



Clean elastomers for pharmaceutical device applications

Introduction

This article provides a synopsis of the paper to be presented on new elastomer developments for drug delivery devices at the Medical Plastics 2005 European Seminar and Conference this November. The presentation by Bespak's Senior Scientist Daljit Ohbi, will discuss the characteristics and benefits of using elastomers for sealing applications in drug delivery devices and will showcase the range of proprietary elastomer compositions developed by Bespak for use in their customer's pressurised Metered Dose Inhaler (pMDI) products.

The demand from worldwide regulatory authorities to ensure that drug delivery devices are safe, reliable and effective in their performance throughout life continues to increase. Manufacturers must ensure that the materials used in the production of their pharmaceutical partners' devices are appropriate for the desired application. The penalties associated with a reduction in performance, functionality or safety can be significant, even to the extent of product recall and consequentially substantial financial penalties.

Various regulatory bodies such as the FDA and ISO 10993-1 – Biological Evaluation of Medical Devices, provide guidelines on the materials and their assessment for use in devices such as MDIs. The device is constructed using medical grade plastic materials. These grades are made from less toxic catalysts and antioxidants and their molecular constituents controlled in the polymerisation process by the polymer manufacturers. Typical plastics used in MDIs are PBT (polybutylene-terphthalate), Nylon and POM (polyoxymethylene). In the liquid pulmonary devices, HFA propellants such as 134a (hexafluoroethane) and 224 (hexafluoroethane) in mixtures with the drug formulations are used. At ambient conditions the device pressure is in the region of 5 bars. The device has to deliver accurate shot weights of medication and must have effective sealing to prevent loss of propellant and ingress of moisture.

For the sealing application elastomers are used. In medical devices the selected elastomer composition for sealing is determined both by device performance and the cleanliness of the elastomer composition.

Elastomers have stable compression recovery characteristics and withstand external influences such as pressure and temperature, making them ideal for sealing applications. They are long chain, high molecular weight polymers and are essentially super condensed gases since their precursor monomers are gaseous. They are amorphous and have a random coiled long chain molecular configuration. To develop rubbery engineering properties, various inorganic fillers and organic additives such as cross-linking agents are mixed with them. The compositions are vulcanised to develop rubbery properties. Vulcanisation is a thermo chemical reaction during which the long molecular chains are cross-linked and the elastomeric properties become stable to the effects of temperature and pressure.

Elastomer Compositions

Elastomers form ideal sealing materials from basic engineering principles. In their crosslinked state they are elastic and show stress recovery characteristics. They require smaller deformation forces and in comparison to steel the equivalent strains in rubbers are 10^{-5} times the value for steel. Elastomers also exhibit very low volume change when subjected to compressive forces. They have a Poisson ratio of 0.499 compared to 0.3 for steel. The types of base elastomers used in pharmaceutical elastomer sealing compositions are EPDM (terpolymer: ethylidene norbornene); Butyl, Chlorobutyl and Bromobutyl; Nitrile and Polychloroprene.

Elastomers are polymers and their constituent monomers such as ethylene, propylene, isobutylene, butadiene are gaseous and thus in various publications described as super condensed gases. They are amorphous materials, having low crystallinity and in comparison to crystalline thermoplastics are more amenable to permeation of gases and fluids and soften by heat. They have low tensile and compressive strength in comparison to semi crystalline plastics. In order to convert these elastomers into useful rubbery materials additives are mixed with them. The additives include inorganic fillers such as clay and talc and are used to reinforce and stiffen the elastomers. Processing aids are required for mixing of the fillers; these are low organic molecular weight additives mainly fatty acid based species and help incorporation of polar inorganic fillers into non-polar elastomers.

Organic additives that function as cross-linking agents are also added to these materials to enhance their stability at higher temperatures.

There are a number of combination factors for elastomer and their additive selection for sealing materials for medical devices:

- Service temperature and length of service requirements
- Environmental and chemical resistance
- Engineering/design requirements
- Permeability to gases and fluids
- Processability
- Toxicity
- Low leachable species.

The elastomer must be compatible with the environment it is exposed to. It must not be swollen or degraded by the chemicals it is exposed to. It must not swell, degrade and leach out chemical species so as to contaminate the medicament. In midi's the elastomer is exposed to HFA and ethanol and must have low permeability to ingress of moisture and maintain uniform elastic properties throughout the life of the device.

Filler dispersion

For the elastomer to have consistent mechanical and sealing properties, a uniform additive and filler dispersion and distribution within the elastomer matrix is necessary. The uniform filler dispersion also enhances filler- elastomer interactions especially in compositions where the filler is coated with a coupling agent. Good dispersion of accelerators promotes uniform cross-linking in the elastomer composition. Filler and additive dispersion is facilitated by the incorporation of processing or dispersion aids. These are low molecular weight organic compounds based on fatty acids and low molecular weight olefin polymers such as polyethylene. These additives do not form part of the crosslinked network and may diffuse out to the surface and therefore are potential leachables and contaminants for medicaments. In medical devices the leachable content has to be kept very low, consequently the use of these materials must be avoided. This poses challenges in the mixing process, since without the processing aids lengthy mixing time and heat generation by shearing is detrimental to the elastomer composition. The accelerators are heat sensitive and premature cross-linking also known as scorching can occur. This will lead to poor flow of the material during the moulding of components.

Dispersion of additives and fillers can be obtained by designing and control of the mixing parameters. The mixing cycle has to be long enough to distribute and disperse the additives in the formulation, otherwise agglomerates of filler are formed and these can dislodge in the medical container or form potential weak sites for rupture and premature failing of the seal.

Bespak, a leading designer, developer and manufacturer of specialty medical devices has developed a range of proprietary elastomer compositions for dispensing asthmatic medications. In 2005 Bespak commissioned a state-of-the-art elastomer mixing and moulding plant to produce clean elastomer compositions. The Bespak elastomer compositions are based on EPDM, Butyl, polychloroprene, and nitrile polymers. The compositions have been designed for uniformity of filler and additive dispersion, long ageing resistance to maintain stable properties through the life of the drug delivery device. The satisfactory device performance in terms of low leakage and drug delivery shot weight has been determined at ambient and elevated temperatures. The potential leachable species from the compositions have been characterised qualitatively and quantitatively by analysing acetone extracts by gas chromatography and mass spectroscopy. A toxicity assessment on the identified species has been carried out. The elastomer compositions have also been tested and meet the USP requirements for Pressurised Metered Dose Inhalers (pMDI's).

Conclusion

Elastomers form ideal sealing materials, however not all are suitable for medical devices. Their elastomer compositions contain base elastomer and a variety of organic additives and fillers that are necessary either for cross-linking, stabilisation or as processing aids. During their mixing cross-contamination from other materials can also occur. There are thus many potential chemical species that can migrate out and be a source of contaminants for medicaments.

For medical device applications elastomers that contain low level residues of polymerising catalyst are selected. The level of elastomer additives is minimised and dedicated mixing equipment used for their production. This helps in avoiding cross-contamination from other materials.

Elastomer mix cycles should be carefully designed to be long enough to disperse fillers and additives but also that they do not cause premature cross-linking of the elastomers.

Bespak is commissioning an Elastomer Plant for the mixing and moulding of medical elastomers. It has developed proprietary elastomers formulations based on EPDM, Butyl, Nitrile and polychloroprene. The formulations have low leachables and have been assessed for safe use in pulmonary medical devices.