BIO & PHARMA ANALYTICAL TECHNIQUES

Chapter 13
Extractable & Leachable

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Chapter Description

- **Aims**
  - Discuss theory, principles and application of analytical techniques used in material characterization, pre-formulation development, manufacturing process and storage stability.

- **Expected Outcomes**
  - Classify the *packaging of drugs* in term of the proximity.
  - Discuss on the *analytical methods* used in extractable & leachable studies in pharmaceutical.
  - Discuss on the *extractable and leachable concern* in pharmaceutical industry.

- **References**

  - Gunzler H. & Williams A. (2002). Handbook of Analytical Techniques. Wiley-VCH, Weinheim, Germany.
  - Mullertz, A., Perrie, Y. and Rades, T. (2016) Analytical Techniques in the Pharmaceutical Sciences (Advances in Delivery Science and Technology). Springer, United States.

Definitions of Extractables

- An *extractable* is a compound that can be extracted or force to migrate from contact (packaging) material under fairly aggressive extraction conditions such as
  - Extended time
  - Elevated temperatures and
  - aggressive solvents, and generally takes place at a solid-to-liquid interface.

Examples of extractables include additives that modify a polymer's properties, or by-products of the manufacturing process for that polymer, such as unreacted monomers or processing aids.

- Point of extractables screening is to assess what **MIGHT** migrate

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Definition of Leachables

- *Leachables:* compounds that leach into the drug or biological product from the container-closure system – *Ex; elastomeric or plastic components, or coatings of the container and closure system.*

- Leaching is occurred when having a direct contact with the formulation under normal conditions of use.

- Leachables → a subset of extractables, and have potential to affect the product in various ways.

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Extractables and leachables

- Extractables may be different than leachables due to:

1. Different extracting conditions
2. Different time frames
3. A particular extractable or leachable can occur in more than one component of the container-closure system (e.g calcium from both plastic resin and elastomer).

Packaging of drugs in terms of the proximity

Primary:

Packaging components that are in *direct contact* with the drug formulation.

- Includes: containers (ampules, vials, bottles), container liners, closures (screw caps, stoppers, metering valves), stopper overseals.

Secondary:

Not or will not has direct contact with the dosage.

- Includes: labels, administrative accessories, shipping containers.
- But, they may still contribute leachable under certain conditions.

Source of extractables and leachables

- Plastic components - Vinyl Monomer & Plasticizers e.g. Phthalates.
- Rubber: Nitrosamines, Vulcanizing Agents, Accelerators, polynuclear aromatic hydrocarbons (PAHs) – carcinogenic
- Packages made of plastic and rubber components: phthalates, PAHs, or nitrosamines could potentially come into contact with the drug product and be harmful.
- Inks & adhesives from labels, coatings, antioxidants, catalyst residues, organic oligomers, heavy metals

- Information on potential leachables maybe obtained from the known ingredients of materials.

- For example :
  - thiurams, dithiocarbamates, and mercaptobenzothiazoles are commonly used sulfur-containing curing agents in rubber manufacturing.

  - Polybutylene terephthalate (PBT) is a widely used polyester plastic in medical device and MDI valve components.

Examples:

- Chemicals in flexible plastic films and tubing,
- Printing inks (labeling stamped directly on containers) Adhesive from labels,
- Overwrapping (flexible containers)
- Elastomeric closures (rigid vials)
- Components of glass (vials, bottles, syringes)

Need & Importance for control

Control of extractables and leachables in drug products is important for ensuring :

1. Safety & Efficacy of drug products
   - Can have considerable influence, especially highly active biopharmaceutical drug formulations, which may contain extremely small amounts of the active ingredient.
   - Perhaps more important than the toxicology of such materials is their potential to elicit serious immunologic responses, even at extremely small dosages.

2. Quality & Stability of drug products
   - Extractables and leachables pose problems at every stage
     - they may interfere with drug assays / medical diagnostic tests;
     - they may increase the impurity level of a drug product to an unacceptable level;
     - they may react with one or more drug product components

Extractables & Leachables Concern

- Extractables and leachables are a growing concern for pharmaceutical manufacturers and regulatory bodies.
  - The development of **unique packaging, novel formulations, delivery systems and drug-coated medical devices** has **worsen** this issue
  - **Single-use disposables (**E.g. filters, tubing, and bags for biopharmaceutical) - can introduce unwanted extractables into the final product.
  - US FDA demands for **more information** about every packaging component and its potential to interact with the drug product.

- Currently, drug manufacturers invest a lot of time and money to identify, quantify, and minimize impurities related to their drug products.

Regulatory requirements

1. Federal Food Drug and Cosmetics Act
2. Good Manufacturing Practices – 21 CFR
3. CDER Guidance Documents for Industry
4. International Guidelines (EMEA, Health Canada, FDA)
5. Standard Compendia (USP, EP, IP, ICH Q4, Q6A, Q8)

FDA Risk analysis

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

Approaches to E/L studies

SAMPLE

Container-closure or single-use bioprocess material

EXTRACTION METHOD

Accelerated solvent extraction technique

ANALYTICAL TECHNIQUE

Certified vials for LC-MS or GC-MS analysis

The object on which the testing is performed:

- ***EXTRACTABLE*** **= the container materials (possible)**
- ***LEACHABLE*** **= the final product (actual)**

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Approaches to E/L studies

1.Extraction

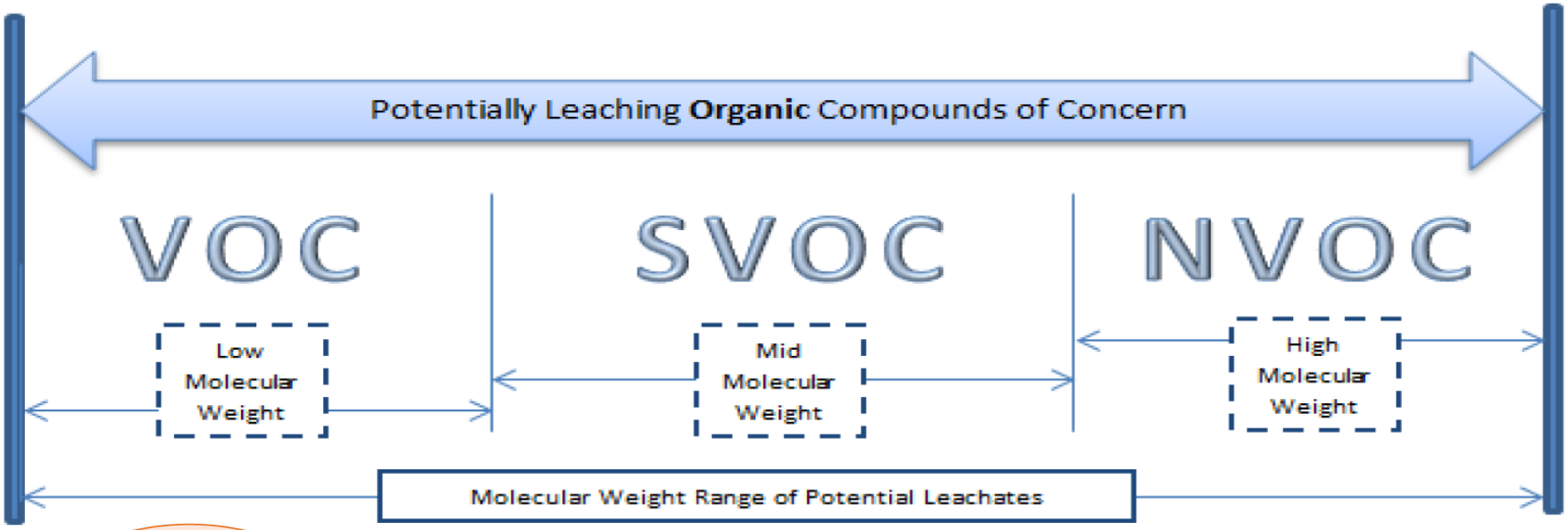
- -Using suitable solvents (e.g. water, ethanol and hexane) selected based on the material in question.
- -Extraction following exaggerated conditions such as boiling to reflux or soxhlet sonication.

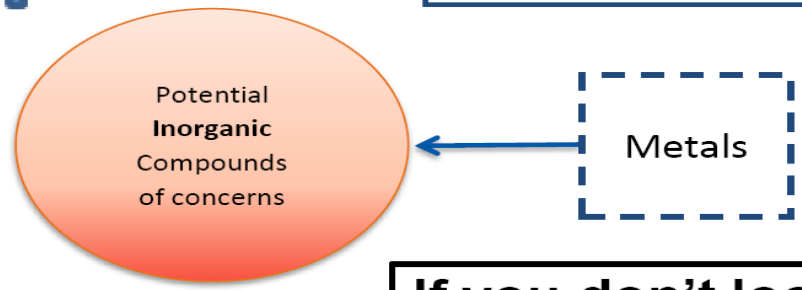
2. Analytical techniques

- Gas chromatography/mass spectrometry (GC/MS), liquid chromatography/mass spectrometry (LC/MS),
- Inductively coupled plasma-mass spectrometry (ICP/MS), headspace GC/MS.

Approaches to E/L studies

Extractable/Leachable sources



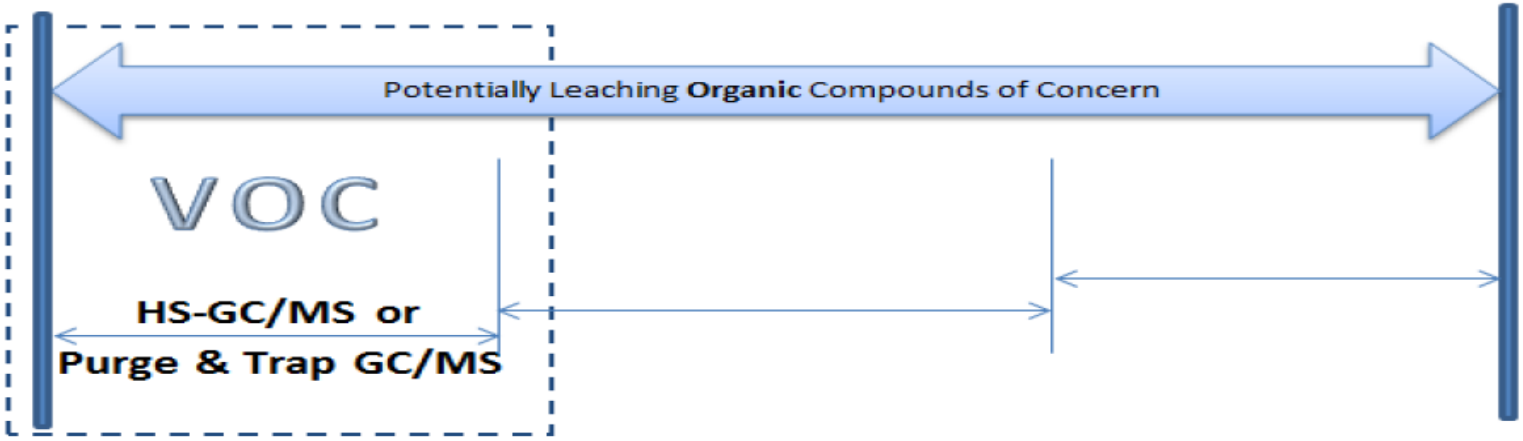


If you don't look for it, you won't find it!

Approaches to E/L studies

Volatile Organic Compounds:

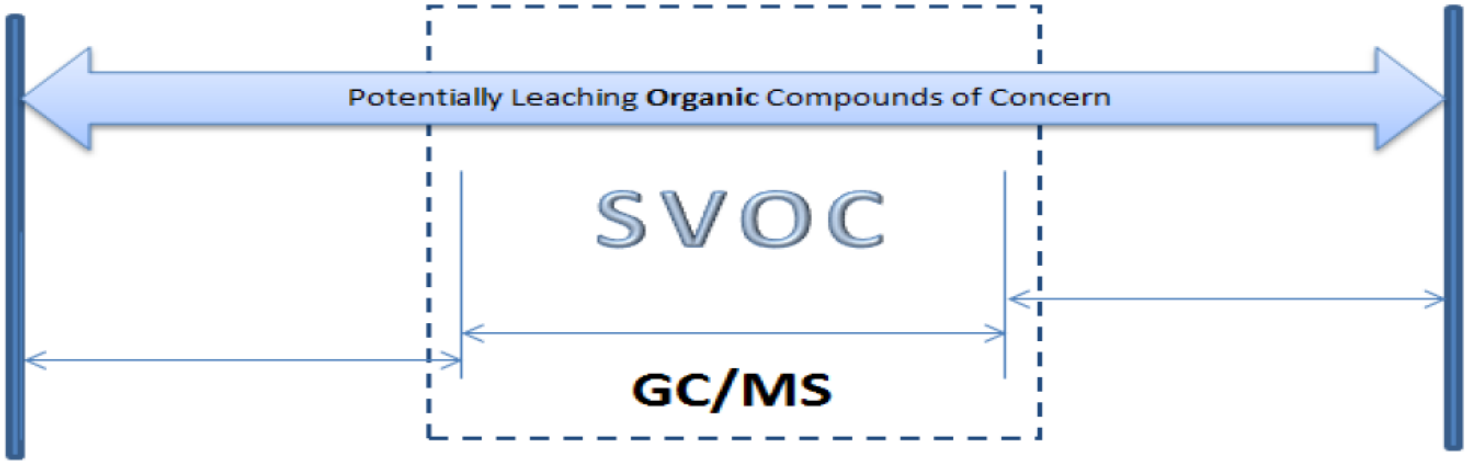
- *Monomer Residues*
- *Solvent Residues from Production steps*
- *residues from polymer treatments (e.g. washing)*
- *Small Polymer Breakdown products*



Approaches to E/L studies

Semi-Volatile Organic Compounds:

- *Lubricants*
- *Plasticizers*
- *Antioxidants*
- *Polymer degradation products*
- *Solvents with an elevated boiling point*



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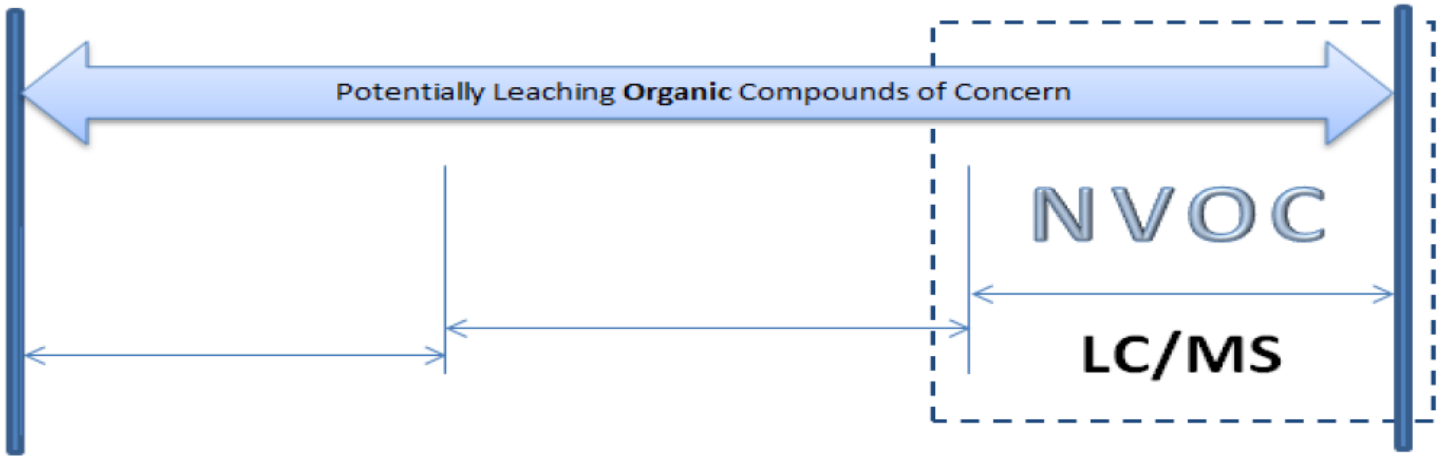
Approaches to E/L studies

Non-Volatile Organic Compounds:

- *Fillers*
- *Plasticizers*
- *Antioxidants*
- Polymerization or Hydrogenation *Catalysts*
- *Anti-slip agents*



Common Analytical Techniques

Analytical Technique	Detects	Identifies	Quantitative
Headspace GC/MS	Very Volatile Organics	Yes	Yes
GC/MS	Volatile to Semivolatile Organics	Yes	Yes
HPLC-DAD-MS	Semivolatile, Non volatile Organics	Yes (hopefully)	Yes
ICP/OES (MS)	Elemental	Yes (not valence)	Yes
Gravimetric/FTIR	Mass and General Compound Class	Characterizes	Not at trace level
IC (Anion)	Anions	Possibly	Yes

Conclusion of The Chapter

- Different types of drug dosage has to be packed with proper packaging.
- Several analytical methods can be used for extractables and leachables studies in pharmaceutical.
- This study plays a main role in pharmaceutical industry.

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Any Question?

Please refer to:

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