Extractables and Leachables Case Studies for Personal Hygiene Products and Inhalation Drugs: Challenges and Solutions

By Barbara Pavan, Ph.D.

About Impact Analytical

Impact Analytical is a contract analytical testing laboratory that provides testing for four main sectors: specialty chemicals including polymers and silicon materials, medical devices, pharmaceuticals, and agricultural products. Impact Analytical provides release testing, R&D support, method development and validation, extractable/leachable studies, stability studies, actives quantitation, raw materials testing, problem solving, and competitive analysis. Impact Analytical is ISO 9001:2015 certified, DEA licensed, FDA registered, cGMP and GLP compliant.

Introduction

Continuous monitoring of extractables and leachables is of paramount importance in evaluating the safety of a finished product for both the pharmaceutical and consumer products industries. Examining the materials' extractables over time and across different lots can show how production processes and raw materials sources affect the extractable profile in the finished product. This type of evaluation is critical when products come in contact with the human body for extended periods of time.

Leachables evaluation for inhalation drug products is included as part of their stability assessment. Both the nature of the drug and the inherently low detection limits required for inhalation products can make the development and validation of analytical methods particularly challenging.

Consumer Products

The consumer products industry has become sensitive to potential extractables & leachables from their products, especially if they come into contact with the body, such as in personal hygiene products. We examined the extractables from one of these products which is comprised of a plastic and a natural fiber component.

The extraction conditions used for the study can be considered "mild", since neither high temperature nor reflux conditions were used, but the extractions were performed at room temperature. For the LC-MS and GC-MS analyses the extractions were performed using two media: water and methanol, for 2 hours without agitation. For the ICP-OES analysis, the extraction was performed for 24 hours using a 10% v/v HNO_3 solution and gentle agitation.

A complex panel of methanolic extractables were identified from the plastics. No significant extractables were obtained from the water extraction. The most relevant chemicals found were esters of fatty acids, ethoxylated oleic acid, erucamide and oleamide, fragrances, and the antioxidants Irganox PS800, 1076, and Irgafos 168 and its oxidation product. Throughout the analysis of different lots/products we observed a similar presence of the fatty acids, but differences in the slip agents used (erucamide vs. oleamide) and the antioxidants. Monitoring these chemicals provides a mean to track variability between lots and products, raw materials suppliers and production processes.

Several extractables were identified from the natural material, from both water and methanol media. The most relevant extractables were fatty acids (i.e. oleic, erucic, nervonic) and their methyl esters, polyethylene glycol, glycols and their ethers, and fragrances. An unexpected extractable was Irganox PS800, which is used as an antioxidant and heat stabilizer for plastics. Its presence can be explained by the fact that the natural fibers are stored in contact with the plastic part of the product, thus some of the additives appeared to migrate from the plastic to the natural material.

Inhalation Drug Product

The leachables study of an inhalation drug product was performed as part of its stability evaluation. Two storage conditions were used: 25 °C/60 %RH and 45 °C/75 %RH, and the drug product

Extractables and Leachables Case Studies for Personal Hygiene Products and Inhalation Drugs: Challenges and Solutions

By Barbara Pavan, Ph.D.

About Impact Analytical

Impact Analytical is a contract analytical testing laboratory that provides testing for four main sectors: specialty chemicals including polymers and silicon materials, medical devices, pharmaceuticals, and agricultural products. Impact Analytical provides release testing, R&D support, method development and validation, extractable/leachable studies, stability studies, actives quantitation, raw materials testing, problem solving, and competitive analysis. Impact Analytical is ISO 9001:2015 certified, DEA licensed, FDA registered, cGMP and GLP compliant.

The target compounds were chosen from the results obtained in a previously performed extractable study. The low analytical evaluation threshold (AET) required for inhalation products, and the physical/chemical properties of the drug product itself made the method development and validation particularly challenging.

One of the greatest difficulties was the volatility of the drug product. During the storage, especially at the higher temperature, some of the containers leaked and were found empty. The analytical sampling had to be carefully done while chilling the drug container and the pipetting equipment to avoid unwanted “dripping” and loss of liquid from the tips. This volatility also created challenges in obtaining accurate spikes for the recovery studies.

During the LC-MS validation, the data acquisition included both positive and negative (APCI) modes to ensure no analyte was missed, thus increasing the analysis and data processing times. Some linearity issues were encountered, for example with Irganox 1076, causing a reduction of the available linear range. Finally, common to all the analytes of interest, was the difficulty of achieving the desired sensitivity due to the technical limitations of the instrument combined with the low required detection limits.

The GC-MS method development and validation were greatly affected by the volatility of the drug product. For example, the drug product could not be directly injected from an autosampler vial, since it was evaporating in the syringe. In order to be able to use autosampler vials, the drug product was diluted 50:50 with a suitable solvent. This introduced a 1:2 dilution factor, affecting the sensitivity and resulted in the screening of several solvents to insure they did not exhibit any co-eluting impurities that could interfere with the analysis and had the desired properties. Volatility was also an issue for the Head Space (HS) GC-MS analysis, where greater care was necessary during the sample preparation to insure all the vials were properly sealed. Interestingly, variability of performances (peak separation and shape) was observed between different column manufacturers, thus practically restricting the choice of viable columns. Finally, in order to achieve the desired sensitivity, all the GC-MS analyses had to be completed both in SCAN and SIM modes (for quantitation), causing lengthy analysis and data processing times.

The greatest difficulty in the ICP-MS method development was the immiscibility of the drug product with water. In order to properly spike and perform the recovery study, methanol was chosen as the spiking solvent, where the elements of interest were dissolved. After spiking of the drug product, a quick extraction into water by manual shaking was performed for the analysis. The use of methanol, even in trace amounts, caused extremely high mercury recoveries. This was solved by limiting the amount of methanol used for the spikes, and by preparing spiking solutions with different concentrations of the elements of interest.

The results of the first 6 months of analyses indicated that in general more leachables were present in the drug products stored at higher temperature and humidity, and in the inverted bottles with respect to the upright containers. The amount of leachables was increasing for all the components until the 3 months data point, at which the concentration of some leachables appeared to level off (for example, dodecane and zinc), while for others it continued to increase (for example Irganox 1076 and ox-Irgafos 168). Some exception to these trends were found for the oxidized Irgafos

Extractables and Leachables Case Studies for Personal Hygiene Products and Inhalation Drugs: Challenges and Solutions

By Barbara Pavan, Ph.D.

168 which was detected only at the higher temperature storage conditions, and for Irganox 1076 (LC) and aliphatic hydrocarbons (HS-GC), for which a similar trend for the upright and inverted containers was observed.

Conclusions

Extractables and leachables studies are of interest for both the pharmaceutical and consumers product industries. Data obtained can be used to monitor how a material change over different lots, and over time and different manufacturers/suppliers, thus ensuring the final product safety for the consumers. Leachables studies for inhalation drug products pose a challenge for their method development and validation, due to the inherently low AET. In addition, the nature of the drug itself can affect the method development, requiring some creative solutions to obtain methods with the desired performances.

About Impact Analytical

Impact Analytical is a contract analytical testing laboratory that provides testing for four main sectors: specialty chemicals including polymers and silicon materials, medical devices, pharmaceuticals, and agricultural products. Impact Analytical provides release testing, R&D support, method development and validation, extractable/leachable studies, stability studies, actives quantitation, raw materials testing, problem solving, and competitive analysis. Impact Analytical is ISO 9001:2015 certified, DEA licensed, FDA registered, cGMP and GLP compliant.