

The challenges faced in developing clean elastomers for medical device applications

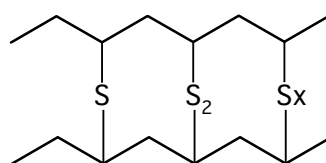
Elastomer Compositions

Elastomers¹ form ideal sealing materials, because in their cross-linked state they are elastic and show stress recovery characteristics. They require smaller deformation forces and 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's ratio of 0.499 compared to 0.3 for steel. The types of base elastomers commonly used in pharmaceutical elastomer sealing compositions are EPDM, Butyl, Nitrile and Polychloroprene.

Elastomers are polymers and their constituent monomers such as ethylene, propylene, isobutylene, and butadiene are gaseous. 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 also have low tensile and compressive strength in comparison to semi crystalline plastics.

A number of additives are mixed with elastomers to convert them into useful rubbery materials. The additives include inorganic fillers such as clay and talc that reinforce and stiffen the elastomers. The particle size of the fillers is generally in the range $0.5\mu\text{m}$ to $10\mu\text{m}$ and generally smaller particle sizes have a greater reinforcing effect. Processing aids are required to mix and disperse the fillers; these are low organic molecular weight additives, mainly fatty acid based species that help the incorporation of polar inorganic fillers into non-polar elastomers. Organic additives² that function as cross-linking agents are also added to effect the curing or the vulcanising process. Cross-linking occurs by a thermo-chemical reaction and the elastomer chains are interconnected by carbon-carbon or carbon-sulphur links known as cross-links. For sulphur cross-linking the elastomer chains must have double bonds.

EPDM has diene and butyl isoprene units that can be sulphur cross-linked. The sulphur cross-links can be monosulphidic, disulphidic and polysulphidic as shown in the diagram below.



The elastomer must be compatible with the environment to which it is exposed. It must not swell or degrade when exposed to the chemicals in the drug formulation. Degradation or swelling weakens the elastomer network and promotes leaching out of chemical species resulting in contamination of the medicament. In Pressurised Metered Dose Inhalers (pMDIs) the elastomer is exposed to a hydrofluoroalkane (HFA) propellant formulation that may also contain solvents such as ethanol and a surfactant as an admixture. Both HFAs and Ethanol are hygroscopic by nature and can promote ingress of moisture. The elastomer should resist loss of propellant vapour, ingress of moisture and maintain uniform elastic properties throughout the life of the inhaler.

The solubility parameter³ (Δ) is a useful tool for assessing an elastomer's compatibility with the solvents used. Generally, the greater the difference between Δ of the elastomer and the solvent, the more resistant the elastomer will be to swelling.

Filler dispersion

Uniform additive, filler dispersion and distribution within the elastomer matrix are required for consistent mechanical and sealing properties. The uniform filler dispersion 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. They do not form part of the elastomer cross-linked network and can diffuse out to the surface. Thus they are potential leachables and contaminants for medicaments. In medical devices the leachable content has to be kept very low, and the use of these materials must be kept to a minimum or avoided. This poses challenges in the mixing process, since without these 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 can occur. This leads to poor flow of the material and defective mouldings.

Designing and controlling the mixing parameters can deliver the effective dispersion of additives and fillers. The mixing cycle has to be long enough to distribute and disperse the additives in the formulation otherwise agglomerates of filler are formed that can dislodge and give rise to potential weak sites leading to failure of the seal.

Results and Discussion

Bespak have a state-of-the-art variable speed high-shear mixer where time, temperature and power can be controlled to keep the mixing cycle as uniform as possible. This cuts down the variability in the viscosity of the mix and leads to production of uniform components.

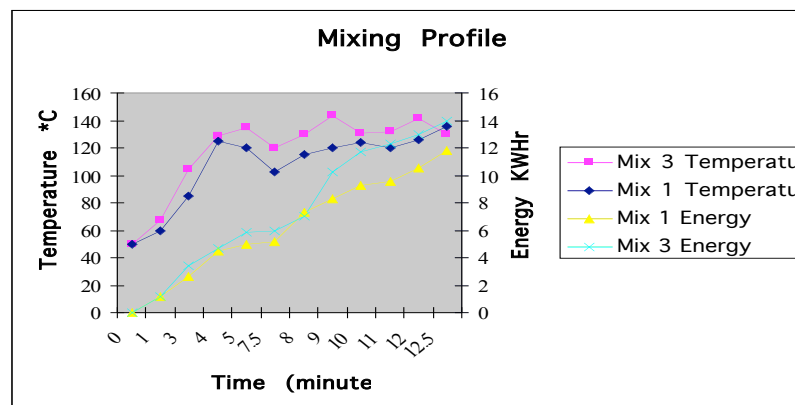
We have studied the effect of varying mixing time and the rotor speed on the mouldability and surface finish of a typical elastomer composition. The mix time /rotor speed variations are given in Table 2.

Table 2: Mix time /rotor speed variations

Mix No	Mixing time (minutes)	Rotor Speed (r.p.m)
1	12.50	22
3	12	25

The mixing profiles (time, temperature and energy) generated are given in Figure 1.

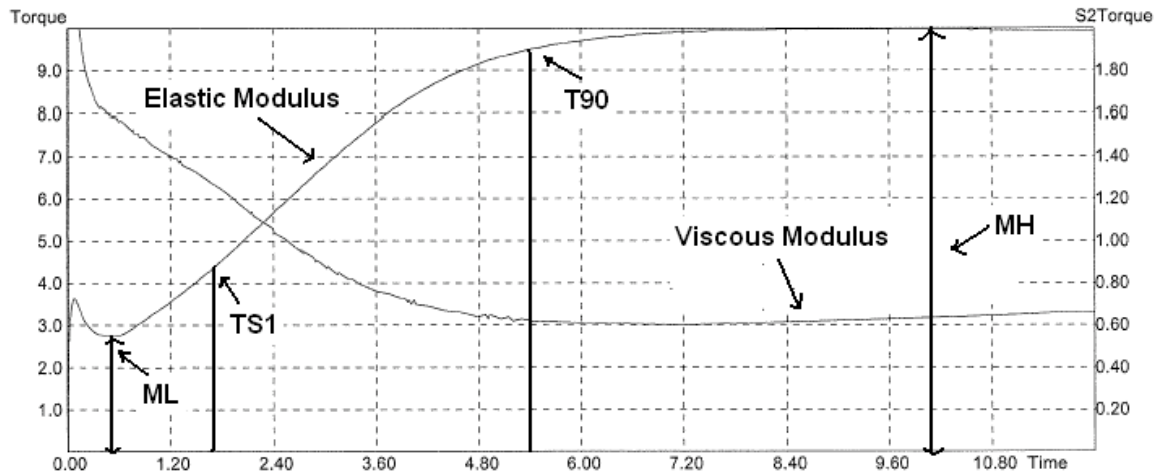
Figure1. Mixing Profiles of Mix 1&3



The curing behaviour of the elastomer mixes was determined at 170°C using the Monsanto MDR200 Rheometer.

A typical rheology curve showing the main parameters for characterising cure profiles of typical elastomers are shown in Figure 2.

Fig 2: A typical Rheology profile of an Elastomer



M_L Minimum torque (elastic modulus) in dN m

M_H Maximum torque (elastic modulus) in dN m

T_{s1} Time in minutes to 1 dN m rise above M_L

T_{90} Time in minutes to 90% of maximum torque M_H

A summary of the cure parameters of the elastomer mixes is given in Table 3. Low value of M_L indicates lower viscosity and faster flow of the elastomer under the curing conditions at 170°C. A high value of T_{s1} (the scorch time) is desirable from a processing view point since this gives the elastomer time to flow and fill the moulding before the cross-linking reaction converts it to a thermo-set material.

Table 3: Elastomer Cure Parameters

Mix No	M_L	T_{s1}	T_{90}
1	2.79	1.28	4.80
3	3.28	1.15	3.44

These differences in the filler dispersion and the surface finish can be explained in terms of the mixing regimes and the rheology of the elastomers. The mix temperature and mixer energy were higher for Mix 3 than Mix 1. This could have led to a higher degree of premature cross linking in Mix 3. Increasing the viscosity of the elastomer makes it more difficult for the filler to be dispersed. This mix would thus have poorer flow during moulding, causing the surfaces to crack. The cure parameters in Table 5 do show that the T_{s1} or the scorch time for Mix 3 is shorter than Mix 1.

We can conclude that derivation and control of mixing parameters is very important both for filler dispersion and the moulding of elastomer components.

Cross-linking conditions for Elastomers

The time and temperature at which cross-linking takes place affects properties such as tensile strength and permeability resistance of the elastomer. The effect of varying these on the moisture permeability of an elastomer composition was studied and is shown in Figures 5.

Figure 5: Interaction Graph

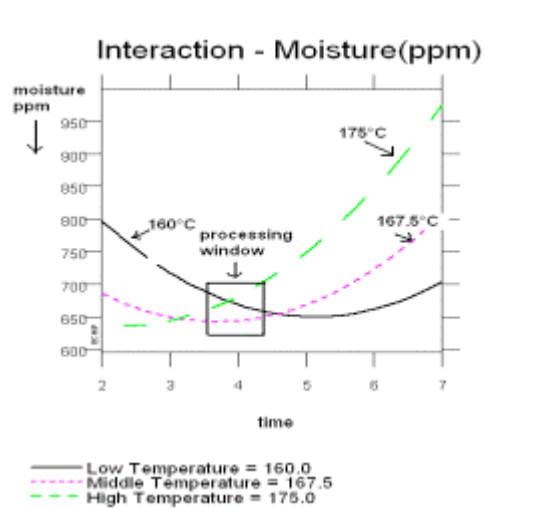


Figure 5 shows that there is a window between about 3.5 to 5.5 minutes within which variations in the temperature range 160°-175°C have little effect on the permeability of the elastomer. The best moulding conditions would be at 4 minutes in this temperature range.

Characterising extractable chemical species from an elastomer and their safety assessment for applications in pMDIs

The elastomer compositions contain potential leachable chemical species and for medical applications there are regulatory and quality control requirements to characterise them

quantitatively and qualitatively. Analysing their acetone extracts using GC-MS identifies the leachable chemical species from the elastomer.

The toxicity of these extracts is assessed by calculating the maximum theoretical daily human dose and referencing this to data in published literature. In carrying out the safety evaluation a conservative approach is adopted in calculating the maximum theoretical human exposure levels to these chemicals. It is generally assumed that each extractable would leach into the pMDI solution from the rubber components at their maximum estimated concentration.

The calculations of the theoretical maximum exposure levels are usually based on the worst-case scenario. Hence, the theoretical amount of extractable present in each MDI can be based on the amount of extractable present “in the valve”.

Example of calculation of theoretical maximum exposure level for ethyl palmitate:

Lets say that the maximum concentration of ethyl palmitate is $15.74 \mu\text{g/g}$ of the rubber.

A “typical” valve assembly can have 0.33 g of rubber.

\therefore Each valve contains a maximum of $15.74 \mu\text{g/g} \times 0.33 \text{ g} = 5.194 \mu\text{g}$

A can holds a maximum of 230 actuations

\therefore Theoretical maximum amount *per* “shot” = $5.19\mu\text{g}/230 = 0.02258 \mu\text{g}$

A maximum recommended dosing regimen for a 50 kg person is 8 shots *per day*,

\therefore Theoretical maximum human exposure = $0.02258 \mu\text{g} \times 8/50$

$$= 0.00361 \mu\text{g/kg/day}$$

$$= 3.61 \text{ ng/kg/day}$$

It is considered that the safety data available in the public domain on these extractables is normally sufficient to indicate that they are unlikely to be hazardous to patients at these low exposure levels. However, for specific medicinal product applications additional toxicity testing is usually necessary.

Leakage of CO₂ in EPDM, Butyl and Nitrile elastomers

In some medical devices CO₂ can be used as a propellant. The elastomer seal for this device must minimise leakage of CO₂. The leakage of CO₂ in EPDM, Butyl and Nitrile elastomers was evaluated using the following test procedure:

Test cans fitted with valves made up of EPDM, Butyl and Nitrile seals were constructed.

The cans were filled with medical grade CO₂ to 23 bar pressure.

Sufficient cans were filled with gas and stored to determine pressure at each time point and environment. 5 cans of each elastomer variant were tested each time to determine pressure of gas.

The gas pressure was determined using a manual pressure gauge. The tested can was discarded after the pressure reading.

The results given in Table 4 show that the cans with Butyl seals exhibited the least decrease in pressure after 4 weeks. This clearly demonstrates that Butyl has the best resistance to the permeation of CO₂ in comparison to EPDM and Nitrile elastomers.

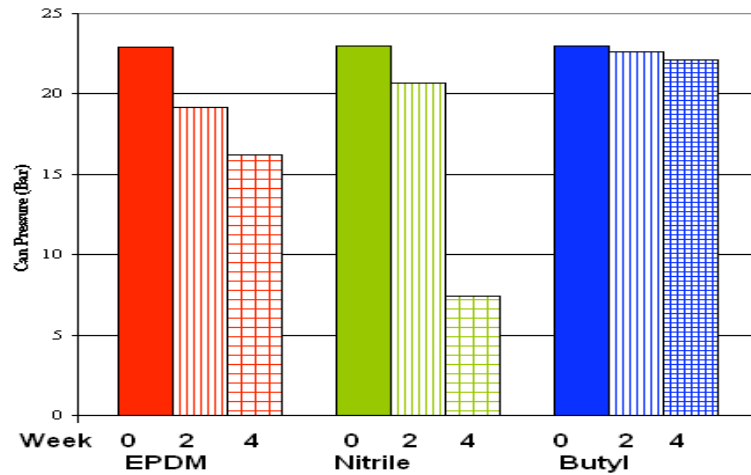
Table 4 – Elastomer resistance to CO₂
Average can pressure and environmental conditions

Elastomer	Time weeks	Environmental Conditions		
		25°C/60% RH	30°C/70% RH	40°C/75% RH
		Av Pressure Bar	Av Pressure Bar	Av Pressure Bar
EPDM	0	22.9	22.9	22.9
	2	20.5	19.9	19.2
	4	17.9	17.8	16.2
Nitrile	0	23	23	23
	2	17.8	17.7	20.7
	4	19.8	15.4	7.4
Butyl	0	23	23	23
	2	22.9	22.5	22.6
	4	22.6	22.3	22.1

Figure 6- Comparison of CO₂ leakage in elastomers.

4 weeks - 40°C and 75% RH

In Figure 6, cans with Butyl seals show the least pressure drop of CO₂ after 4 weeks storage at 40°C and 75% RH, making it a suitable choice for this medical device.



Conclusion

Elastomers form ideal sealing materials, however not all are suitable for medical devices. Their 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 impurities.

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 and minimization of impurities.

Elastomer mix cycles should be carefully designed to be long enough to disperse fillers and additives, but short enough to prevent premature cross-linking of the elastomer.

General References

¹ A N. Gent Engineering with Rubber, 2nd Edition ISBN: 1 – 56990 – 299 – 2

² M Morton Rubber Technology, ISBN: 0 – 442 – 26422 – 4

³ J A Brydson Plastics Materials, ISBN: 0 – 408 – 00538 – 6