PRIMARY PACKAGING MATERIALS AND THE EUROPEAN PHARMACOPOEIA

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Das Europäische Arzneibuch definiert bei Arzneistoffen die Identifizierung, die Reinheit und den Gehalt. Im Hinblick auf Primärpackmittel, die ja unmittelbar mit dem Arzneimittel in Berührung kommen, beschreibt Ph.Eur. im allgemeinen Teil (3.1) zunächst nur die Anforderungen an die Ausgangsmaterialien. An ausgewählten Beispielen wird auf die Identifizierung, Reinheit und Gehaltsbestimmung eingegangen. Dabei wird versucht, den prinzipiellen Aufbau und die „Philosophie“ dieser Monographien zu verdeutlichen. Die Identifizierung der Hauptkomponente erfolgt bevorzugt mit Hilfe der IR-Spektroskopie. Additive werden in zusätzlichen Tests chromatographisch (DC, HPLC) identifiziert und gleichzeitig quantifiziert. Die Anforderungen an die Reinheit sind in der Regel wesentlich schärfer als bei vielen Arzneistoffen. Typische Prüfpunkte sind saure, basische und reduzierende Verunreinigungen und vor allem Metalle (Aluminium, Chrom, Titan, Zink, Zirkon). Hinzu kommen in Spezialfällen zusätzliche Tests auf verschiedene Antioxidantien mit Hilfe der DC oder HPLC. Weitere Prüfpunkte wie z.B. Monomere finden sich im Abschnitt Produktion, sind also für den Hersteller des Ausgangsmaterials verbindlich und keine Prüfpunkte bei späteren Kontrollen. In dieser Sektion werden auch zulässige Additive (Weichmacher, opakisierende Zusätze, Antioxidantien) und ihre zulässige Menge festgelegt. Gehaltsbestimmungen sind nur in einigen Fällen vorgeschrieben, z.B. bei Polyethylen-Vinylacetat, da der Gehalt an Estern vom Verwendungszweck abhängt. Ein weiterer allgemeiner Teil (3.2) gilt den Behältnissen aus Glas oder Plastik-Materialien. Hier nehmen Definitionen einen großen Umfang ein. Daneben werden ähnlich wie bei den Ausgangsmaterialien Anforderungen an die Reinheit gestellt. Hinzu kommen physikalische Prüfungen wie

Druckfestigkeit. Der Umfang dieser Monographien verdeutlicht die enorme Bedeutung der Primärpackmittel für die Arzneimittelsicherheit.

RESPONSIBILITIES OF DRUG PRODUCT MANUFACTURERS IN THE QUALITY ASSURANCE OF PACKAGING MATERIAL

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The monograph of the current Ph.Eur. for different plastic materials and elastomers as the most important packaging materials for pharmaceutical products give information of accepted additives as well as extensive ambitious test methods for them and for any potential impurities derived from the respective manufacturing process. Nevertheless, a rational quality control is practically impossible unless the manufacturer reveals the qualitative composition of the materials and the different aids used for the polymerisation process. Compatibility tests of the immediate packaging materials with the drug product aim at the exclusion of sorption losses, particularly of low concentrated components of the dosage form and at the migration of low molecular components of the packaging materials (e.g. monomers or additives) into the product. These sorption and migration phenomena primarily occur with liquid or semisolid, scarcely with solid preparations. The rational selection of the separation and detection conditions of analytical tests accompanying the respective studies also need information of the composition of the respective materials. The chemical sterilisation with ethylene oxide and the ionising radiation sterilisation using a radioactive source (γ-sterilisation) or an electron generator as alternatives to the thermic standard sterilisation procedures require a sound validation with respect to the sterilisation success on the one hand and to the physical and chemical safety of the sterilised product on the other hand. Safety risks of the latter type can be excluded by test for residuals of the sterilisation agent in the case of EO sterilisation, but require material specific tests for degradation products potentially formed from the respective polymer or its additives at doses needed for acceptable SAL values. The rational design of packaging materials provides an improved product information of the

pharmaceutical manufacturer by the manufacturer of the respective materials on a confidential base.

THERMAL ANALYSIS COMBINED WITH RAMANMICROSCOPY FOR THE INVESTIGATION OF PACKAGING POLYMERES

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The increasing application of polymeres as primary packaging materials such as bottles, infusion bags, in BFS-technology, and blisters as well as secondary packaging such as pouches or as application devices such as syringes, applicators, and inhalers lead to a considerable change in the analytics to control these materials. The application of IR- and NIR-technology besides chromatografic methods for the identification and investigations on polymeres is nowadays assisted by further highly sophisticated analytical techniques. Beside others the combination of thermal analysis methods (TA) like DSC, thermogravimetry, and dynamic-mechanical analysis with Raman-microscopy turned out to be a really effective tool.

TA-methods exhibit the advantages of the speed and broad information content when investigating qualitative properties like identity, degree of polymerization, additives, and excipients and their quantitative amounts like content and crystallinity. The results can be combined with those from independant spectroscopic methods. Ramanmicroscopy delivers information on the identity of analytes with a high spatial resolution below 1µm without destroying the analyte. It thus generates information on the layers of laminates, the distribution of discrete particles in matrices, or the identity of small particles in the µm-range as constituents or contaminants.

The principles of the analytical methods are presented along with applications and practical examples to show the possibilities and the effectivity of these methods alone and in combination in routine analysis of packaging materials as well as in trouble shooting.

SPECTROSCOPIC SURFACE ANALYSIS (TOF-SIMS, XPS, ATR-IR, SEM) FOR THE INVESTIGATION OF PACKAGING MATERIALS

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The spectrum of packaging materials reaches from organic polymers and elastomers to inorganic materials such as glass and metals or mixed organic/ inorganic systems. As well, material coatings or multilayer systems gain increasing importance. Surface analysis techniques like XPS and TOF-SIMS have frequently been used to investigate the properties of materials but are not used as standard tools in the pharmaceutical field. More popular are SEM/EDX and ATR-FTIR. In the course of packaging development a many instrumental analytical techniques are available, however often not capable to investigate special surface derived phenomena. Typical fields of use for specialized surface analysis tools are process studies and surface phenomena like drug – material interactions and surface contamination.
The principles of the analytical methods are briefly presented. Furthermore, applications and case reports from the pharmaceutical packaging development practice are given. Among them are the investigation of a drug product silicone coating interaction in pre-filled syringes by XPS and TOF-SIMS, studies on wetting/repelling phenomena on the surface of parenteral rubber and glass components conducted by XPS, SEM and ATR-FTIR, coating material interface properties studied by XPS and a metallic surface contamination analysis of complaint injection vial samples using TOF-SIMS and environmental SEM/EDX. With all of the examples the employment of surface analysis techniques was the key to the understanding of the respective effects or phenomena.
The presentation shows that modern surface analytical techniques alone or in combination are powerful tools to contribute to the clarification of pharmaceutical packaging material related issues.

BOROSILICATE GLASS AS PRIMARY PACKAGING MATERIAL FOR THE PHARMACEUTICAL INDUSTRY

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SCHOTT-Rohrglas GmbH is the leading supplier of special glass tubing for technical and pharmaceutical applications. Most important borosilicate glass types for pharmaceutical packaging are FIOLAX®- clear, FIOLAX®-amber and BORO-8330TM. The production of high quality borosilicate glass tubing starts with carefully selected raw materials. The dosage and mixing of raw materials is done in a completely automated and computer controlled batch house. The finished mixture (batch) is transferred via a pipeline to the continuously running melting tanks. The whole melting process is also computer controlled. Exact measuring and controlling of important parameters like temperatures, glass level and material flow into and out of the tank make sure that an excellent glass melt leaves the tank. The hot forming of the glass melt into FIOLAX® tubing on the Danner drawing line is also a continuous, computer based process. 100 % in-line inspection of the dimensional and visual quality as well as several additional quality control steps in the production line ensure the high quality of the final product. The quality assurance system of SCHOTT-Rohrglas is certified according to DIN EN ISO 9001:2000. The quality standard for our glass tubing is published in the TLB 2002 (technical terms of supply, revision every two years). The properties of borosilicate glass are dependend on the composition. The most important properties and testing methods for pharmaceutical glass containers are laid down in Pharmacopoeias (Ph. Eur., USP, JP), ISO Standards (ISO 719, ISO 720, ISO 4802) and e. g. the Defect Evaluation List of F. R. Rimkus: Hydrolytic resistance (glass grain test, container surface test), light protection of amber glass containers (light transmission measurement) and cooling stress (Friedel-Kabine, stress measurement with Laser).

TOPOGRAPHY OF JUVENILE GLASS SURFACES

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Glass is known as a hygienic and dimensionally stable packaging material which inhibits permeation and sorption. For pharmaceutic uses special glass compositions and surface treatments have been developped which minimize migration. If extreme chemical stability is essential, glass is the chosen packaging material.
However, there are reactions of glass surfaces with the surrounding medium or the contents. Dealing with low dosage ingredients or sensitive contents, these extremely small interactions with glass have to be taken into account.
Modern high resolution and highly surface sensitive imaging methods can visualize the first stages of alteration even before a precise chemical analysis of the reaction products is possible. The typical topography of juvenile glass surfaces will be presented with new results from scanning force microscopy and electron microscopy. Changes of this topograpy on the nanometer scale can occur during production and in the time until use. Probable chemical reactions which initiate these changes are explained.

MASS SPECTROMETRY IN THE ANALYSIS OF ADDITIVES AND IMPURITIES IN PLASTICS USED FOR PACKAGING

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The choice of an appropriate pack can be crucial to provide appropriate protection of the pharmaceutical product, but also to make sure that there is no detrimental effect of the pack on the quality of the product and vice versa. Nowadays plastics are widely used for packaging of pharmaceutical liquids, semisolid and solid formulations. Although synthetic organic polymers tend to be stable towards a wide range of pharmaceutical solvents and excipients, frequently it is required to use additives to obtain the desired material quality, and the presence of polymerization residues and other impurities cannot be totally avoided. The qualitative and quantitative assessment of these compounds in the pharmaceutical product after contact with the pack is therefore an analytical challenge. Three different techniques of mass spectrometry can help to solve these problems. Classical GC/MS is used to determine nonpolar compounds. Matrix-assisted Laser Desorption Ionization (MALDI) in combination with a time-of-flight mass analyzer is predestined for the analysis of polymers and larger oligomers. Although it can be considered a robust and reliable technique, it is limited to qualitative and semiquantitative determinations. Electrospray mass spectrometry is the method of choice for the quantitative analysis of polar compounds in liquids, particularly in combination with HPLC. Structural identification of unknown impurities is possible using tandem (MS/MS) and multiple stage (MS^n) mass spectrometry. These techniques are based on different types of collision-induced dissociation, namely the tandem-in-space principle used in triple quad instruments and the tandem-in-time principle used in ion traps. The sensitivity that can be achieved depends on the ionization ability of each particular compound. Fortunately, many substances of interest, such as the phthalates, can be detected in the pg/ml range. Less polar compounds may

require the use of alternative ionization techniques such as APCI or photoionization.

NONDESTRUCTIVE IDENTIFICATION AND CHARACTERIZATION OF POLYMERIC PACKAGING FOILS WITH NIR SPECTROSCOPY

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Near infrared (NIR) spectroscopy is a fast and nondestructive analytical method that allows for the assessment of both, chemical and physical material characteristics. This paper addresses the potential of NIR spectroscopy for identification and characterization of polymeric packaging materials using a Foss spectrometer model 6500 (Foss, Silver Spring, USA) in transmission, transflectance and/or diffuse reflectance mode. NIR measurements were carried out at 32 scans in the wavelength range of 400-2500 nm with 2 nm resolution. Qualitative and quantitative calibration models were developed using Cluster Analysis (CA) and Partial Least Squares Regression (PLSR), respectively.

NIR transmission, transflectance and reflectance spectra of polymeric packaging foils showed strong correlation with their chemical and physical properties. Calibrations were established and optimised separately for each quality parameter of interest. CA was able not only to distinguish various types of polymers, but also to monitor batch-to-batch variability with respect to microstructural features and related thermal and mechanical properties. Quantitative calibration models based on conventional reference data revealed reliable results for the determination of several quality parameters such as foil thickness, plasticizer content, glass transition temperature (Tg), and moisture uptake.

The effect of measuring mode, selection of calibration and validation set, data pretreatments, and data processing on the robustness and validity of qualitative and quantitative calibration models will be discussed.

THE IMPORTANCE OF THE DETERMINATION OF EXTRACTABLES FROM PRIMARY PACKING MATERIALS FOR PARENTERAL APPLICATIONS RELATED TO A SUCCESSFUL PRODUCT APPLICATION

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An extractable is a species which can be emitted from a drug product closure or container, potentially contaminating the drug product. It may cause an interaction of the closure with the drug. This presentation will discuss the importance of a primary packaging system for biotech and pharmaceutical products as well as the advantages of pre-screening closures in order to assure compatibility between the drug product and the closure. The proper selection of the elastomeric closure and accurate leachables profiling in the intended final drug product are key to a successful and timely drug product launch. Factors such as the nature of the drug product, method of sterilization, shelf life and storage temperature of the product are all considerations.
This paper will summarize the results and recommendations for a complex emulsion-based drug product as determined by package pre-screening, methods selection and development for monitoring extractables. Technical specifications and options for glass containers and elastomeric closures will also be examined.

ANALYTICS OF PACKAGING MATERIALS AND COMPONENTS – BASIC CONSIDERATIONS

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The different pharmacopoeias (e.g. Ph.Eur. or USP) describe several materials used for packaging of drug products (glass, plastic polymers, rubber). In the respective monographs the analytical tools for evaluation of these materials are defined. These are mainly classical methods (extraction, limit tests, titration, UV-spectroscopy) checking the overall extractable profile of the materials. In addition, specific tests for plastic additives based on HPLC are provided. Besides these compendial tests a lot of other methods based on industrial standards (e.g. DIN, ISO or ASTM) are commonly used to evaluate packaging materials and components. For the most important and widely used packaging components specific defect evaluation lists were prepared, fixing general requirements on quality. These lists also include sampling plans for in-process controls and randomized release testing. One major aspect of packaging testing is checking the dimensions of components and evaluating the tolerances. These tolerances may influence typical characteristics of packaging systems like force to open or integrity. An overview of the currently used methods for routine testing of packaging materials and components will be provided.