data for these impurity classes to identify what additional research is required to reduce potential dangers associated with the finished product.

Regulations

For the time being, no one regulated procedure is recommended for analyzing extractable and leachables. In general, the industry accepts the Product Quality Research Institute (PQRI) recommendation document in the table below as the key suggestion to adhere to because it was created with input from the U.S. FDA. It hasn't, nonetheless, received official acceptance as of yet. Several draft methods are now being taken into consideration.

Product Quality Research Institute (PQRI)[3]

PQRI is a group of nonprofit organizations that collaborate to produce and distribute timely, meaningful information that improves the quality, manufacture, and regulation of pharmaceutical products.

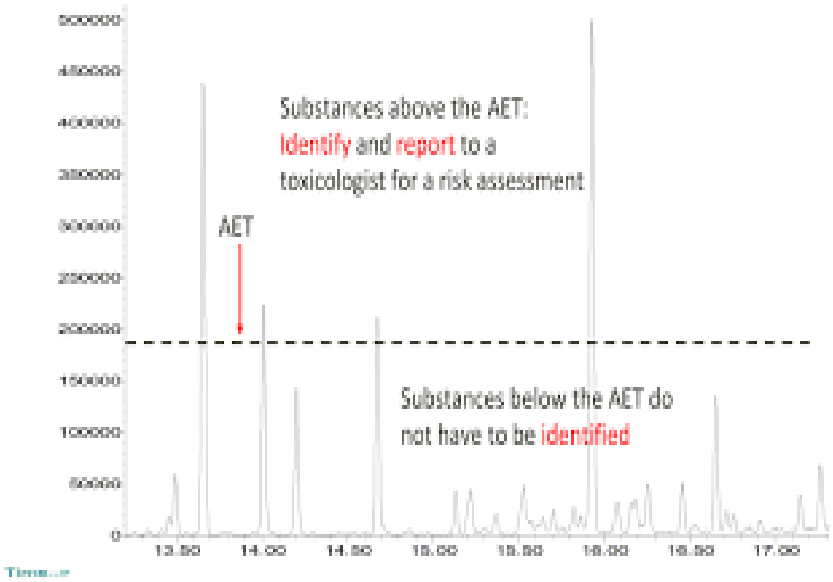
To reduce leachable uncertainty in Orally Inhaled or Nasal Drug Products (OINDP) utilizing a scientific and risk-based approach, the PQRI Leachables and Extractables (L&E) Working Group was founded in 1999. Toxicologists, analytical chemists, and other highly skilled professionals from business, government, and academia made composed the Working Group. L&E recommendations to the US FDA are the outcome of these efforts' culmination. The FDA and other international regulatory bodies have since acknowledged the publication of "Safety Thresholds and Best Practices for Leachables and Extractables in OINDP" in 2006.

The OINDP risk-based method for evaluation and safety qualification of leachables was expanded upon by the Parenteral and Ophthalmic Drug Product Leachables and Extractables (PODP L&E) Working Group in 2008.

Threshold Concepts PQRI Confidential

Safety Concern Threshold (SCT) − The threshold below which a leachable would have a dose so low as to present negligible safety concerns from mutagenic and nonmutagenic toxic effects − represented as absolute exposures, expressed in total daily intake (TDI) converted into relative amounts − SCT is risk-based and specific to the route of administration

- **Qualification Threshold (QT)** − Assessment of non-mutagenic Identified leachables • > 5 µg/day for OINDP
- **Analytical Evaluation Threshold (AET)** − Identification threshold calculated from the SCT and utilized for potential toxicological assessments Threshold concepts introduced by the September 2006 PQRI-OINDP E&L Recommendations.



PDP Identification Threshold: SCT Derived

Analytical Evaluation Threshold (AET) (1.5 ug/day)x-Doses per container
_____*UF
Container volume(ml)*doses per day

For PODP: SCT=1.5ug/day total daily intake. If not mutagenic, QT-5ug/day, UF= Analytical uncertainty

AET expressed as leachables per container

$$\text{Leachables Estimated AET} = \left(\frac{1.5\,\mu g\ /\ day}{1\,dose\ /\ day}\right) \times (1\,\text{labeled dose / PFS}) = 1.5\,\mu g/PFS$$

AET expressed as leachable concentration

$$\text{Leachables Estimated AET} = \left(\frac{1.5\,\mu g\ /\ day}{1\,dose\ /\ day}\right) \times \left(\frac{1\,dose}{1.2\,mL}\right) = 1.3\,\mu g\ /\ mL$$

AET expressed as extractable (wt/wt) device component

$$\text{Extractables Estimated AET (stopper)} = (1.5\,\mu g/PFS) \times \left(\frac{1\,PFS\ /\ stopper}{0.22\,g\ elastomer\ /\ stopper}\right) = 6.8\,\mu g/g$$

Adjustment of SCT for Treatment Duration?

ICH M7 allows adjustment of acceptable daily intake for individual DNA-reactive

Impurities based on treatment duration

Duration of treatment	1 month	>1-12 months	>1-10 year	10 years -lifetime
Daily intake (ug/day).	120	20	10	1.5

PORI does not intend for SCTs to be adjusted in this manner.

The recommended SCT should remain consistent as an ID threshold.

ICH M7 is an assessment/qualification tool for identified mutagenic impurities.

Guidelines[2]

- 1993 CDRH- Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators
- 1998 FDA - MDI/DPI Draft Guidance
- 1999 FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics
- 2002 FDA – Guidance on Inhalation solution, suspension, spray, and nasal spray products
- 2005 CHMP, CVMP - Guideline for Plastic Immediate Packaging Materials

- 2006 PQRI – Safety Thresholds & Best Practices for Extractables & Leachables

ICH guidelines

- ICHQ3A: Chemical Impurities in New Drug Substances
- ICH Q3B: Impurities in new drug products
- ICH Q3C: Impurities: Residual solvents ICH Q3E: Guideline for Extractables and Leachables (E&L)
- ICH Q5E: Comparability of biotechnology/biological products subject to changes in their manufacturing process 2005
- ICH Q7A: GMP of active pharmaceutical ingredients
- ICH Q8: Pharmaceutical Development 2006
- ICH Q9: Quality Risk Management 2006

Test methods for extractable and leachables[4]

Testing for extractable and leachables can be done using a variety of techniques.
Inductively coupled plasma (ICP-MS),
Gas chromatography (GC-MS),
Liquid chromatography (LC-MS), and other types of mass spectrometry are among the analytical techniques used to identify contaminants in addition to HPLC (high-performance liquid chromatography).

One can also distinguish between different substances that can be dangerous.
There are four types of organic substances:

1. Elemental impurities
2. Semi-volatile organic compounds (SVOCs)
3. Non-volatile organic compounds (VOCs)
4. Volatile organic compounds (VOCs)

The substances that will be examined must be known to select the best study design.

Using the correct tests to find extractable and leachables

Using a variety of analytical techniques, extractable and leachable investigations uncover the following main components:

- Volatile organic molecules, which are usually carried out utilizing headspace GC-MS
- High-resolution accurate mass (HRAM) or GC-MS is frequently used to analyze semi-volatile organic substances. GC-MS
- Non-volatile organic chemicals are commonly used in HRAM. LC-MS/MS
- Metals are examples of elemental impurities; often used ICP-MS
- Apply the proper extraction methods. For instance, microwave digestion and soxhlate extraction. Using the proper solvents: Mid-polar, Polar, and Non-Polar
- If necessary, employ various techniques. Examples include GC-MS/MS, GC-MS/HS, LC-MS/MS, ICP-MS, and ion chromatography.
- Report the amount of analytes that were detected when they were tested in the quantitative mode.
- If qualitative analysis was used, compare the reported masses with data based on the NIST library and indicate the likely discovered chemicals.

Solvent Selection Based on Formulation Type

- If the Product is an MDI (organic propellant):
- Hexane
- Methylene chloride
- 2-propanal
- If the Product is an aqueous parenteral
- Water Alcohol/water mixtures
- Consider pH effects
- Hexane for an aqueous product: not reasonable
- Water for a water/oil emulsion formulation

Extractable procedure

	Thermal	n-hexane	Isopropanol	Isopropanol /water	Ph2.5 aqueous	Ph9.5 aqueous
Headspace	X	--	--	--	--	--
Reflux	--	X	X	--	--	--
Soxhlet	--	X	X	--	--	--
Sonication	--	--	--	--	X	x

Solvents with different polarities give a better knowledge of the material.
Autoclaving for 121 degrees.

Leachables study

Detection of leachable within the formulation

- Elements
- Volatile compounds
- Non-volatile compounds
- Semi-Volatile compounds

Sample preparation is required.
Potentially Leaching Organic Compound

VOC	SVOC	NVOC
Low	Mid	High
Molecular	Molecular	Molecular
Weight	Weight	Weight

Using Mass GC/Q-TOF, Analysis of Extractable and Leachable (E&L) SALINE Compounds

Preparation of a sample

- It was extracted using flow-through extraction with saline solution at 37 °C for 72 hours from a fully integrated single-use bioprocessing system.
- The phosphate buffered saline tablet (Sigma) was dissolved in 200 mL of distilled water to create the saline solution, which had the following

composition: 137 ml NaCl, 2.7 ml Kcl, and 10 ml phosphate buffer (pH 7.4 at 25 °C).
- To show how different extraction solvents differ, the device's filter was extracted using ethanol and DCM/ethanol (1:1) solutions.
- For each extraction experiment, control blanks were made. Except for ethanol, all extract solutions were extracted using an identical volume of dichloromethane, a concentration step for GC/Q-TOF analysis.

Method Programming
- Column Agilent DB-5 MS UI, 15 m × 0.25 mm, 0.25 µm Inlet S/SL, 310 °C
- Carrier gas 1.5 mL/min Helium
- Oven program 50 °C for 5 minutes 10 °C/min to 320 °C, 10 minutes
- Transferline 280 °C
- Source mode EI, 70 eV, 10-15Ev
- Source temperature 200 °C
- Quad temperature 150 °C
- Spectral range 50 to 1,000 m/z

The findings of the differential analysis between the sample and control were performed using MASS HUNTER software, and a representative data set was the saline extract results. The findings show that 113 chemicals are found in the full device's saline extract when compared to the control lists of the elements that are most prevalent.

Identification of impurities in Saline Extract
- Caprolactam
- Dowanol 62b isomer 1
- Phenol
- Tri(1,2-propyleneglycol),
- Monomethyl ether
- Benzoic acid,
- 4-ethoxy-, ethyl ester
- Vanillin.
- Hexanamide
- Divert-butyl-1,7,9-oxaspiro(4,5)deca-6,9-diene-2,8-dione
- Ethylparaben
- 1-methyl-2-pyrrolidinone
- Imidazolidinone,
- 1,3-dimethyl
- Di-tert-butyl-phenol

CONCLUSION

Extractables and leachables are becoming a major source of concern for both the pharmaceutical sector and regulatory organizations. The presence of extractables and leachables in a therapeutic product can have a negative impact on both its safety and efficacy. As a result, extractables and leachables should be examined and handled early in the drug development process. It has never been more important than now, as the FDA is requesting more information regarding every packaging component, as well as its potential to interact with the drug. A thorough characterization is also required since extractables and leachables can have a negative impact on product quality by influencing toxicity or interfering with desirable formulation properties such as lowering drug potency or modifying drug formulation.

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