A NOTE ON BACTERIOLOGICAL TOXICITY TESTS OF SILICONE RUBBERS FOR MEDICAL AND PHARMACEUTICAL USES

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Tests of the effect on the growth of a number of organisms of several silicone rubbers has been made. The toxicity of suitably compounded rubbers which could be used in pharmacy, medicine and in contact with foodstuffs is very low.

Properly formulated and processed silicone rubbers have been found useful in medicine and pharmacy because of their general inertness, non-toxic and non-irritant properties. Typical applications have been blood transfusion tubes, drainage tubes, baby bottle teats and pharmaceutical vial stoppers. The rubbers used in these applications have generally been formulated to contain, when processed, only silicone polymer, usually a polydimethyl siloxane, and a fine particle size filler, either an amorphous precipitated or a fume silica.

The elastic properties of silicone rubbers are obtained by making a cross-linked structure between the polymer and the filler by means of curing agents which are usually organic peroxy compounds, for example, benzoyl peroxide. In the past it has been felt necessary to ensure removal of the decomposition products of these curing agents and silicone rubbers intended for medical and pharmaceutical applications have, therefore, usually been given long cures in air at high temperatures, for example, 24 hr. at 250°.

For some applications like baby bottle teats, it would be advantageous if a lesser cure than 24 hr. at 250° could be given, since better physical properties, particularly tear strength, would then be obtained. Accordingly it was decided to arrange a series of bacteriological toxicity tests of such rubbers, to assess suitable cures and formulations for rubbers for medical use.

Details of Rubber Formulations

Most modern general purpose silicone rubber stocks are formulated with siloxane polymers having predominantly methyl side groups with a small proportion of unsaturated groups, usually vinyl. One advantage of these vinyl groups is that they enable a wider range of peroxy compounds to be used as curing agents.

Since it was thought that any toxic effects of the cured rubbers were likely to arise from decomposition products of the curing agents, the effects of using several curing agents at various states of cure in a base mix consisting of a polymethyl vinyl siloxane polymer and a fume silica filler, were investigated.

Three curing agents were chosen for the tests, 2,4-dichlorobenzoyl peroxide, dicumyl peroxide and di-tertiary-butyl peroxide. The 2,4-dichloro compound was used because it is the curing agent for most silicone rubber stocks. Dicumyl peroxide was included as an example of the newer curing agents used with polymers containing vinyl groups and so was di-tertiary-butyl peroxide. This latter compound was also thought to have highly volatile decomposition products and might, therefore, show a lower toxicity.

For comparison purposes some tests were also included on two proprietary grades, Silastomer 156 and DP.2452 (Midland Silicones Ltd.). Silastomer 156 is a translucent silicone rubber based on a dimethyl polymer and fume silica filler which has been widely used in medical and pharmaceutical applications and DP.2452 is a more recent development based on a polymethyl vinyl siloxane polymer.

Various formulations were made from a rubber masterbatch containing 100 parts by weight of a polymethyl vinyl siloxane gum and 37·5 parts by weight of a fume silica. This was prepared by mixing 10 parts by weight of Aerosil K3 (Bush Beach and Segner Bayley, Ltd.), with 100 parts by weight of Polysil 2432 (Midland Silicones Ltd.).

Formulation	A	B	C
Rubber masterbatch	100	100	100
2,4-Dichlorobenzoyl peroxide*	0·65	—	—
Dicumyl peroxide	—	0·68	—
Di-tertiary-butyl peroxide	—	—	0·9

* Added as a 40 per cent dispersion of the peroxide in a dimethyl silicone fluid.

Toxicity Tests

There is no generally accepted test of toxicity for medical rubbers. For transfusion rubbers, the toxicity test in common use tests the inhibitory action of the rubber on the growth of a single species of bacteria, *Streptococcus pyogenes*, on a solid medium. This test is described and recommended in the appropriate British Standard (B.S. 2463:1954, Appendix B, page 12). Inhibition of bacterial growth by the substance under test is taken as an indication of its unsuitability for transfusion purposes.

The toxicity test used by us was an extension of the B.S. test for transfusion rubbers, by testing the samples against a number of different bacterial species, instead of against one species only.

Test Method

Samples of the various rubbers were prepared by moulding sheets of nominal thickness 1/16 in. in a press at a temperature appropriate to the curing agent. Subsequent cures in a standard air circulating oven varied from 1 hr. at 150° to 24 hr. at 250°. Pieces of sheet 0·5 × 0·5 cm. were used in the tests. These samples were subjected to one of two types of preliminary treatment: (1) washing in acetone and water, and drying between strips of blotting paper, or (2) sterilising in a domestic pressure cooker for 20 min. at 15 lb./sq. in. steam pressure.

Blood agar plates were heavily inoculated over the entire surface with young glucose broth cultures of the particular bacterium. Pieces of silicone rubber sheeting, after preliminary treatment, were placed at intervals over the surface of the plates. The plates were then incubated at 37° for 24 hr., and then examined. Any inhibition of bacterial growth around the rubber samples were noted. The bacteria used were *Streptococcus pyogenes*, *Staphylococcus pyogenes*, *Bacterium coli*, *Pneumococcus sp.* (except with some washed samples of rubber), *Streptococcus viridans* (with autoclaved, and with a few washed samples) and *Pseudomonas aeruginosa* (with washed samples only).

Results

The results indicate an extremely low toxicity. Even where some inhibition of bacterial growth has been observed, the effect is very small.

TABLE I

THE EFFECT OF DIFFERENT RUBBER FORMULATIONS ON THE GROWTH OF FIVE DIFFERENT BACTERIA. THE SAMPLES WERE AUTOCLAVED FOR 20 MIN. AT 15 LB./SQ. IN. STEAM

Formulation	Oven cure	*Strep. pyogenes*	*Staph. pyogenes*	*B. coli*	*Pneumo coccus*	*Strep. viridans*
A	Nil	0	0	0	0	0
	4 hr./150°	0	0	0	0	0
	4 hr./200°	0	0	0	0	0
	4 hr./250°	0	0	0	0	0
B	Nil	0	0	0	0	0
	4 hr./150°	0	0	0	0	0
	4 hr./200°	0	0	0	0	0
	4 hr./250°	0	0	0	0	0
C	Nil	0	0	0	0	*
	4 hr./150°	0	0	0	0	0
	4 hr./200°	0	0	0	0	0
	4 hr./250°	0	0	0	0	0
Silastomer 156 ..	Nil	0	0	0	*	*
	4 hr./150°	0	0	0	0	*
	4 hr./200°	0	0	0	*	*
	4 hr./250°	0	0	0	0	*
DP.2452	Nil	0	0	0	0	0

0 indicates no detectable inhibition of growth. * indicates inhibition of growth.

The results of some of the tests on autoclaved samples are given in Table I which includes nearly all the positive results but only a small proportion of the negative ones.

Formulations A and B had no detectable effect on the growth of any of the organisms tested both with washed and autoclaved samples and using rubbers at all states of cure. Formulation C gave similar good results in most tests but slight inhibition of the growth of *Streptococcus viridans* was detected with two samples (press cured and oven cured 1 hour/150°) prepared by autoclaving.

Of all the rubbers tested Silastomer 156 gave the greatest number of inhibitory results though in all tests the effect was small. In addition to those noted in Table I, a washed sample of Silastomer 156 oven cured for 4 hr./250° and one of press cured DP.2452, caused slight inhibition of the growth of *Streptococcus pyogenes*. These are the only two of the

samples tested which would have been found unsuitable for transfusion purposes according to the test recommended in the British Standard for transfusion rubbers.

Conclusions

Suitably compounded and processed rubbers have a very low toxicity which makes them suitable for use in pharmacy, medicine and in contact with food stuffs. For the most stringent applications a silicone rubber compounded from a polymethyl vinyl siloxane, a fume silica and either dicumyl or 2,4-dichlorobenzoyl peroxide is to be recommended.