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Compatibility of packaging materials for pharmaceuticals

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Plastics have become indispensable as packaging materials for food items and medicinal products. In order to cover the demand of Swiss private households alone in this area, we require 300 000 metric tons of plastic annually[1]. A wide variety of materials is used in order to protect the products against environmental influences in the best possible way, and to make dispensing and dosing the product as easy as possible for the consumer. Depending on the purpose, the materials utilized exhibit certain properties that require the use of additives. For instance, plasticizers are applied in order to ensure the flexibility of the plastic over a long period of time. However, such additives, when combined with other ingredients such as monomers or byproducts from the manufacture, can pass into the product itself by means of diffusion or migration.

A well-known example within this context is the compound bisphenol A. This substance is used as the base material for manufacturing various plastics and as an antioxidant for plasticizers. Therefore it may be contained in various packaging products, such as beverage cans, milk cartons and bottles[2].

Due to the hormone-like effect of bisphenol A, a controversial public debate on its use in plastics manufacturing and the potential health risks of plastic packaging was conducted. This example illustrates that when developing packaging, in addition to safe handling, we must also consider safety-related aspects with regard to the potential migration of substances contained in the construction materials into the product, and consequently into the consumer's organism.

The planning and conduct of studies in this area is complex as the reciprocal effects involving the separation of ingredients contained in the packaging material, and subsequent migration thereof into the product, are dependent on both the storage conditions and the temperature. For pharmaceuticals, the United States Pharmacopeia (USP)[3] can be referred to as a basis for guidance. It details the systematic approach to compatibility testing of packaging with respect to patient safety.

1 Process overview

1. Step

Material Assessment; Characterization, Screening and Selection

Characterize materials of construction, and determine that they are appropriate for their application; *USP <661.1>*

2. Step

Packaging System Assessment and Qualification

Test packaging system for extractables and assess the potential safety impact of the xtractables profile; *USP <661.2>* with reference to *<1663>*

3. Step

Product Assessment and Qualification

Test the packaged product for leachables, and assess the potential safety impact of the leachables profile; *USP <661.2>* with reference to *<1664>*

The entire process in three steps (see 1)

The **first step** concerns the base materials of the packaging material. In this step, the manufacturing materials are subjected to detailed testing, including the following tests:

- Identification
- Testing for extractable components (so-called extractables, such as metals)
- Biocompatibility

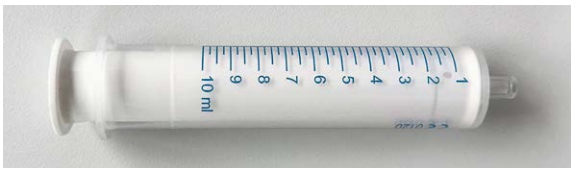
Details on the performance and the recommended specifications of the individual tests are described in section 661.1 of the United States Pharmacopeia.

During the **second step**, the finished packaging system is tested. It may consist of numerous individual components, and in some circumstances, it may have passed through various processing steps. In addition to a number of simple tests on extractables, the analytical process entails a biocompatibility test. Furthermore, a profile of the extractables is created by means of specific extraction tests. Based on the resulting data, an initial risk assessment with respect to the long-term storage of the product can be made. For further information, please refer to sections 661.2 and 1663 of the United States Pharmacopeia.

During the **third step**, the potential reciprocal effects between the product and the packaging system during long-term storage are tested. These tests include comprehensive testing of the product for components of the packaging material, which may migrate during storage under standard conditions and contaminate the product. These substances are generally referred to as leachables.

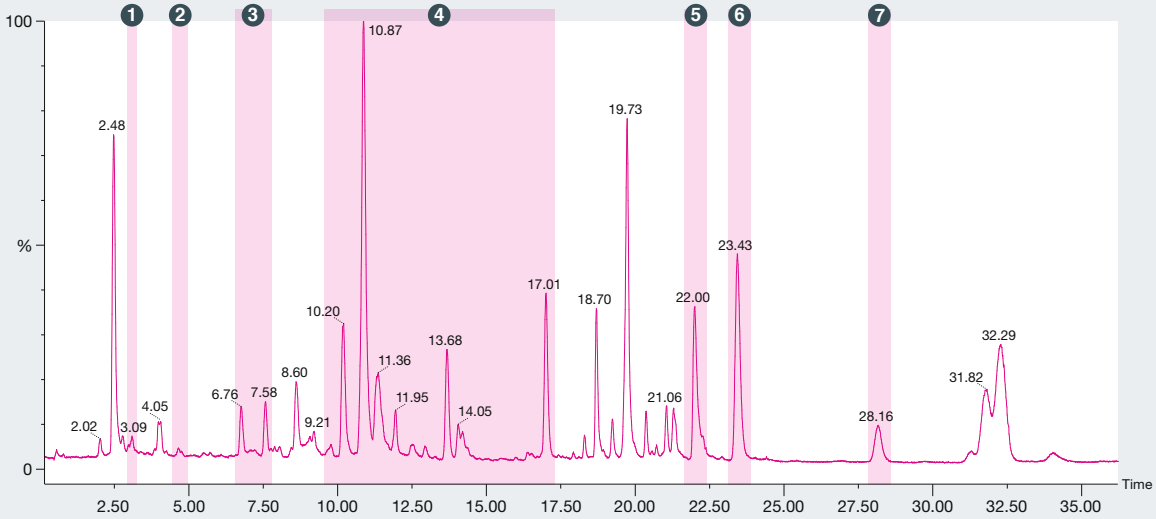
The scope and level of detail of the studies are primarily dependent on the formulation of the medicinal product and on the method of administration. For instance, liquid and solvent-containing medicinal products carry a significantly greater risk of being contaminated as a result of packaging components migrating into the product during storage than solid pharmaceutical forms, such as tablets, do. In terms of the pharmaceutical form, products that are inhaled carry a greater risk of impairing patient health through leachables than this would be the case for products administered orally or topically.

PRACTICAL EXAMPLE: analysis of an applicator



Based on the findings of the tests performed in steps 1 to 3, we can make a well-founded assessment of the suitability of a packaging system for the intended purpose pursuant to section 1661 of the United States Pharmacopeia.

2 Chromatographic profile of extractables



1 2 Degradation products of Irganox 1010
3 Stabilizer, mould separating agent
4 Lubricant
5 Antioxidant
6 Degradation product of Irgafos 168
7 Antioxidant

The identity of all signals of the chromatogram is known. For reasons of clarity, only the relevant signals were labelled.

In practice, this multi-stage process can be presented by means of a **polyethylene applicator for orally administering liquid medicinal products**.

Initially, information on the base materials of the applicator is collected in the first step. In the given case, the applicator is made of polyethylene, which, according to the manufacturer, contains only approved additives such as fatty acids, Irganox 1010 and Irgafos 168. In order to ascertain whether this information is correct and to gain a first impression of the extractables, the applicator is extracted with 2-propanol; the extract obtained is tested by UPLC coupled with a high-resolution mass spectrometer. As the chromatogram (see 2, previous page) shows, this process can detect numerous substances.

However, this experiment still does not allow for a reliable statement regarding practice, as more extreme extraction conditions were applied. Although no further conclusions can be made regarding the toxicological risk to the patient, the information obtained allows target substances to be defined. Next, as described in the second step, an extracting agent nearer in composition to the product is used, such as a propanol-water mixture. Following storage in an appropriate container, the actual product is then tested in accordance to the third step at the end of the intended shelf life. Sensitive methods for determining the analytes depicted in the chromatogram have been developed for this purpose; these methods are selective for the analytes in comparison with the composition of the product. Consequently, every study on the compatibility of packaging materials entails the development of an individual analytical procedure.

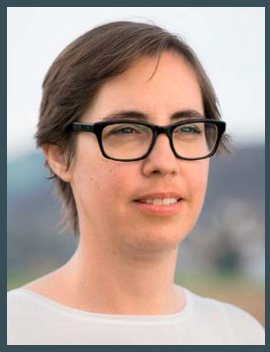
Conclusion

In order to ensure the safety of a packaging material with respect to the health of the consumer, we require not only a detailed knowledge of the packaging, the product and the production process, but likewise also analytical know-how and the appropriate instruments. Furthermore, we cannot fall back on standard methods. Instead we strongly recommend that prior to the market launch of a product, a tailor-made analytical packaging safety concept is prepared. □

References

1. *http://www.swissrecycling.ch/fileadmin/rd/pdf/wertstoffe/kunststoff/KURVE/KuRVe_Bericht_oeffentlich_01.pdf*
2. *Nutzen und Gefahren von Bisphenol A – BLV – Admin.ch (Benefits and risks of bisphenol A – FSVO)*
3. *USP 40-NF35; http://www.uspnf.com/*

About the author



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