Packaging

Illegal migration

Consumer protection requires that harmful chemicals be prevented from gaining access to food products or pharmaceuticals designated for human consumption. While packaging generally keeps products fresh and protects them from direct contamination, materials used to manufacture the packaging can themselves be an unintended source of migrating chemicals. Apart from performing routine migration studies, food producers or packaging suppliers need to determine barrier properties of primary food packaging. In the case of pharmaceutical packaging, leachables and extractables studies are required to determine if packaging will leach contaminants into the product under normal storage conditions or if contaminants can be extracted by the product under well-defined more aggressive conditions. Thermal desorption combined with GC/MS has proven to be an efficient and sensitive screening method for contaminants in packaging

Modern packaging and packaging materials offer tremendous advantages with respect to hygiene, product freshness, easy handling, efficient transport, extended storage time, low price and a clear product declaration. But as with every advantage in life, there is a trade-off. Use of these materials can involve risk: Solvents, additives and pigments are used in the production of and printing onto packaging materials and these may contaminate the packaged product. A careful assessment of potential risks needs to be made in order to protect consumers and/or patients against harmful migration of unwanted by-products of packaging production.

Food packaging: the aim of migration studies is to demonstrate whether chemicals contained in or on the packaging, such as plastic additives, pigments, printing solvents or bonding systems, remain where they are or migrate into the food. The studies are generally carried out with three food simulants under standard conditions (e.g. 10 days at 40°C). The substances used are: aqueous acetic acid, an aqueous alcoholic solution, and edible oil. These studies determine is the concentration of the target compound in the food simulant during and/or after the incubation period. The results are used to define specific migration levels (SML) for the target substance. The target compounds are approved in general for the plastic tested and/or for the application in question based on the SMLs. Approved and/or acceptable limits for SMLs are defined in regulations issued by the appropriate agency (see box).

Regulations on extractables & leachables studies for pharmaceutical packaging

- EU Pharmacopeia Chapter 3, incl. Supplement 5.1, 5.2 & 5.3
- USP e.g. <381> for elastomers, <661> for polymer characterisation
- FDA Guidance for Industry: Container Closure Systems for Packing Human Drugs and Biologics
- FDA Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
- FDA Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products
- EMEA CPMP/QWP/4359/03, Guideline on Immediate Packing Materials
- EMEA CPMP/QWP/2845/00, Note for Guidance for Metered Dose Inhalation Products Packing Materials
- EMEA CPMP/QWP/158/96, Note for Guidance on Dry Powder Inhaler

Regulations on migration studies for food packaging

- FDA Guideline: "Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations" (December 2007)
- EU Directive 82/711/EEC (including amendments)
- EU Directive 85/572/EEC
- EU Directive 2002/72/EC

Pharmaceutical packaging: the aim of what is known as "extractables & leachables" (E&L) studies is to demonstrate whether the packaging of a pharmaceutical product is safe and/or whether the drug contained is being contaminated by migrating chemicals. The necessary tests are performed in two stages.

1. "*Extractables" study:* a worst-case scenario is simulated, in which the pack is extracted with solvents of varying polarity and at a high temperature without destroying it. Extensive analytical characterization is performed of the obtained extracts, in order to gain as complete a picture as possible into all the compounds that might potentially contaminate the pharmaceutical.

2. "*Leachables" study:* following a toxicological evaluation of the "extractables" study, substances classified as critical are analyzed in the pharmaceutical itself using validated methods. This is generally performed during stability testing.

Incidentally: there are no official upper concentration limits for "extractable" substances; each E&L study has individual characteristics and has the aim of identifying potentially risky compounds in each specific case and of investigating them in detail.

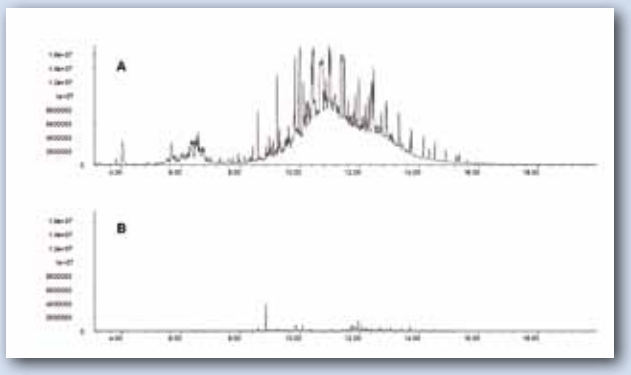
Migration tests and E&L studies are to some extent performed based on official standard methods and regulations. Numerous very different techniques and methods are used in order to get a complete picture. Once the complete puzzle has been meticulously put together, the information can be used to optimize any packaging system with regard to migration properties.

Thermal desorption GC/MS (TDS-GC/MS) plays a key role in seeing the whole picture. The technique is more efficient than practically any other in determining the emission potential of volatile and semi-volatile organic compounds from packaging materials. In addition, thermal extraction is a solvent-free extraction technique, which means that peaks of interest are not masked by solvent. Potential analytes are oligomers from polyolefins, anti-oxidants and their degradation products, plastic additives, solvents from printing inks, plasticisers, monomers from bonding systems, contaminants from pigments, photoinitiators, countless compounds and compound classes from recycled board like diisopropylnaphthalene, phthalates or hydrocarbons. If required, the initial screening with TDS-GC/MS can be followed by further analyses using liquid extraction combined with GC/MS, LC/UV, LC/MS, elemental analysis, TOC etc.

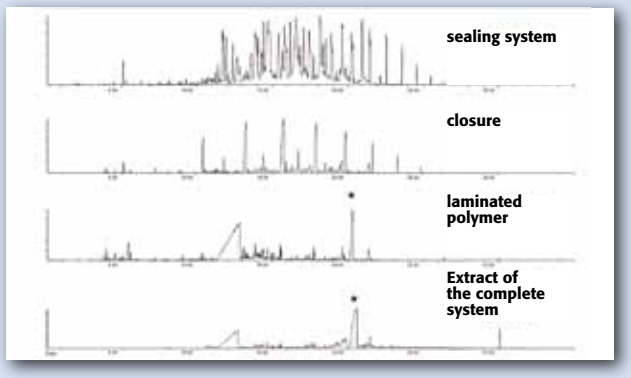
Migration from food packaging

A food product is stored in nine different plastic primary packs, including polyole-

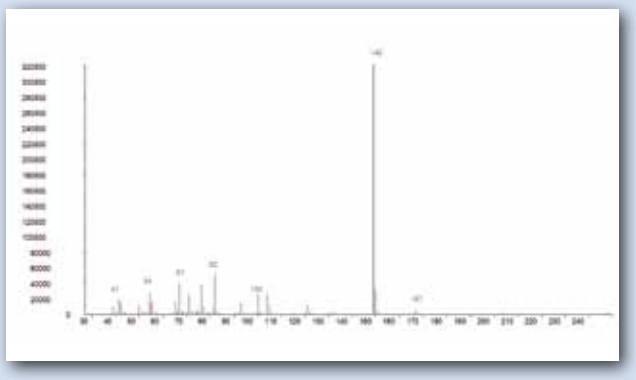
Recycling brings advantages, but also involves risks due to the potential of significant contamination. GC/MS chromatogram of identical quantities of recycled (A) and newly produced (B) paper board, following thermal desorption in the TDS.



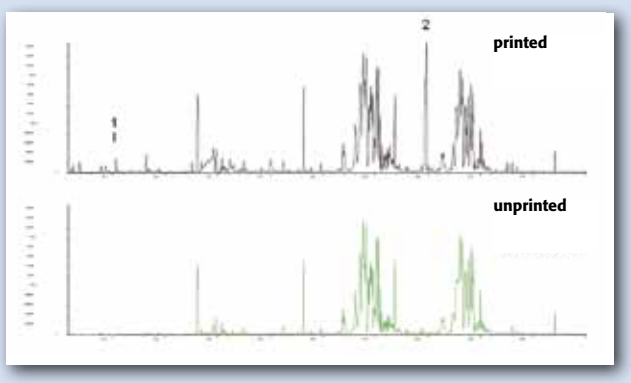
TDS-GC/MS chromatograms of individual parts multicomponent pharmaceutical packaging system as well as an organic extract. It was not possible to identify the compound marked with * just based on GC/MS.



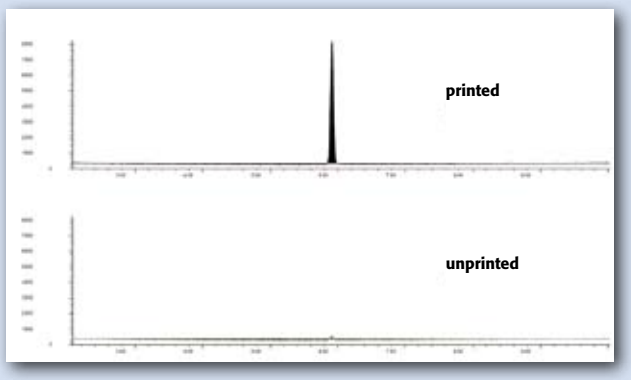
EI mass spectrum of the unknown compound in the laminated packaging system. The dominating fragment at 149 m/z gave a strong indication that this compound is a phthalate.



TDS-GC/MS chromatogram from a sample of a polymer packaging material onto which text has been printed (A) and packaging material without printed text (B) for a pharmaceutical product. Compound 1: benzene; compound 2: diphenyl sulphide.



Comparison of two HS-GC/MS chromatograms (SIM mode) of pharmaceutical product stored in A: Polymer packaging material onto which text has been printed; and B: Polymer packaging material onto which no text has been printed. The compound shown is benzene.



fin films, laminated multilayer film systems or metallised films. They in turn are in a secondary pack made from recycled board. In order to obtain an impression of the migration kinetics in the packaging system, the food is investigated by TDS-GC/MS after different storage periods to determine marker substances from the recycled board, in this case diisopropylnaphthalene isomers (DIPN). The aim is to find the primary container / packaging with the best barrier properties.

Procedure: the food is homogenized and a 50 - 100 mg sample is transferred to the thermal desorption tube. Volatile compounds are then extracted from the food sample at temperatures between 150 and 200°C under a flow of inert gas. The volatile analytes are trapped on a suitable adsorbent (e.g Tenax) in the Cooled Injection System (CIS), a PTV_type GC inlet, which is kept at -50°C. After trapping is complete the CIS is heated and the analytes are transferred to the GC column. GC/MS determination is performed in Single Ion Monitoring (SIM) mode.

Result: It was determined that the DIPN concentration in all packaged foods increased over time. In other words: no polymer-based primary packaging material represented an absolute migration barrier even though some were very good. Simple polyolefin systems tended to be much poorer barriers to migration than, for example, complex laminates or metallized polymer films.

Migration from laminated pharmaceutical packaging

An "extractables" study was performed on a laminated multicomponent pack consisting of the following individual components: flexible bag, sealing system, closure, catheter system etc. The pack contained a liquid, lipophilic pharmaceutical product. The study strategy involved initially determining individual compounds in the lipophilic product by TDS-GC/MS. The multicomponent pack was then emptied, refilled with a non-polar solvent, and stored at high temperature (worst-case scenario). The resulting extract was subsequently analyzed and several compounds were identified and quantified.

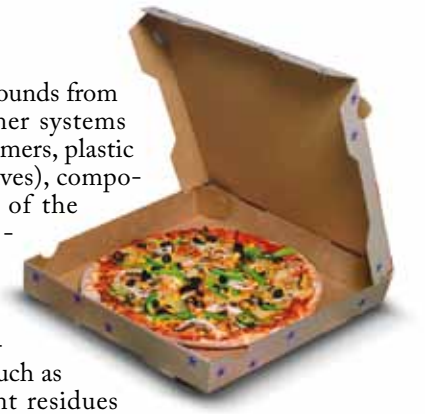
One component, present at a concentration of >100 ppm, could not be identified, however, comparison of the extract chromatogram with the chromatogram of the individual components finally revealed the source: the laminated polymer material. The mass spectrum of the unknown component indicated that it was a phthalate, since the main fragment was observed at m/z = 149. However, no commercially available phthalate was identified that corresponded to the unknown compound in terms of its chromatographic characteristics and mass spectrum.

The molecular weight of the unknown compound was determined by Chemical Ionization (CI)-MS and the empirical formula was subsequently determined using high-resolution Electron Impact Ionization (EI) -MS and the main fragment (m/z = 149) was clearly associated with the empirical formula $C_8H_5O_3^+$, which is a typical phthalate fragment. The TDS-GC/MS analysis of the individual polymer materials and adhesives finally showed that the compound came from an adhesive component. According to the manufacturer of the adhesive, it was based on a polyester diol, consisting of phthalic acid and diol units, which allowed conclusions to be drawn about the a proposed structure (low-molecular degradation product of the polyester diol). The compound was subsequently synthesized, cleaned, structurally characterised (^{1}H and ^{13}C-NMR), qualified and analyzed as a reference by GC/MS at Ciba Expert Services. Result: Both the GC retention time and the mass spectrum matched those of the "unknown" compound.

A toxicological evaluation of the compound then provided a specification of the acceptable daily dose. With the help of the synthesized reference and use of specific and sensitive analytical procedures (LC/MS), the compound was detected in the pharmaceutical product that was stored in the packaging system, although the level was lower than the specification. Conclusion of this study: The source of a highly concentrated extractable compound in a multi-component packaging system was quickly and easily identified by performing thermal extraction of the individual packaging components using TDS-GC/MS. The available analytical and chemical expertise enabled us to determine the structure of the compound. Further leachables studies had to be performed in order to demonstrate that the compound does not migrate from the packaging into the stability sample in any significant concentration even after a lengthy storage period.

Migration from printed pharmaceutical packaging

A further extractables study focused on polymer-based pharmaceutical packaging, onto which information had been printed. The content was a liquid, aqueous pharmaceutical product. The strategy followed in this study was the same that was used in case study II: At first, TDS-GC/MS screening of the printed and unprinted polymer was performed. Subsequently, the packaging was filled with a polar solvent and stored at an elevated temperature (worst-case scenario). The extract was then analyzed using a variety of different methods. Apart from typical extractables



compounds from polymer systems (oligomers, plastic additives), components of the printing formulation such as solvent residues and degradation products of the photoinitiator – a triaryl sulfonium salt – were found in the printed polymer. Benzene (a carcinogenic compound) was one of the substances involved, a targeted analysis was performed to determine the benzene concentration in the polar extract of the printed polymer using HS-GC/MS, with quantification in the ppm range.

The HS-GC/MS method was validated in accordance with ICH rules in a subsequent leachables study. Benzene in the 1 ppb range was quantified in stability samples of the pharmaceutical product (stored in the printed pack). The presence of this carcinogenic substance requires a risk assessment to be performed: whereas the administration of about 1 mL of a pharmaceutical product (typical for pre-filled syringes) per day (corresponds to 1 ng of benzene) represents a comparatively negligible risk for patients, the administration of one litre of a pharmaceutical product– which happens in infusions, for example, and corresponds to the intake of about 1 µg of benzene – proves to be a risk the patient should not be expected to take.

Conclusion: benzene was easily identified in a polymer pack with the help of TDS-GC/MS screening. The printed packaging system was then extracted and the extract analyzed to determine the benzene concentration specifically. Finally, the benzene concentration in the pharmaceutical product was determined as well.

Thermal desorption GC-MS can provide detailed information on properties of packaging material in terms of barrier functions as well as migration, leaching or extraction of chemicals from the material into the packaged product. TDS-GC/MS enables efficient screening for trouble shooting as well as support for development of suitable packaging of food and pharmaceutical products as demonstrated in the case stories described in this article.

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