AN EXAMINATION OF RUBBER USED AS A CLOSURE FOR CONTAINERS OF INJECTABLE SOLUTIONS

PART II. THE ABSORPTION OF CHLOROCRESOL

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THE examination of rubber has continued with the investigation of the absorption of chlorocresol. Many of the rubbers examined for phenol absorption[1] have been used and are referred to under the same sample numbers and their composition is given in Table I.

TABLE I

PARTICULARS OF RUBBER SAMPLES EMPLOYED

Sample number	Type of tubing	Rubber content, per cent.	Main filler	Other details
1	Red	33	Calcium carbonate	Laboratory tubing
2	Red	50	Calcium and magnesium carbonates	Drainage tubing
3	Latex	90	Magnesium carbonate	Transfusion tubing
4	Black	50	Carbon black	Anti-static tubing
5	Red	—	—	General purpose tubing
6	Red	—	—	"
7	Latex	—	—	Transfusion tubing
8	Latex-silicone	—	None	Vulcanising ingredients:—sulphur, zinc oxide and organic accelerator of dithio-carbamate series. Latex is pre-vulcanised and afterwards centrifuged to remove surplus vulcanising ingredients
9	Silicone	—	Silica	Transfusion tubing
10	Red	50	Calcium and magnesium carbonates	Drainage tubing

EXPERIMENTAL AND RESULTS

Estimation of Chlorocresol

The method used, as with phenol, was based on the production of a blue colour with Folin-Ciocalteau reagent in alkaline solution, the intensity of which was estimated in a Spekker absorptiometer.

A calibration curve was produced using dilutions of an 0·2 per cent. solution of chlorocresol containing 0·032, 0·064, 0·096, 0·128, 0·16, 0·24 and 0·32 mg. per 4 ml. To each was added 0·6 ml. of Folin-Ciocalteau reagent and 1 ml. of 25 per cent. solution of sodium carbonate. The solutions were mixed, heated for 15 minutes in a water bath at 37° C. and readings obtained in a Spekker absorptiometer using filter number 608 with the test and blank solutions in 1 cm. cells.

When determining solutions which had been in contact with rubber, suitable dilutions were made to contain 0·05 to 0·12 mg. per 4 ml. when using the 1 cm. cell. The concentration of chlorocresol was read from the calibration curve and the strength of the original solution obtained from the following equation.

$$\text{Chlorocresol concentration (percentage w/v)} = \frac{\text{No. of mg. per 4 ml. of dilution} \times 25 \times \text{dilution}}{1000 \times \text{thickness of cell in cm.}}$$

Rate and Extent of the Absorption of Chlorocresol

Rubber sample No. 10 was used to investigate the effect of time, temperature and the concentration of chlorocresol solutions upon rate and degree of absorption.

Tubes containing approximately 2 g. of rubber immersed in 10 ml. of 0·1 and 0·2 per cent. solutions of chlorocresol were flame sealed. Half were placed in a refrigerator at 2° C. and half in an incubator at 37° C., pairs being removed at intervals and analysed for chlorocresol content. Controls without rubber were similarly treated.

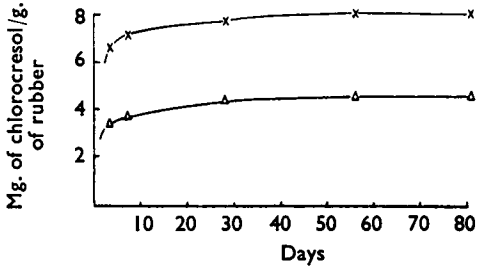

FIG. 1. Rate and amount of chlorocresol absorbed by rubber sample 10 when immersed in chlorocresol solutions of ×—× = 0·2 per cent. and △—△ = 0·1 per cent. at 2° C.

Table II shows that whereas the absorption of chlorocresol by rubber is rapid at 2° C. and about 75 per cent. of the final absorption is achieved in 3 days, complete absorption is not reached until about 7 weeks after contact with the solution. This is shown more clearly in Figure 1.

TABLE II

CHLOROCRESOL CONTENT OF RUBBER AND IMMERSING SOLUTIONS AFTER INTERVALS OF STORAGE AT 2° C.

Chlorocresol content of original solution per cent. w/v	Storage time	Weight of rubber g.	Chlorocresol in rubber mg.	Chlorocresol in 10 ml. of solution mg.
0·1	86 hours	1·96	6·95	3·05
	181 hours	1·99	7·39	2·61
		2·01	7·35	2·64
	28 days	1·97	8·69	1·24
		1·96	8·69	1·24
	58 days	2·02	9·22	0·88
		1·99	9·22	0·88
	81 days	2·01	9·22	0·88
0·2	86 hours	1·99	13·2	6·8
	181 hours	2·02	14·83	5·17
		2·04	14·40	5·60
	28 days	2·00	15·98	2·62
		2·01	15·72	2·88
	58 days	2·04	18·6	1·90
		1·99	18·6	1·90
	81 days	1·99	18·65	1·85

Table III shows that absorption is almost complete in one day when stored at 37° C.

The partition coefficients at equilibrium

$$K_{0\cdot1}^{2^\circ C.} = 62,\ K_{0\cdot2}^{2^\circ C.} = 59,\ K_{0\cdot1}^{37^\circ C.} = 42{\cdot}9,\ K_{0\cdot2}^{37^\circ C.} = 42{\cdot}9$$

TABLE III

CHLOROCRESOL CONTENT OF RUBBER AND IMMERSING SOLUTIONS AFTER INTERVALS OF STORAGE AT 37° C.

Chlorocresol content of original solution per cent. w/v	Storage time	Weight of rubber g.	Chlorocresol in rubber mg.	Chlorocresol in 10 ml. of solution mg.
0·1	1 day	2·06	8·62	1·38
		2·03	8·62	1·38
	3 days	2·06	8·73	1·28
		2·06	8·73	1·28
	7 days	2·03	8·68	1·32
		2·00	8·63	1·37
	23 days	2·01	8·61	1·20
		2·00	8·62	1·19
0·2	1 day	2·04	17·15	2·85
		1·99	17·05	2·95
	3 days	1·97	17·33	2·67
	7 days	2·00	17·28	2·72
		2·00	17·33	2·67
	23 days	2·03	17·24	2·38
		1·99	17·28	2·34

show that whereas the amount of chlorocresol absorbed was directly proportional to the concentration of the immersing solutions, this was less at 37° C. than at 2° C. being approximately 86 per cent. and 92 per cent. respectively.

TABLE IV

PARTITION COEFFICIENTS FOR RUBBER SAMPLES 1 TO 9

Sample	Specific gravity or rubber	K 2° C. 0·1		K 2° C. 0·2		K 37° C. 0·1		K 37° C. 0·2	
		Readings	Mean	Readings	Mean	Readings	Mean	Readings	Mean
1	1·37	37·2 36·3	36·7	36·8 36·8	36·8	30·2 33·2	31·7	33·1 33·0	33·0
2	1·22	52·8 53·6	53·2	55·9 56·1	56·0	39·5 40·9	40·2	46·3 47·5	46·0
3	0·994	26·7 27·2	26·8	25·0 24·4	24·7	24·8 26·2	25·5	22·8 22·7	22·7
4	1·176	39·1 40·2	39·7	33·0 34·1	33·5	27·7 27·3	27·5	24·4 21·7	23·0
5	1·112	35·9 35·6	35·7	33·4 33·8	33·6	25·4 26·0	25·7	24·8 24·9	24·8
6	1·125	40·2 39·7	39·9	40·2 39·7	39·9	29·6 29·9	29·8	29·5 29·0	29·3
7	0·923	16·6 16·7	16·6	14·4 14·8	14·6	14·7 14·9	14·8	12·2 12·5	12·3
8	0·915	14·1	14·1	18·2 18·5	18·3	14·5 14·8	14·6	14·2 14·5	14·3
9	1·176	7·1 7·2	7·1	7·1 6·9	7·0	6·3 6·6	6·4	6·5 6·5	6·5

The Partition Coefficients of Chlorocresol for Several Rubbers

The same series of rubbers 1 to 9 mentioned in the previous paper[1] were examined to determine the amount of chlorocresol absorbed under several set conditions. Tubes containing approximately 2 g. of rubber were immersed in 10 ml. of 0·1 per cent. or 0·2 per cent. chlorocresol solution, heat sealed, and stored either at 2° C. or 37° C. The solutions

were examined after 55 and 21 days respectively. In Table IV are given the partition coefficients for chlorocresol where

$$K_c^t = \frac{Cr}{Cw} \text{ where } K = \text{partition coefficient}$$

at temperature t determined for rubber immersed in chlorocresol solution of strength c expressed as percentage w/v; Cr = concentration of chlorocresol in rubber expressed as mg./ml.; Cw = concentration of chlorocresol in water expressed as mg./ml.

It is seen that in all instances there is a higher absorption of chlorocresol at 2° C. than at 37° C., but that variation of the concentration of the immersing solutions, between 0·1 and 0·2 per cent. has little effect upon the partition coefficient. The proportion of chlorocresol absorbed is much higher than with phenol. For silicone tubing it is just over 50 per cent., for translucent latex rubber tubings between 73 and 80 per cent. and for other rubbers up to 91 per cent. This results in partition coefficients which are approximately 20 times greater than for phenol with the same rubber.

Berry[2] has also mentioned a similar degree of absorption from 0·1 per cent. solutions of chlorocresol.

Summary

1. The absorption of chlorocresol from aqueous solution by rubber has been shown to proceed to a state of equilibrium under controlled conditions of storage.

2. The amount of chlorocresol absorbed bears a direct relation to the concentration of chlorocresol in the solution in contact with the rubber.

3. The rate of absorption increases with rise of temperature.

4. The amount absorbed is less at 37° C. than at 2° C.

5. The amount absorbed varies with the type of rubber.

References

1. Wing, *J. Pharm. Pharmacol.*, 1955, **7**, 649.
2. Berry, *ibid.*, 1953, **5**, 1014.