

I want to use material X in an OINDP: What do I need to do?

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Summary

Selecting materials for use in OINDPs (Orally Inhaled and Nasal Drug Products) is a complex challenge. In addition to acceptable biological and physical characteristics the major area of activity in selecting a new material is in testing and evaluating extractables. This article focuses on method selection options for extractables and leachables, with particular emphasis on the controlled extraction studies. The requirements for limits of detection are also discussed. It also, briefly covers supplier interactions and their importance for easing the challenges associated with extractable and leachable testing. Evaluating the potential for interaction between the active ingredient(s) and contact materials is another area that can be important for OINDPs.

Introduction

Selecting materials for use in OINDPs (Orally Inhaled and Nasal Drug Products) can be a complex challenge if all aspects are considered. One of the most important areas to consider when selecting materials is the potential for leaching of species from the materials. The leaching of species from the container closure system is a very important area for OINDPs and especially for pressurised metered dose inhalers (pMDIs) which combine a high degree of concern associated with route of administration with a high likelihood of packaging component dosage interaction. See Table 1 below[1]. A controlled extraction study is key in ascertaining the potential leachables

Table 1 Risks associated with various pack types

Degree of Concern Associated with Route	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

The reason for this potential leaching, is the long term contact of polar solvent, primarily the fluorinated hydrocarbon propellant, with polymeric and elastomeric critical components. The most critical components are those that contact either the patient or the formulation, components that affect the mechanical performance of the device, or any necessary secondary protective packaging.

In a pMDI, extended contact with the polar solvent (propellant) can result in leaching of chemical species from both the polymeric and elastomeric materials. Consequently, extractables and leachables require extensive study. In addition to the valve and the can, other potential sources of extractables and consequently leachables include secondary packaging and labels. For other OINDP dosage forms such as DPIs (Dry Powder Inhalers) and nasal sprays that do not have the prolonged exposure to a polar solvent the levels of leachable species are typically lower. However extractable testing of the critical components is required. To help understand what testing is required, the following definitions are useful;

Extractables: Chemical Species that migrate from packaging materials under appropriate solvent, temperature and time conditions. Using the latest guidance the extractable testing that is required is

well defined with appropriate limits that are based on dosing regime and the amount of material present in the device.

Leachables: Chemical species that are found in the product under normal conditions. Leachables should always be a subset of extractables. Leachables can therefore be correlated with the extractables from contact materials.

Guidance Available

General guidance has existed for a number of years [1-5] but these have lacked some details on the basic approach to performing extractable and leachable testing and also suitable target LOQs and LODs. This has been rectified by the recent PQRI document L/E recommendations to the FDA [6]. A number of important points raised in these recommendations are mentioned below.

Extraction techniques

Controlled extraction involves extracting from the material in question. Typically for pMDIs, at least three solvents of differing polarities (typically dichloromethane, iso-hexane and an alcohol, methanol, ethanol or isopropanol) with at least one of the following techniques: Soxhlet, sonication, microwave, thermal desorption, headspace –including solid phase microextraction (SPME), supercritical fluid extraction (SFE), ASE (Accelerated Solvent extraction) and shaking [7]. In addition, for DPIs, solventless extraction techniques may be employed.

Each of the above techniques has their own strengths and weaknesses, which are summarised in Table 2 below.

Table 2: The pros and cons of various extraction techniques

Equipment	Pros	Cons
Soxhlet	Standard equipment	Slow
Reflux	Standard equipment	
Sonication	Can be quick, equipment easily available	Possibly not the most efficient extraction
Microwave	Fast, high efficiency	Possible additional curing of elastomers
Thermal desorption	No solvent interaction	Extraction will depend on volatility of species
Headspace incl SPME	No solvent interaction	Extraction will depend on volatility of species
Supercritical fluid extraction (SFE)	Could mimic the same solvents	Difficult and expensive to set up
Shaking	Easily automated, fast, high throughput capacity	Efficiency to be determined
ASE (Accelerated Solvent extraction)	Very fast, very efficient	Labour intensive to prepare samples
Sealed container (eg autoclave)	Fairly standard equipment and easy to set-up	Limited on temperature

For the controlled extraction studies a wide range of analytical techniques should be employed to quantify and where required identify the extractable species. The selection of techniques depends on a number of factors. These factors would include but not limited to, the following;

- Solute characteristics (what is the target Compound)
- What is the matrix
- Concentration level of solute (% - ppb)
- Molecular weight (impact on volatility)
- Polarity (determines volatility, solubility adsorption etc)
- Log P
- Functional groups
- Thermal stability and reactivity
- Chromophore/detectability

Figure 1 below shows a potential aid for selecting the most appropriate analytical technique based on molecular weight and polarity. However, selecting the most appropriate analytical technique requires the inclusion of a number of other factors. This can be summarised in the feedback diagram in Figure 2 below. The analytical method requires feedback from the various aspects required of the method along with potential limitations such as limits with sample preparation, the sample matrix etc. By talking to the material supplier and possibly their supplier, a list of ingredients are available and hence their physical and chemical properties will be available to help choose the most appropriate sample introduction and detector selection areas. Without understanding the various aspects of the entire process it is very difficult to develop a suitable analytical method. The method feedback also requires the knowledge and understanding of the analytical evaluation threshold (AET) which is derived from the safety concern

threshold (SCT) of 0.15 µg/day. The AET is defined as the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment. The calculation for the estimated AET is shown below. The estimated AET is converted to the final AET by taking into account any uncertainty in the method by either using a response factor of 50% or a statistical approach based on common response factors which ever is the greater. For pMDIs the AET is of the order of 1-10 ppm but is dependent on the dosing regime.

$$\text{Estimated AET} = \left(\frac{0.15 \mu\text{g/day}}{4 \text{ actuations/day}} \times 60 \text{ labeled actuations/canister} \right) = 2.25 \mu\text{g/canister}$$

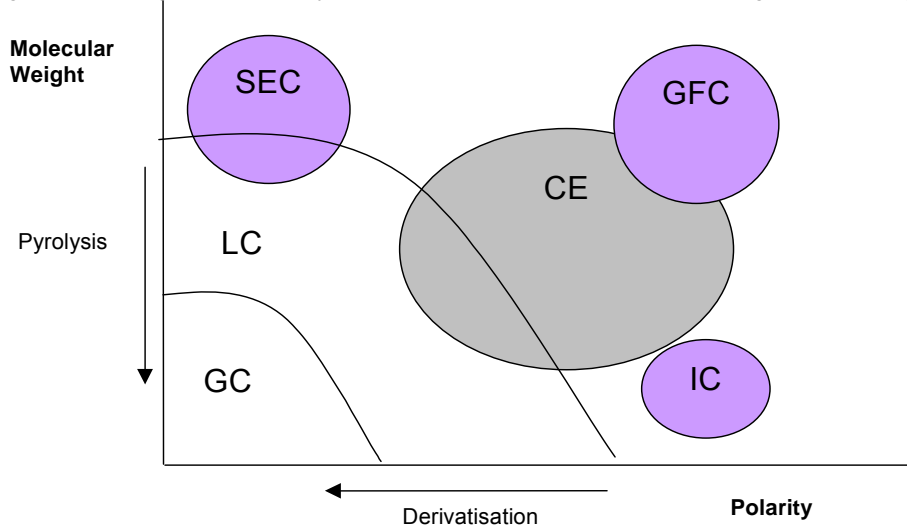
Converting to an Estimated AET for individual extractables in an extractables profile of a particular elastomer:

$$\text{Estimated AET} = \left(\frac{(2.25 \mu\text{g/canister}) \times (1 \text{ canister/valve})}{0.25 \text{ g elastomer/valve}} \right) = 9 \mu\text{g/g}$$

There are two AET's one being derived from the other. Shouldn't they be titled differently.

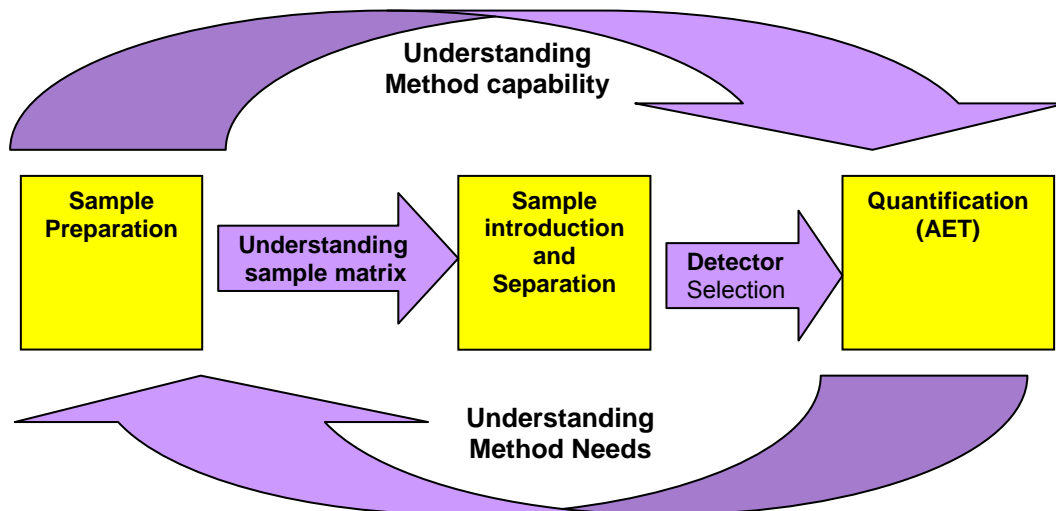
Final AET = 4.5 µg/g

Figure 1 showing possible analytical techniques based on molecular weight and polarity



In general pyrolysis can reduce the molecular weight allowing high molecular weight species to be analysed by GC and by utilising derivatisation, species can be analysed by HPLC or GC.

Figure 2 showing the feedback loop required to develop a suitable extractable or leachable analytical method



These analytical techniques typically include hyphenated techniques such as gas chromatography and liquid chromatography, often run in gradient mode, with mass spectrometry but could also include various other detectors where particular selectivity and specificity is required. These detectors can include, for GC, flame ionisation detector (FID), nitrogen phosphorous detector (NPD), thermal energy analyser (TEA) and electron capture detector (ECD). For HPLC these can include UV, charged aerosol detector and evaporative light scattering detector. Total organic carbon (TOC) could be used to help determine that all the potential extractable species have been identified. No single technique and/or detector can hope to complete the complete suite of extractable and leachable analysis. For non-volatile species analytical techniques can include Inductively Coupled Plasma (ICP) and Ion Chromatography (IC). For routine extractable testing, simplified or more routine detectors may be employed, such as LC-UV and GC-FID. The appropriate method development guides should be studied for each of the appropriate analytical techniques.

Special cases (Species that give rise to specific safety concern)

There are an additional three classes of compounds that are deemed special cases and they have even lower limits than the safety concern threshold (SCT) of 0.15 µg/day and primarily use specialised analytical techniques. The limits for these species can be defined as ALARP limits (As Low As Reasonably Practicable).

- N-Nitrosamines require testing with limits at the ppb level and typically use gas chromatography with thermal energy analyser. Advances with GC-MS mean sub ppb is possible with standards but still in the ppb range when a sample matrix is introduced.
- PNAs or PAHs (Polynuclear Aromatics), these originate from the use of carbon black as additives. Even though carbon black is no longer typically used the testing of PNAs is still required. GC-MS is used to identify the PNAs, typically at or below ppm level.
- 2-Mercaptobenzothiazole an additive in sulphur cured elastomers.

Important areas

Other key areas that need to be considered when selecting materials are supplier interactions, including along as much of the supply chain as possible. From the final device manufacturer (known as N-1) through to the base polymer supplier (known as N-2 or N-3). By having clear communication, an understanding of the composition of materials and their manufacture can aid dramatically in material selection and testing. The importance of communication along the supply chain cannot be overstressed. In some cases, with new suppliers to the pharma industry, an understanding of the importance of communicating and managing change needs to be explained. An excellent guide for suppliers is available from the IPAC-RS [9]. In addition, interactions between the materials and the drug substance need to be considered and investigated.

Conclusion

This article has covered briefly some of the challenges and issues with selecting materials for OINDPs, primarily extractable and leachable testing. Developing an understanding of the component materials that are used to manufacture OINDP's along with suitable controls, is a critical part of the quality management system which will result in safer products for the patient. This can be achieved by a suitable extractable and leachable testing program, which uses a wide range of trace organic analytical techniques. This is underpinned by good supplier interactions.

References

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- 5 "Development of Scientifically Justifiable Thresholds for Leachables and Extractables" Product Quality Research Institute (February 2002)
- 6 "Safety Thresholds and Best Practises for Extractables and Leachables in Orally Inhaled and Nasal Drug Products" Developed by PQRI submitted to the FDA September 2006
- 7 Anatum application note AS61S
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- 9 IPAC-RS Good Manufacturing Practices Guidelines for Suppliers of Components for Orally Inhaled and Nasal Drug Products