

ANALYSIS AND COMPLIANCE TESTING OF PHARMACEUTICAL PACKAGING MATERIALS

The methods of analysis of all types of packaging materials will be presented with special emphasis on polymeric multilayer packaging materials and newer polymers.

A short presentation on how the physical and barrier properties of packaging materials are measured will be followed by the test requirements of the various pharmacopoeia especially USP, Ph.Eur. and JP.

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INTRODUCTION

Packaging materials for pharmaceuticals are not controlled in isolation but are considered in the light of the whole product. as a result any change in a pack or its constituents is notifiable to the regulatory authorities.

Only packaging in contact with a product or which directly affects the quality of the medicine over its shelf life is considered.

In selecting a suitable packaging material a primary requirement is a knowledge of the raw materials, the composition and the manufacturing process so that any potential hazards or unsuitability in terms of product can be assessed.

The packaging of pharmaceuticals has two main purposes; to provide a barrier between the product and the environmental and to assist in the delivery of the correct dose to the intended patient. No pack or packaging material is totally inert to either the environment or to materials packaged within. Again all plastics and rubbers are “porous”. Potential physico-chemical interactions between a pack and its contents. Interactions can be divided into three types:

- (a) Permeation of gases such as oxygen and water vapour.
- (b) Sorption either adsorption of the product or desorption from the pack into the product.
- (c) Leaching of additives and low molecular weight polymer.

Tampering of the pack could be considered as another type of interaction. A packaging material chosen for any particular pharmaceutical preparation should be such that the components of the product in contact with the plastic materials are not significantly absorbed on to the surface of the containers and do not significantly migrate into or through the packaging. The packaging material should not affect the preparation substance in terms of its physical or chemical stability and its safety and efficiency.

The British Pharmacopoeia (BP) for instance requires type samples of the intended pack to be made and tested under conditions that reproduce those that will be encountered in use. These tests should include careful examination of the packed product to ensure that the pack affords the required protection. To ensure that the type sample is representative, at least two distinct batches should

be tested. If a change in formulation of a product is made, it may be necessary to assess the pack/product combination for compatibility. The BP further states that the technical quality control of the manufacturing process must ensure reproducibility of the pack or pack components. Manufacturers must ensure that the packaging materials from the bulk production conform to the type sample in every respect. It is important that there should be no significant change in composition or in the manufacturing procedures used by the compounder or the fabricator of the materials. Only polymeric materials and their additives included in and conforming to the specifications of the Code of Federal Registration and/or approved under the EU directives as being suitable for food contact use should be used for pharmaceutical products. Similarly it is preferable to use materials, the details of which have been registered with the FDA to avoid extensive biological tests by the packaging user. Such tests on extracts using appropriate techniques (e.g. BS5736, draft BS2463 part 1, or USP) include:

- Tissue culture toxicity,
- Systemic injection of mice,
- Intracutaneous injection of rabbits,
- Ophthalmic instillation of rabbits,
- Pyrogen tests and
- Tests for haemolytic activity.

According to the BP, no scrap materials shall be used, an important fact when there are ecological pressures to reprocess scrap.

Nowadays environmental considerations should be taken when a new pack or packaging material is being elected. In particular the use of PVC and other chlorine containing polymers should be avoided.

Samples from production runs should be tested to ensure conformity to typed samples. Polymers for packaging are usually chosen because of their molecular structure, which offers the desired properties, and it is important to test for departures from the characteristics of the type sample.

Closures should always be tested as part of the complete pack. They should be tested not only for compatibility of their product contact materials but for their efficiency for tamper evidence and child resistance if such a claim is made.

The guide to Good Manufacturing Practice requires that each packaging material shall have a specification held on file. The specification should include a description of the nature, dimensions and material of construction of the component with quality standards, control limits, mould references,

drawings and text, as applicable. Details of tests for determining compliance with the specification should also be included.

Consequently there is a clearly identified Regulatory need for testing and for the presentation to the licensing authorities of the information from these tests. There is thus a need for test methods to;

- Select,
- Evaluate,
- Confirm the identity, and
- Control the quality of pharmaceutical packaging.

Many of the test methods will be common for the above, but in general will consist of:

- Metrology.
- Analytical/chemical tests.
- Physical performance tests.
- Barrier tests.
- Compatibility / stability tests.

METROLOGY

Often the most neglected of test regimes but if a cap does not fit a bottle, the no matter how good the components are the pack will not protect the product.

The dimensions of many packaging materials such as paper, board, some plastics and rubbers are dependent on both temperature and humidity. It is important that materials are conditioned to the test conditions which must be universally recognised 23°C and 50% RH.

ANALYTICAL TESTS

Information generated from the analytical tests can be used to predict packaging material performance. If it can be shown that a new material is identical to a current registered material, then no further work may be necessary other than

informing the relevant authority of the change with a submission of the analytical evidence.

All physical and chemical properties are dependant on the chemical species making up the polymer, the molecular arrangement of those species and their molecular weight and distribution.

Chemical type imparts:

Chemical computability.

Barrier properties.

Temperature resistance.

Crystallinity (molecular packing) influences the:

Density.

Melting point.

Tensile strength.

Chemical resistance.

Barrier properties to gases.

Molecular weight influences:

Melt viscosity and processability.

Impact resistance.

Stress crack resistance.

Migration.

There are many analytical identification tests that may be applied to plastics and rubbers. The three most common techniques are spectroscopy, thermal analysis and chromatography.

Infra red Spectroscopy

The most common spectroscopic technique used in analysis of polymers is infra red spectroscopy. Infra red spectroscopy will yield quantitative and qualitative information regarding the chemical species contained in a specimen both the basic polymers and inorganic fillers.

Until recently it was difficult to identify each component of a multilayer coextrusion for example a flexible tube for creams. The combination of FTIR and microscopy has now made this relatively simple. Shown is the visible image of a microtomed image and line scan spectra of a multilaminate tube for creams.

Unfortunately the spectra of similar chemical species are of themselves similar- so infra red spectroscopy has difficulty in differentiating between different polyethylenes such as LDPE, LLDPE and HDPE, the newer metallocenes and the various polyamides.

Thermal analysis

Thermal analytical techniques measure changes of the properties of materials normally as they are heated or cooled.

Two techniques are currently used: differential scanning calorimetry which measures changes in heat flow into and out of a sample, and thermal mechanical analysis which measures changes in size of specimen. Other techniques such as thermal gravimetric analysis (changes in mass) and dynamic mechanical thermal analysis (changes in modulus or stiffness) are also widely used.

Differential scanning calorimetry can give information on how the chemical species in a polymer are combined. The physical properties of a polymer change significantly at the transition points. Especially relevant are the changes in barrier properties of polymers at the glass transition temperature for example changes in oxygen transmission rates of polyamide films. DSC also gives information on the molecular arrangements of polymers e.g. differentiate between LDPE, LLDPE, HDPE, different nylons, differentiation of homo and copolymers and polymer blends, and can be used to differentiate finer points of multilayer laminates. DSC can also be used to determine the thermal stability of polymers especially to oxidation and hence the effectiveness of antioxidants. Oxidation may impart odour into a product. This property is becoming more important with aseptic form fill seal packs, especially as the polymers do not contain antioxidants.

Thermal mechanical analysis

Thermal mechanical analysis is more sensitive at detecting the glass transitions of polymers. TMA yields quantitative information on the orientation set into packaging films to improve their barrier properties, or for their use as shrink films. TMA can also predict the maximum operating temperature of a polymer and compare the softening temperatures of polymers such as heat-seal lacquers on lidding foils for blister packs.

Chromatographic techniques

Three techniques are currently routinely employed:

- Gas chromatography for the analysis of volatile components.

- Size exclusion chromatography to measure molecular weight distributions.

- High performance liquid chromatography to determine non volatile components of polymers, and absorbed products into packaging.

Gas chromatography

Typically gas chromatography is used to measure monomers, solvents retained after printing and laminating packaging materials, and analysis of the head space of packs. An interesting application is the measurement of the permeability of volatile compounds through packaging materials. Although no commercial instruments are available, a number of laboratories have adapted chromatographs with a kathetrometer detector and a diffusion cell in place of the injection head for this purpose.

Size exclusion chromatography

SEC is a means of determining the molecular weight distributions of polymers by liquid chromatography. Shown are the molecular weight distributions of an ultra HDPE, a LDPE and a LLDPE. The quantity of a low molecular weight polymer influences the amount of polymer that may be extracted by products, solvents etc. It may influence the rates of migration of additives from a polymer into a product.

High performance liquid chromatography

Shown are three applications of HPLC: slip additives from polyurethanes, additives from PVC and isocyanates extracted from polyurethane adhesives. Methods have also been developed to determine components of products that are absorbed into a packaging material.

Nuclear Magnetic Resonance

When placed in a rapidly changing magnetic field many molecular groups will cause absorption of an incident radio signal. The most common application is caused by the various grouping of hydrogen atoms in a molecule

In the field of polymers it is usually the C13 atom that is normally analysed.

Polymers may be examined in the solid state, but the signals are weak and the instrument very expensive.

Solid state NMR can be used to typify the different polyolefins and copolymers, being extremely good at typifying the chain branching caused by the comonomers used in linear low density polyethylenes.

PHYSICAL TESTS

Some of the properties of packaging materials can be predicted from the results of analytical tests. Where the processing-moulding etc. modifies the structure of the materials then physical tests must be performed. Two main types of physical tests are often used, one is to measure mechanical properties and the other diffusion properties, both are important when considering product protection.

The cost of moulding prototype packs from new materials can be excessive. Instead of evaluating whole packs of often complex design, the polymers as supplied to a packaging manufacturer in the form of granules and powders may be tested. To this end a compression mould press for forming sheets and films for diffusion and migration studies and / or an injection moulding machine for mechanical and computability test specimens may be used.

Melt flow rate

Polymers are specified by their density and their melt flow rate. MFR is a measure of the viscosity of a molten polymer and are graded as to use-injection moulding requires a low viscosity/high MFR, and a grade for blown film or container manufacture require a high viscosity/low MFR. If the MFR is determined under two different loads a measure of the polydispersity of the polymer can be determined

Universal testing machines

Many of the mechanical properties can be determined using a universal testing machine such as the Instron. The machine consists of a rigid frame between which a crosshead can move up, down or cycle. To the crosshead and base may be attached load cells to measure the forces in a variety of applications. The tests that can be performed on such a machine are only limited by the operators ingenuity. The various arrangements of load cells and grips can be used to measure tensile properties, compression strength, bond and seal strength and coefficient of friction. The tensile properties are dependent on the type of polymer being examined. For polymers also the speed at which the test is conducted is of extreme importance. Again measurement of the frictional properties can provide information of surface additives and morphology. Of these tests perhaps the most common is the evaluation of the sealability of flexible packaging materials. Seals are made up using a laboratory heat sealer produced at varying temperatures; dwell time and seal pressure may also be varied. From the results, a graph of strength versus temperature can be produced and comparisons between different materials made.

One restriction of a screw operated machine such as an Instron is the limited range of crosshead speeds. In practice forces are either constant such as those encountered when packs are stacked, or extremely rapid such as when a pack is dropped. As a result care must be taken in the transposition of laboratory results to the real world. However this problem can be overcome by the use of creep testers, servo hydraulic machines or high speed impact testers.

The Proprietary Association of Great Britain issued suggested test methods and test limits for the testing of strip and blister packs and their component part, to

give assurance that packs meeting the requirements could be claimed to be child resistant. These are now the subject of a British Standard BS7236.

BARRIER TESTS

Water vapour permeation

The compendial and hence the most common method of measuring the WVP of packs is to fill them with calcium chloride and weighing them at intervals whilst exposing them to extremes of humidity and temperature. By comparing the desiccant properties of products with calcium chloride, prediction of shelf lives can be made.

A simple method of measuring WVP of flat films is by the ISO dish method. Dishes are filled with calcium chloride and the sample sealed over the mouth. The dishes are placed in humidity cabinets and weighed periodically. However the above method has certain constraints, it is messy, smelly and needs a skilled operator to reduce specimen failures. The test also takes at least 14 days.

The testing of films or new materials cast as films use is best made of instruments such as the MOCON Permatran series of instruments. The instrument works by passing dry air over one side of a test film and measuring the absorption of infra red energy at 1.5 μ m by the water vapour permeating through the film. The humidity is provided by a saturated salt solution chosen to give the required humidity at the temperature of test. Calibration is made using films of known water vapour permeation.

Oxygen transmission rates.

Oxygen transmission rates are tested using instruments such as the MOCON Oxtran series of instruments. Oxygen is passed over one side and nitrogen over the other side of a film held in a sealed cell. The nitrogen and the oxygen permeating through the film is passed through a coulometric cell whose current output is proportional to the oxygen transmission rate. The Oxtrons can be modified to test packages as well as films.

The permeation rates are dependent on temperature and the concentration differences of the permeant either side of the barrier. Also changes in polymer morphology such as occurs at the glass transition temperature increases the rate for example of oxygen permeation.

Light

For products that are sensitive to light – mainly ultra violet, the packaging must be able to provide a suitable barrier. For example brown bottles and white

pigmented polymers. To measure the light transmission of transparent materials such as glass a UV spectrophotometer operated in a conventional mode may be used. But for pigmented plastics where light scattering of the light by the pigment particles occurs, then the spectrophotometer must be equipped with an integrating sphere.

COMPATABILITY TESTS

Tests to show pack-product compatibility are synonymous with migration testing. The term migration refers to the transfer of non volatiles compounds between a pack, the product or the environment. “Migration” of volatile compound is more correctly termed Permeation – see Water vapour and oxygen above. When a product or a component of a product penetrates a polymer network, routes are opened for migration. Migration does not occur without penetration of the polymer matrix and thus rarely occurs between a solid product and a packaging material. An exception, for example is between a gelatin capsule and a plasticised PVC.

Interactions may occur between quite minor components of polymers. For example, clioquinol used as a preservative for creams causes colour reactions in HDPE, Polypropylene and LLDPE – the colour being due to the particular catalyst used in the polymer manufacture.

A number of techniques are being developed to measure penetration of the polymer network. One method is the use of FT-IR microscopy, where a migrant’s migration is tracked by monitoring a particular wavelength due to the migrant through the thickness of the polymer.

This technique may also be used to measure loss of a polymer component into a product.

Many products, especially those containing surfactants or detergents cause environmental stress cracking of in particular polyethylenes. To measure the Environmental Stress Crack Resistance of a polymer, test pieces are notched, flexed and put into contact with the test product. A note is made of propagation of cracks from the notch and the results recorded graphically.

COMPLIANCE TESTING

All the pharmacopoeia have monographs for packaging or the materials used for packaging. Unfortunately the extraction methods and the test limits of the

various pharmacopoeia, the EU food directives and the USA Code of Federal Regulations differ widely.

There is a fundamental difference between the USP and others such as the Ph.Eur. in that the former is for containers per se and the latter is for the materials used to manufacture containers.

To assess the potential for migration, pharmacopoeia have limits on the amounts of extractives into solvents.

For example the United States Pharmacopoeia has limits for the amounts of non volatile residues extracted from HDPE & LDPE containers. Strips are cut from the packs or compression moulded sheets and immersed for 24 hours in Hexane at 50C

Ethanol at 70C

Water at 70C

Besides the non volatile residue, the pH and heavy metal content of the aqueous extract are measured.

The European pharmacopoeia only tests for aqueous and hexane extractives.

The Ph.Eur. is more comprehensive in the types of polymers and on analysing the types of additives and catalyst residues.

TESTING FROM DESIGN TO PRODUCTION

As an example of the way test methods have been chosen for the selection, evaluation and quality control of a new pack, those for a polymer used for a Blow-Fill-Seal unit dose pack for an aqueous product are discussed.

At the design stage and selection it was shown that the polymer needed to be flexible, transparent, additive free for ophthalmic preparation, and have a low water vapour permeation. A suitable polymer was deemed to be low density polyethylene made specifically on a tubular reactor rather than autoclave reactors to negate catalyst residues etc. The particular blow-fill-seal machine required a melt flow rate of less than 0.5g/10minutes.

Several short-listed grades of polymers from a range of suppliers were obtained to produce packs under normal production conditions to demonstrate suitability of use.

To confirm that the correct material had been supplied and that it was not contaminated with other polymers, the infra-red spectrum and DSC thermogram were recorded. At the same time, because the polymers were additive free, a test was devised to measure the degree of oxidation occurring during the manufacturing cycle. To confirm that the product would conform to

the pharmacopeial tests, these were conducted. Also since the product contained a surfactant the environmental stress crack resistance was measured. The latter test showed that certain polymers were better than others, which further narrowed the range of suitable polymers.

Finally samples were examined in a formal stability program to confirm the stability of the product during its intended shelf life.

The comprehensive test routines were applied to the first five batches of polymers used for production to ensure suppliers quality and to confirm and establish quality acceptance limits.

During this period the polymer manufactures were subjected to a quality audit which included an assessment that they would meet the requirements of Good Laboratory Practice.

After the initial batches had been processed, testing of incoming batches were tested only by IR spectroscopy and DSC. Every tenth batch was tested to confirm compliance to the pharmacopoeia of the country to which the product was intended for sale.

CONCLUSION

To conclude, testing is necessary at the initial design and material selection stage, when various alternatives are being evaluated and for quality assurance.

Selection of test methods should follow the requirements of the pertinent Pharmacopoeia but apart from the regulatory requirements should be chosen at the earliest stage possible with discussions with the designers and suppliers of packaging.

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