Development, manufacture and qualification of seal materials in aseptic valve designs

Manufacturing pharmaceuticals is complex and demanding. In addition to product development, the manufacturing process in particular plays a central role. To avoid cost-intensive loss of production and ensure optimal product quality, the production plants used must satisfy the strictest quality requirements.
Aseptic valve designs play a key role in the product manufacturing process. They allow media flows to be distributed, brought together and regulated under sterile process conditions.
The safe operation of the diaphragm valves used for this is dependent on the seal materials used, i.e. the diaphragms, in particular. Due to sometimes extreme conditions in the production plants during product manufacture, cleaning and sterilization processes, contradictory requirements for the properties of the seals used sometimes emerge. This is why the development of material mixtures, manufacturing processes and qualification and approval processes, taking into account international regulations and standards, is highly complex and requires specialized expertise, in addition to in-depth knowledge of materials and physicochemical processes.

In the manufacture of complex, high-quality pharmaceuticals, there is a particular focus on product quality and consumer safety. That is why pharmaceutical production processes are subject to standards and guidelines, compliance with which aims to ensure quality.

To avoid cross contamination, the collection of dust or dirt and other effects that would adversely affect the quality of the product, the production equipment must be designed accordingly.

Media is regulated in the production plant under aseptic conditions during manufacture or cleaning and sterilization using appropriate valve designs. According to good manufacturing practice (GMP), you must be able to clean these easily and thoroughly, and they must not constitute a danger to or adversely affect the products with which they come into contact during production. Diaphragm valve technology, in particular, fulfils these criteria.

Diaphragm valves

Diaphragm valves comprise three subassemblies – the actuator (generally driven manually or pneumatically, or motorized), the seal (the diaphragm) and the valve body. The diaphragm is joined to the actuator spindle via a diaphragm pin and compressed between the actuator and valve body. Due to the design, the medium to be regulated comes into contact only with the diaphragm and the inside of the valve body. The operating mechanics and the valve actuator are located entirely outside the media wetted area. Diaphragm valves are cavity filled and the area that comes into contact with the product is easy to clean and easily sterilizable.

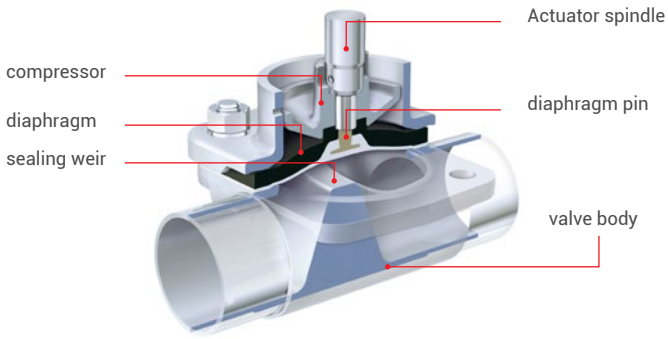

Figure 1: Section of a GEMÜ diaphragm valve when open

The valve opens or closes when the actuator is activated, whereby the diaphragm joined to the actuator spindle via a compressor is pressed onto the sealing weir found in the body or lifted off it.

During the product manufacture, cleaning and sterilization process, diaphragm valves are exposed to extreme conditions. The diaphragms used here are subjected to different types of stress:

1. Mechanical load, due to the functional compression between valve body and actuator, and, when closed, also between compressor and sealing weir, as well as the predominant operating pressures of up to ten bar, but also the flexing when opening and closing the valve;
2. Thermal stress, due to hot working media and sterilization temperatures above 121 °C;
3. Chemical stress, due to the ingredients of the media and auxiliary materials during cleaning and disinfection (e.g. alkaline and acidic solutions).

Diaphragm valve bodies in aseptic plants are often made of high-alloy, rust-proof, austenitic stainless steels (e.g. 1.4435) and the diaphragms are made of elastomers (e.g. ethylene propylene diene monomer rubber (EPDM) or thermoplastic materials (e.g. polytetrafluoroethylene (PTFE).

Seal materials

The faultless and reliable functioning of a diaphragm valve is, in addition to perfectly tuned components, particularly dependent on the quality of the diaphragms.

Leakages between the valve body and diaphragms or faults in the diaphragms themselves can cause the medium from the closed system to leak out or become contaminated with invasive germs. There can also be leakages in the valve itself, as soon as a medium gets through the valve seat when closed. In both cases, the valve is not doing its job. Cost-intensive product losses, impurities, failure of the production plant and, in the worst case scenario, personal injury are possible consequences.
In addition to valve sealing, the quality of the diaphragm materials used plays a key role. Direct contact with foodstuffs or pharmaceuticals, and consequently potential material migration from the diaphragms into the media, could cause unwanted changes to product features or even endanger the health of the consumers.
In aseptic or sterile areas, diaphragms made from elastomers and thermoplastic materials have proven suitable and are used most frequently.
Due to the many different material components, their combination options and their production processes, the respective diaphragm properties are also very different from each other. Analysis of the respective application is essential before selecting the appropriate seal materials.
Due to differing operating conditions in production plants, the use of various different diaphragms may be required. In particular, the chemical and physical stresses predominant in the plant, such as working media, media temperatures, operating pressures and aggregate states, are important for selecting an appropriate diaphragm material. However, auxiliary processes such as cleaning cycles and sterilization and disinfection processes (CIP/SIP) must also be considered.

Elastomer diaphragms made from ethylene propylene diene monomer rubber (EPDM)

Features

Elastomer diaphragms for sterile and aseptic applications are generally made from EPDM. In addition to being highly resistant to many acidic and alkaline media, demineralized and deionized water and various inert and other industrial gases, these are also highly resistant to superheated steam and ozone.
Despite their wide range of uses, EPDM diaphragms cannot be used for all media. They are not, for instance, resistant to vegetable and mineral oils, animal fats, aromatic or aliphatic hydrocarbons, halogenated solvents or concentrated acids.

Development

The material composition of EPDM diaphragms is complex and must be adapted to the respective application in order to achieve the specific property profile required.
The basic polymer, ethylene propylene diene monomer rubber, determines the main features, such as resistance to media and ageing and, to a certain extent, the mechanical and thermal properties. Additives such as fillers, processing aids, anti-ageing agents and crosslinking agents are added to the basic polymer and serve to vary and optimize its features. This mixture of plastics is designated as a compound. However, compounding has limitations. For instance, it is difficult to increase the mineral oil resistance of EPDM diaphragms by mixing them with additives in this way.
The elastomer mixture is manufactured via demanding and strictly monitored processes. Active fillers represent a large portion of the mixture. These are added to adjust the desired properties of the elastomer accordingly. Without fillers, adapting the mechanical or chemical diaphragm properties, for example, would hardly be possible. A large part of the volume comprises carbon blacks or silicic acids.
Processing aids are used, among other things, to improve the mixing process. In addition, they allow the fillers to be distributed more homogeneously, which is a prerequisite for high-quality elastomer diaphragms.
To minimize the chemical ageing of the diaphragms under stress, effective anti-ageing agents are added in very small quantities. Due to the different causes of ageing, a specialized combination of various protective substances may be advisable.
Chemical crosslinking agents are substances that can transfer the polymer chains to a three-dimensional network, consequently affecting vulcanization. Through this network, the material properties are fundamentally altered, giving rise to the essential elastic properties of the diaphragm. Peroxides are mainly used for this.
Developing elastomers is highly complex and requires many years of experience and specialized expertise. Even slight deviations in mixture components can have a negative impact on the desired product features and make the diaphragms unusable for the respective application.

Manufacture

The individual components of a developed elastomer mixture are available in different forms. The basic polymer is often a viscous compound, the processing aids highly viscous and other additives generally pulverulent.
Optimal diaphragm quality depends particularly on the mixing process, in addition to the components and their mixing proportions. In a process specification, the exact order and compounding mixing times and temperatures are precisely predetermined and monitored.
Before the mixing process, the individual components are evaluated. If there are deviations here, the diaphragm batch will later be unusable or will not fulfil the desired requirements. Using kneading and rolling mills and in line with the defined procedure, the basic polymer and additives are mixed and guided by a roller, cooled, pre-assembled and drawn off as narrow strips.

The mixed and moulded raw material for the diaphragms is further processed, depending on the diaphragm structure, in different ways:

- Compression moulding
- Injection moulding

Compression moulding
Diaphragms with fabric reinforcement and threaded pins are generally manufactured using a compression process. For this, the raw material that has been produced as strips must first be moulded into the shape required for further processing.
Using a calender, the mixture is made into sheets or panels of equal strength. Rollers installed in parallel that can be heated and cooled are used for this. The spacing and rotational speeds of the rollers are adjustable on a case-by-case basis. To ensure reproducible quality, you must consider that viscosity anomalies, surface faults and formation of blisters may arise during the calendering process. [2] This is why it is necessary to precisely define, monitor and strictly comply with the process times and conditions, such as humidity and temperature. The calendered panels are then covered with a plastic sheet on one side and rolled up. This prevents the viscous raw material from sticking together.
The diaphragm blank is composed of several layers. To this end, different moulded parts are stamped out from the calendered panel and then put together on a case-by-case basis with the fabric and threaded pin. The moulding process is developed taking into account the corresponding profile of requirements. The combined diaphragm blank is processed via a compression procedure.
The compression procedure produces three-dimensional networked elastomer diaphragms, under the influence of pressure and temperature. Hydraulic presses and heated moulding tools, comprising a top and bottom section, are used for this. The tools themselves are shaped such that they form a cavity when closed that features the desired diaphragm mould.
Before closing the tools, several diaphragm blanks are inserted into the pre-heated mould cavities. Closing the press and the consequent temperature and pressure increase starts the vulcanization or networking process.

Figure 2: Mould cavities for manufacturing GEMÜ diaphragms

Under the influence of pressure and temperature, the individual blank components are connected together, and chemical bonds are formed within the material itself. An elastic diaphragm with its own specific properties is developed from the plastic blank.
As elastomers are poor heat conductors, but the desired vulcanization temperature must nevertheless be reached, defined heating times are required for the compression procedure. To avoid trapped air in the finished diaphragm, the process is carried out in a vacuum.

The mould cavities must be completely filled by the diaphragm blank to ensure diaphragm geometry later. For design reasons, the volume of the blank is greater than that of the finished diaphragm. The excess material is pressed out of the cavities at defined openings during the press moulding process, and the projecting burr is removed in a following processing stage.

Figure 3: Vulcanized GEMÜ diaphragms before further processing

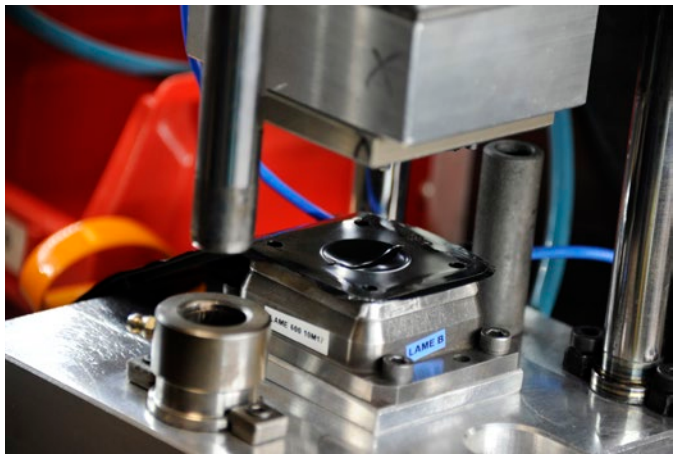

Figure 4: Removing the projecting diaphragm burr

To achieve optimal product features, a depressurized after-cure or tempering is required after the moulding vulcanization under a certain pressure and at a certain temperature, to ensure complete crosslinking. To this end, the diaphragms are warmed in ovens and under pre-defined process parameters. Tempering can take up to 24 hours for special processes.

Figure 5: Finished GEMÜ EPDM diaphragms with fabric reinforcement and threaded pin

Injection moulding

The raw material, which is available as strips after the mixing process, is processed in an injection unit. A rotating screw inside the unit plasticizes, compresses and warms up the elastomer mixture and conveys it to a cylinder or screw vestibule. It is then injected into the mould cavities under high pressure using an injection piston or by translational movement of the screw. Plasticizing and pre-warming the mixture decreases the vulcanization time. [2] As with the compression procedure, the diaphragms can likewise be tempered after injection moulding.

Figure 6: Finished GEMÜ EPDM diaphragms without threaded pin

Elastomer diaphragms with polytetrafluoroethylene (PTFE) face

Features
Elastomer diaphragms with a PTFE face offer maximum chemical resistance to strong acids, alkalis and salts, as well as solvents and chlorine. They can also be used at high operating temperatures (e.g. WFI loops) or for steam applications.
What is especially advantageous in comparison with EPDM diaphragms is their resistance to nearly all media. Working, cleaning and sterilization media come into contact only with the PTFE face, and the EPDM back serves to increase and absorb the force of the operating pressures.

Development
The diaphragm faces made of PTFE are manufactured at GEMÜ out of a chemically modified compression-moulding powder. Due to the modification, the material features a lower deformation under load, a sealed, low-porosity polymer structure with lower permeability and better recovery at high temperatures, in comparison with standard PTFE.

Manufacture
Compared with other thermoplastic materials, PTFE cannot be processed directly from the melt. Due to its high molecular weight and high melt viscosity, it is manufactured via press moulding and sintering technology.
Depending on diaphragm structure, the pulverulent PTFE is processed and the diaphragm manufactured in various different ways. One-piece and two-piece PTFE/EPDM diaphragms are differentiated between here.

Two-piece PTFE/EPDM diaphragms
Two-piece PTFE/EPDM diaphragms comprise a PTFE diaphragm face with threaded pin and an EPDM back made separately via a compression procedure.

Figure 7: GEMÜ PTFE face with threaded pin and EPDM back

To manufacture the PTFE face, the pulverulent raw polymer and the diaphragm pin are first compressed under pressure at room temperature in a press mould to form a blank. The geometry of the blank differs from the final diaphragm mould. Optimally distributing the PTFE powder in the press tool before compressing the material requires great manufacturer expertise and has an impact on the quality of the final product. The process occurs after a predetermined procedure, in which the timing of the applied pressure (maximum pressure and pressure-retaining and release times) is precisely defined. Before further processing of the still fragile blank, a full quality control is carried out.

In the consequent sintering process, the still fragile blank is heated up under predetermined process parameters and introduced to the sintering process once it exceeds a defined threshold temperature (crystallization melting point). This produces a solid, homogeneous structure made of PTFE. To protect the blank against stresses, a defined cool down phase is required for the warmed material.

The desired diaphragm mould is generated in a downstream quenching process. The blank, which will already have cooled down, is reheated and moulded, then cooled down again in a more controlled manner. The final cooling process, in particular, ensures that the PTFE face has the desired material properties, such as elasticity and stability. The quenched PTFE face is then stamped out and subjected to a new quality control.

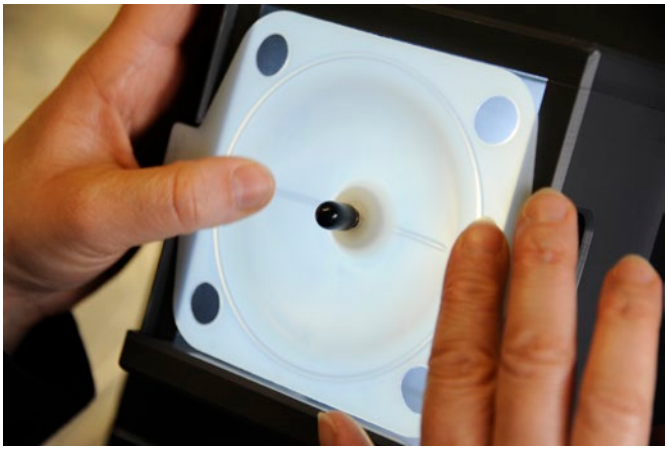

Figure 8: Quality control of the finished PTFE face

Fully laminated PTFE/EPDM diaphragms

In contrast to two-piece PTFE/EPDM diaphragms, fully laminated ones consist of an adhesive joint between the PTFE face and EPDM back.

Figure 9: Fully laminated GEMÜ PTFE/EPDM diaphragms

Instead of the PTFE face, a thin PTFE foil is used.
To manufacture the foil, PTFE powder is first compressed and sintered into a cylinder. The foil is stripped off from this cylinder at the desired thickness.
The foil is etched on one side for further processing, to then allow a chemical bond to be formed with the EPDM back. The etched side is sprayed with a bonding agent and cut to the required size. As with the fabric-reinforced EPDM diaphragm, the PTFE foil, EPDM panels, threaded pin and fabric are combined in a defined way and vulcanized in a cycle using a compression procedure.

Quality assurance and qualification

Quality assurance plays a key role throughout the entire product development and manufacturing process. The quality of the final product is determined as early as in the selection of high-quality raw materials from qualified suppliers. Before further processing, specific product tests, e.g. for checking density, hardness or humidity, are carried out. Materials must be stored under controlled conditions. Ongoing and automated testing and documentation processes, ranging from with incoming goods inspections to production and qualification, are mandatory.
Direct contact between diaphragms in sterile and aseptic applications with foodstuffs, and especially with pharmaceuticals, demands maximum product quality. Legal requirements and regulatory codes determine, among other things, what materials may be used and their maximum extraction values under specific conditions, or their effect when they come into contact with pharmaceuticals, foodstuffs or consumers.
The materials are certified by independent institutes, and the certification comprises occasional examinations in line with the following specifications:

- FDA (US Food and Drug Administration) 21 CFR, section 177.2600 and section 177.1550
- USP (United States Pharmacopeia) Class VI, Chapters 87 and 88
- Regulation (EC) No 1935/2004
- 3-A® Sanitary Standard

Product quality with regard to lack of defects and ability to cope with stress is ensured under realistic test conditions. To this end, several diaphragms from each production batch are subjected to extensive static and dynamic tests.
In addition to valve sealing, the pull-out strength of diaphragms and the pin is checked. To do this, both the required force in the axial direction and the required torque are recorded. For fully laminated PTFE/EPDM diaphragms, the chemical bonds between the components are also checked.

Figure 10: Checking the pin pull-out strength (on the left) and the connection between PTFE and EPDM (on the right)

Cost-intensive endurance tests simulate use under extreme operating, cleaning and sterilization conditions. During these tests, the diaphragms are exposed to different operating pressures, acidic and alkaline cleaning agents and sterile steam, and the valve is thereby clocked. To this end, the ASME BPE standard defines various diaphragm tests and assessment criteria in Nonmandatory Appendix J.
The market release of a diaphragm batch is possible only once all tests have been successfully completed.

Figure 11: GEMÜ CIP/SIP test rig

Conclusion

Based on the many influential factors in the development and manufacture of seal materials for aseptic valve designs, specific expertise is particularly crucial, in addition to in-depth knowledge of materials and physicochemical processes. Even minimal changes in compounding or manufacture can seriously alter the material properties. As well as validated processes and process-integrated quality assurance, each production batch must be qualified and approved for use. The quality of the diaphragms is always a priority, and can form the basis for the safe and successful production of pharmaceuticals.

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