

Formulation of clean bromobutyl elastomer composition using a xanthogen polysulphide accelerator for sealing medical devices

D.S.Ohbi¹, R Warby¹, T. Shah², and E.Siores²

¹Bespak Division, Consort Medical plc, King's Lynn, Norfolk PE30 2JJ, UK.

²Centre for Materials Research & Innovation, University of Bolton BL3 5AB, UK

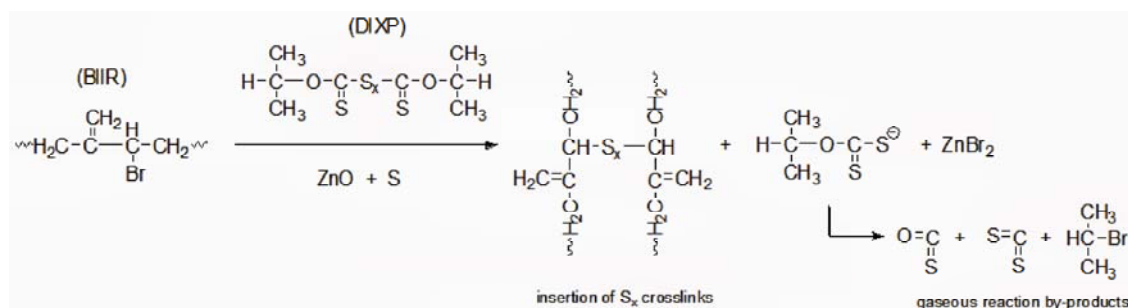
Summary

A clean bromobutyl composition using a xanthogen polysulphide accelerator for sealing MDIs has been developed. The accelerator is consumed during the curing reaction producing mainly gaseous carbonyl sulphide, carbon disulphide and isopropyl bromide by-products which diffuse out of the elastomer leaving it largely free of accelerator related residual chemical species. The curing reaction has a dual reaction order (n), initially n=1, and in the latter part a lower n = 0.6 – 0.7 is obtained where it is believed, some of the polysulphide crosslinks rearrange to form the more stable mono and di-sulphide crosslinks. The moisture ingress in MDIs fitted with bromobutyl and EPDM seals filled with HFA 134a and 227 stored at 40°C/75%RH were determined. Bromobutyl showed a significantly higher resistance to moisture ingress.

Introduction

Bromobutyl elastomer (BIIR) is an ideal material for sealing pressurised metered dose inhalers (MDIs) as it is highly impermeable to moisture, gases and propellants. However it has very low unsaturated sites (2-3 mole %) in comparison to most elastomers and requires the addition of high doses of accelerators such as thiazoles and sulphenamide to achieve an acceptable curing rate. These accelerators are known to liberate amines which can react with nitrosating agents to produce nitrosamines some of which are carcinogenic¹. They also produce residual curing reaction by-products e.g. sulphenamide accelerators produce 2-mercaptobenzthiazole (MBT)². These chemical species are not connected to the elastomer network and can diffuse in to the medical device and contaminate drug products.

The aim of this study was to develop a clean BIIR composition free of residual accelerator related leachable species. The novel BIIR composition³ is crosslinked using a fugitive xanthogen polysulphide (DIXP) accelerator which is totally consumed during the curing reaction producing gaseous carbonyl sulphide, carbon disulphide and isopropyl bromide reaction by-products⁴ as shown (Figure 1). These species diffuse out of BIIR and after curing, the elastomer is free of residual accelerator related leachable species.



⁴Figure 1 – Curing reaction of BIIR with DIXP accelerator.

The curing kinetics of BIIR using the DIXP accelerator were determined⁵. The resistance to moisture ingress of BIIR was compared with an EPDM elastomer.

Methods

Reaction kinetics

The isothermal cure reaction curves of the BIIR composition were obtained from torque (Y) measurements using a rheometer (RPA 2000). The change in (Y) with respect to time is an indirect measure of the rate of curing⁶.

Elastic Shear Modulus (G')

The elastic properties of BIIR were determined by measuring G' using the RPA 2000. The measurements were made at 50°C with the strain fixed at 1.95% and frequency 0.1 Hz.

Determination of moisture ingress into the MDI

50µl MDI valves fitted with BIIR and EPDM seals were crimped onto 19 ml aluminium cans. The MDIs were filled with HFA propellants and allowed to equilibrate in a valve down position at room temperature for 1 week. The moisture ingress into the MDI was determined using the Metrohm 831 Coulometric Karl Fischer titrator. The titrator was calibrated using certified Hydranat[®] 1.0 standard solution which contains 1.00 ± 0.003 ppm water. The MDI test unit was connected to the titrator using an adaptor and fired 5 times and the water content determined. The weight determinations were made using an analytical balance with resolution of 0.01mg. This procedure was repeated 3 times to determine the average water content. After moisture content measurements, the MDIs were stored in a valve down position in an environmental chamber maintained at 40°C and 75% relative humidity (RH). At defined time points, the test samples were removed from the chamber and allowed to equilibrate at 20°C and 33% (RH) for 4 hours before taking the final readings.

Results and Discussion

Reaction kinetics

The cure reaction curves of BIIR using DIXP accelerator have two stages and the kinetics of each stage (Table 1) were determined using the rate equations⁶ (1) and (2).

⁵Table 1 - Kinetic summary for the crosslinking of BIIR.

Crosslinking Temperature	150°C	160°C	170°C	180°C	190°C
1 st part n=	1	1	1	1	1
k	0.1009	0.2274	0.5709	0.9617	2.0978
C	0.4359	0.4717	0.4697	0.6454	1.0688
RSQ	0.9937	0.9916	0.9919	0.9960	0.9995
2 nd part n=	0.61	0.65	0.7	0.6	0.6
k	.0612	0.0951	0.1812	0.3463	0.7688
C'	1.7592	1.4692	1.5097	1.3394	1.5738
RSQ	0.9954	0.9970	0.9955	0.9972	0.9944

For reaction order (n) =1, equation (1) is applicable and when n ≠ equation (2) is used.

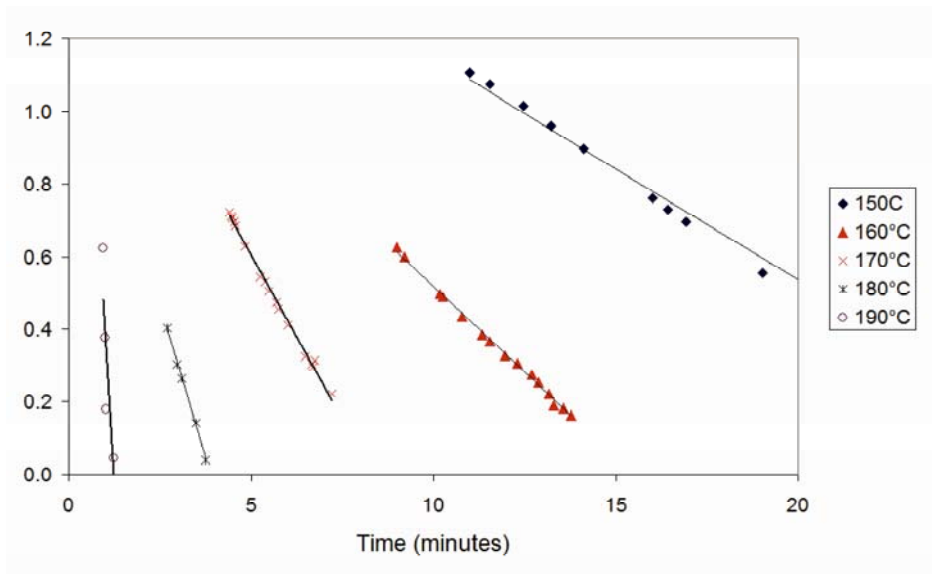
$$\ln\left(\frac{Y_{\infty} - Y}{Y_{\infty} - Y_0}\right) = C - kt \quad (1)$$

$$\frac{1}{1-n} \left(\frac{Y_{\infty} - Y}{Y_{\infty} - Y_0}\right)^{1-n} = C' - kt \quad (2)$$

Y_0 = initial torque, Y = torque at time t, Y_{∞} = maximum torque at $t = \infty$, C and C' are constants and k = rate constant.

The first stage of the curing reaction was determined to be of 1st order (n=1). In this stage, the reaction of DIXP with the unsaturated sites in BIIR creates polysulphidic (S_x) crosslinks (Figure 1).

The curing reaction rates for the second stage fitted equation (2) as shown in Figure 2. The reaction order (n = 0.6 - 0.7) and rate constant (k) obtained were lower than the first stage. It is believed that in the second stage of the curing reaction shortening of the initially formed (S_x) crosslinks⁷ to form more stable di and mono sulphur crosslinks occurs.

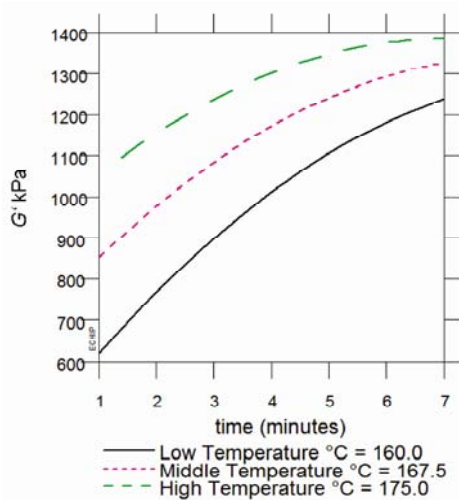


⁵Figure 2 - Determination of the second stage rate constant k for the BIIR-DIXP reaction.

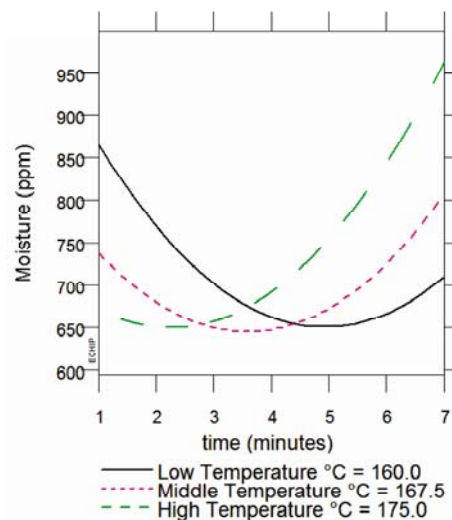
$$\text{Vertical axis shows } \frac{1}{1-n} \left(\frac{Y_{\infty} - Y}{Y_{\infty} - Y_0} \right)^{1-n}$$

Effect of curing conditions on G' and resistance to moisture ingress in BIIR

The effect of variation in the time and temperature of curing BIIR on elastic (G') and resistance to moisture ingress properties is shown in Figure 3 and 4.



⁵Figure 3 – Effect of curing conditions on G' .



⁵Figure 4 – Effect of curing conditions on the resistance to moisture ingress after 3 months storage at 40°C/75% RH.

The G' for BIIR increased with increase in the time and temperature of curing in accordance with the kinetic theory of crosslinking elastomers (Figure 3). However, the moisture ingress showed a concave response at all curing temperatures with respect to time (Figure 4). The initial decrease in moisture ingress with time is due to the build up of crosslink density in BIIR and the process is quicker at higher temperature due to the temperature effect on k (Table 1). The increase in moisture shown by the curvature appears to be related to the gaseous cure reaction by-products evolved during curing. These could affect the microstructure of BIIR causing the increase in moisture ingress. This aspect is being investigated and will form part of a future publication. The optimum curing condition for maximising the BIIR resistance to moisture ingress and a high elastic modulus was found to be 4 minutes at 170°C.

Comparison of the resistance to moisture ingress of BIIR and EPDM

The resistance to moisture ingress of BIIR and EPDM seals was compared (Figure 5) using MDIs filled with HFA 134a and 227 stored at 40°C/75%RH. Bromobutyl showed a significantly higher resistance to moisture ingress than EPDM in MDIs filled with either propellant.

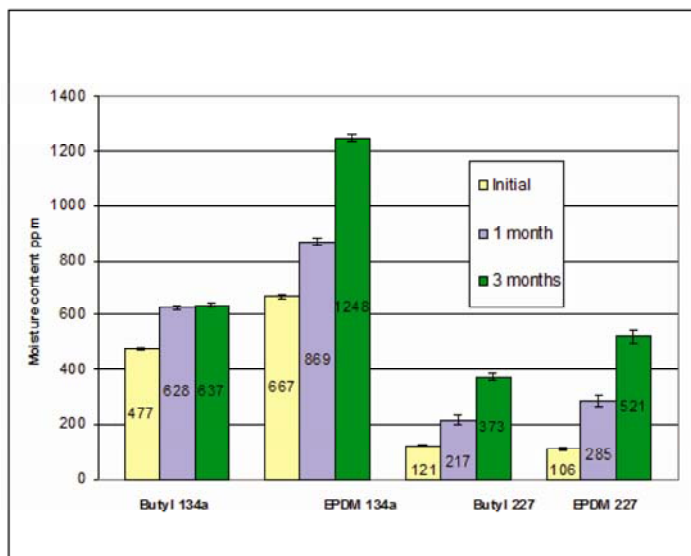


Figure 5 – Comparison of the resistance to moisture ingress of BIIR and EPDM seals in MDIs filled with HFA134a and HFA 227 at 40°C/75%RH.

Conclusions

A novel BIIR composition cured using a fugitive xanthogen polysulphide accelerator has been developed by Bepak. It is free from accelerator related leachable species. The crosslinking kinetics of BIIR and the optimum curing conditions required for maximising both the elastic modulus and resistance to moisture ingress properties have also been determined.

The use of BIIR in MDIs filled with HFA 134a or HFA 227 propellants provides a significantly superior resistance to moisture ingress than EPDM.

References:

1. Layer, R. W.; Chasar, D. W., Rubber Chem and Technol 67, 299 1994.
2. Coran, A. Y. In Science and Technology of Rubbers; Mark, J. E.; Erman, B.; Eirich, F. R., Eds.; Academic Press: Sav Diego, 1994, Chap. 7.
3. Ohbi, D. S.; Beken, S., European Patent EP 1 485 443 B1: 2007.
4. Ohbi, D. S et al., J Appl Polm Sci 107, 4013 2007.
5. Ohbi, D. S et al., J Appl Polm Sci 106, 526 2007.
6. Sheele, L., Katusch.Gummi.Kunst. 43, 138 1965.
7. Aprem, A. S.; Joseph, K.; Thomas, K., Rubber Chem and Technol 78, 458 2005.