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

PART I. FACTORS AFFECTING THE ABSORPTION OF PHENOL

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INTRODUCTION

RUBBER closures are used extensively to seal containers of a variety of injectable solutions and these are composed of rubber of widely differing compositions. The British Pharmacopœia 1953 states simply that rubber closures are made from suitable heat vulcanised rubber of good quality, and does not define any controlling chemical tests or physical standards. It does recognise, however, the property of rubber in absorbing sulphite and bacteriostatic substances. It directs that closures to be used for sealing containers, in which the injection containing these substances is enclosed, shall be subject to refluxing or contact with solutions equal to or double the strength of the sulphite or bacteriostatic substance concentration in the final injection. These requirements in no way standardise the type of rubber, particularly in limiting its physical variation or chemical reactivity with the ingredients of the injections into which it comes into contact. In a recent paper Wiener[1] has shown the ability of rubber to absorb thiomersalate from solution. Burrell[2] mentions the absorption of phenol, chlorbutol, chlorocresol and phenylmercuric nitrate by pure latex rubber. McGuire and Falk[3] have shown that phenol is absorbed by rubber caps on prolonged storage and Berry[4] has noted the amount of chlorocresol withdrawn from solution by rubber caps, and has referred to the absence of detailed evidence about this subject.

ESTIMATION OF PHENOL

The writer has employed a method for the estimation of phenol using Folin-Ciocalteau reagent. Initially a calibration curve was produced using dilutions of a stock standard solution of phenol containing 0·03, 0·06, 0·09 and 0·12 mg. of phenol per 4 ml. 0·6 ml. of Folin-Ciocalteau reagent and 1 ml. of 25 per cent. solution of sodium carbonate was added to each. After shaking to mix and heating for 15 minutes in a water bath at 37° C. readings were obtained in a Spekker absorptiometer using filter number 608 and with the test and blank solutions in 1 cm. cells.

When determining the solutions which had been in contact with rubber, suitable dilutions were made to contain approximately 0·05 mg. per 4 ml. or 0·1 mg. per 4 ml. when using 0·5 cm. cells.

4 ml. of this solution was treated as above and the readings made in the Spekker absorptiometer. The concentration of phenol was read from the calibration curve and the strength of the original solution obtained from the following equation.

Phenol concentration = No. of mg. per 4 ml. of dilution × 25 × dilution.
(Percentage w/v) — Thickness of cell in cm.

Composition of Rubber

Rubber is a complex mixture in which latex or acid precipitated latex dried in smoke houses or the air is combined with a number of chemical substances. Sulphur is usually included as the vulcanising agent, zinc oxide as the activator and such organic substances as aldehyde amines, guanidines, dithiocarbamates and benzthiazoles as accelerators. Fillers are also added; these including such substances as chalk, magnesium carbonate, zinc oxide, china clay, silica and carbon. Latex contains proteins, resins, querbrachit and sugars, and also in its preservation, ammonia is commonly added.

In this investigation a number of rubbers have been chosen mainly from commercial sources. Particulars of these tubings are 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

Rate and Extent of the Absorption of Phenol

Apart from the different compositions of rubber, additional factors involved in the absorption of phenol are time, temperature and the concentration of the phenol solution in contact. Rubber sample No. 10 was used to investigate these factors, two series of tubes being stored at 2° C. and 37° C.

In the first series, four tubes containing 7·5 cm. of rubber tubing were immersed in 15 ml. of 0·5, 1, 2 and 4 per cent. solutions of phenol together with four tubes containing phenol solutions only. These were placed in a refrigerator at 2° C. In the second series five sets of eight tubes were set up, each containing 5 cm. of rubber tubing and immersed in 10 ml. of 0·5, 1, 2, 4, and 7·5 per cent. solutions of phenol. Five sets of each of the phenol solutions were similarly prepared. All tubes were flame-sealed and placed in an incubator at 37° C.

Measured volumes were removed at intervals from the first series, and the phenol content of the solution determined. Similarly, the tubes of

the second series were taken at intervals, opened and the contents analysed for phenol.

Table II shows the amount of phenol which was absorbed by the rubber after increasing periods of time in the phenol solution at 2° C., and for comparison is expressed as mg. of phenol absorbed per g. of rubber. This

TABLE II

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

Phenol content of original solution per cent. w/v	Storage time	Total phenol absorbed in mg.	Amount of phenol absorbed per g. of rubber	No. of mg. of phenol in solution	Volume of solution in ml.
0·5	7 hours	4·5	1·50	70·5	15·0
	26 ,,	4·8	1·60	67·9	14·5
	170 ,,	4·8	1·60	65·5	14·0
	3 weeks	13·0	4·25	62·0	15·0
	6 ,,	16·9	5·53	54·6	14·3
	24 ,,	18·4	6·02	45·4	13·6
0·98	7 hours	2·0	0·65	145·0	15·0
	26 ,,	6·2	2·00	136·0	14·5
	170 ,,	14·5	4·71	123·0	14·0
	3 weeks	25·9	8·41	121·0	15·0
	6 ,,	25·9	8·41	112·6	14·4
	24 ,,	32·0	10·40	95·1	13·6
1·95	7 hours	5·25	1·70	287·3	15·0
	26 ,,	13·0	4·13	270·0	14·5
	170 ,,	35·0	11·10	238·0	14·0
	3 weeks	44·4	14·10	247·5	15·0
	6 ,,	44·2	14·10	240·0	14·6
	24 ,,	66·8	21·20	194·4	13·8
3·90	7 hours	15·0	4·76	570·0	15·0
	26 ,,	26·1	8·29	539·0	14·5
	170 ,,	71·4	22·70	474·6	14·0
	3 weeks	91·2	28·90	494·0	15·0
	6 ,,	90·2	28·60	463·5	14·6
	24 ,,	124·4	39·50	412·4	13·8

TABLE III

PHENOL CONTENT OF RUBBER AFTER INTERVALS OF IMMERSION AT 37° C. IN DIFFERENT STRENGTHS OF PHENOL

Approximate strength of phenol solution, per cent.	Period of storage	Total phenol absorbed in mg. (average of two determinations)	Amount of phenol (mg.) absorbed per g. of rubber
0·5	7 hours	3·55	1·71
	26 ,,	9·85	4·76
	7 days	11·85	5·72
	21 ,,	12·15	5·87
1	7 hours	13·50	6·52
	26 ,,	20·35	9·83
	7 days	22·00	10·62
	21 ,,	23·00	11·11
2	7 hours	21·70	10·48
	26 ,,	30·60	14·78
	7 days	45·70	22·08
	21 ,,	44·10	21·30
4	7 hours	35·40	17·10
	26 ,,	60·45	29·20
	7 days	84·00	40·60
	21 ,,	83·70	40·43
7·5	7 hours	94·50	45·65
	26 ,,	127·80	61·73
	7 days	145·60	70·30
	21 ,,	145·00	70·10

is also shown more clearly in Figure 1. Similarly Table III and Figure 2 show the amount of phenol absorbed during storage at 37° C.

It is seen that a similar state of equilibrium is eventually reached, but more slowly, at the lower temperature. At 37° C. the absorption is rapid
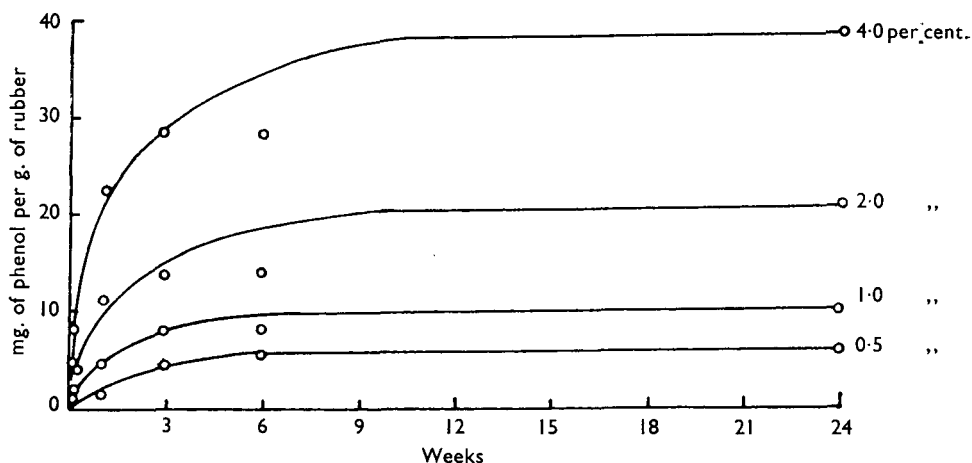

FIG. 1. Rate and amount of phenol absorbed by rubber sample 10 when immersed in phenol solutions at 2° C. of the strength indicated.

during the first day and equilibrium is reached about the sixth day of contact. At 2° C. an appreciable proportion of phenol is absorbed after 3 days but equilibrium seems to be delayed for 7 to 15 weeks depending on the concentration of phenol solution. It also appears that the amount of phenol absorbed is almost directly proportional to the concentration of the original phenol solution. After equilibrium is reached this sample of rubber did not continue to absorb phenol, contrary to the inference of the Pharmacopœia.

In order to determine to what extent this process was reversible the final samples under examination at 37° C. were transferred, after the sealed tubes had been opened for analysis, and after solution had been
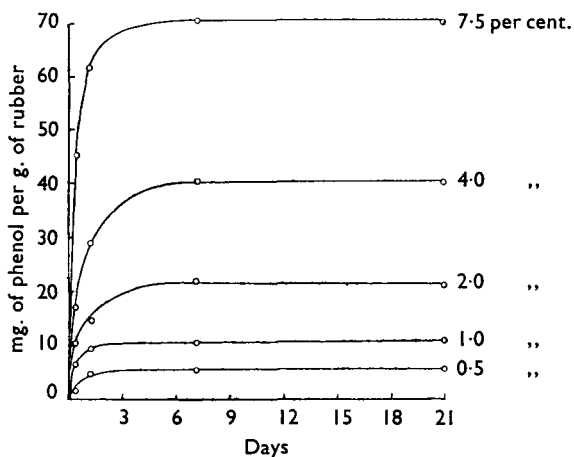

FIG. 2. Rate and amount of phenol absorbed by rubber sample 10 when immersed in phenol solutions at 37° C. of the strength indicated.

removed from the rubber with a dry cloth, to 10 ml. of water in test tubes. These were sealed by heating the glass and replaced in the incubator at 37° C.   After 10 days the solution in the tubes was analysed.   The results of this are shown in Table IV.

TABLE IV

THE PHENOL CONTENT OF A SAMPLE OF RUBBER AFTER IMMERSION IN PHENOL SOLUTIONS AND AFTER THE SAME SAMPLE HAD SUBSEQUENTLY BEEN PLACED IN WATER FOR 12 DAYS AT 37° C.

A. Rubber immersed in phenol solutions		B. Rubber containing phenol immersed in water	
Amount of phenol in rubber in mg.	Concentration of phenol in water as mg. per 10 ml.	Amount of phenol in rubber in mg.	Concentration of phenol in water as mg. per 10 ml.
12·15	37·15	2·85	9·30
23·00	75·60	6·25	16·75
44·10	153·40	11·90	32·20
83·70	313·40	18·60	64·60

When one divides the amount of phenol, expressed as mg. in the 10 ml. of aqueous phenol solution in contact with the rubber, by the phenol content of the rubber at the points of equilibrium shown in Table III and Table IV the figures obtained point to a similar relationship in the distribution of phenol.   One can thus conclude that the reaction is reversible. The figures for comparison are given in Table V.

TABLE V

Strength of original phenol solution (approx.), per cent.	Concentration of phenol solution at equilibrium in mg. per 10 ml. divided by total amount of phenol in rubber in mg.	
	A. Rubber immersed in phenol solution	B. Rubber containing phenol immersed in water
0·5	3·06	3·36
1·0	3·29	4·25
2·0	3·49	2·71
4·0	3·75	3·47

PHENOL ABSORPTION BY DIFFERENT RUBBERS

It was felt that the results obtained in the examination of one sample of rubber tubing should be extended to other rubbers to see whether the absorption process followed a common pattern.

Nine rubber tubings, samples 1 to 9, were taken and ten 5 cm. lengths of each were weighed.   Four of each sample were placed in tubes with 10 ml. of 0·5 per cent. w/v phenol solution.   Two of each were stored respectively at 2° C. for 44 days and 37° C. for 7 days.   Six of each sample were similarly placed in 10 ml. of 4 per cent. w/v phenol solution and two of each were stored for 16 hours, 64 hours and 10 days respectively. All tubes during storage were sealed by flame sealing of glass.   At the end of the period of storage all were opened and the phenol content of the solution determined.   At the same time the strength of solutions containing approximately 0·5 per cent. and 4 per cent. of phenol were similarly determined and the pH value of all solutions from the opened tubes was determined electrometrically.   In addition, a further duplicate set of

ten tubings including sample 10 were placed in 4 per cent. w/v phenol solution at 37° C. for 12 days.

In order to see whether the process was reversible, the tubings which had been stored at 2° C., in 0·5 per cent. w/v phenol solution after removal of the phenol solution in which they had been immersed, were transferred to 10 ml. of water and stored for 13 days at 37° C. in sealed tubes. Similarly the second series which had been stored at 37° C. in 4 per cent. w/v phenol solution were subject to 7 weeks storage at 37° C. in 10 ml. of water. All were examined at the end of storage for both phenol content and pH value.

From an examination of the amounts absorbed by the sample tubings 1 to 9 stored for 16 hours, 64 hours and 10 days, it can be seen that the results show a close comparison with the rate of phenol absorption by sample 10 as illustrated in Figure 1, namely, that at 37° C. roughly 75 per cent. of the total absorption is completed in 16 hours and 95 per cent. and upwards of total absorption is reached after 64 hours storage. The results are shown in Table VI.

TABLE VI

SHOWING THE AMOUNT OF PHENOL IN MG. ABSORBED BY 5 CM. OF TUBING FROM 4 PER CENT. W/V PHENOL SOLUTION AT 37° C.

Sample	Time of storage		
	16 hours	64 hours	10 days
1	48, 55	66, 59	72, 63
2	69, 57	77, 78	83, 79
3	—, 38	50, 46	56, 51
4	52, 47	49, 44	56, 54
5	53, 51	53, 57	—, 64
6	44, 55	53, —	54, 63
7	29, 38	46, 38	47, 39
8	43, 37	42, 44	51, 41
9	23, 21	24, 21	29, 18

When the rubber tubings had been in contact with the phenol solutions for periods of time which had been shown from the previous results to be sufficient for the establishment of equilibrium, it became apparent that in the case of each rubber,

(1) the amount of phenol absorbed was constant when in contact with the same strength of phenol solution,

(2) the amount of phenol absorbed was almost directly related to the concentration of the phenol solution,

(3) the process was reversible and proceeded to a point of equilibrium whether the rubber was receiving phenol from phenol solution or transmitting it to water, and

(4) the rate of absorption of phenol increased with temperature.

In this process it appeared that rubber acted as a solvent.

Tables VII and VIII show the results upon which these conclusions are based.

It can be seen from Table VIII that the phenol content of the aqueous solution in contact with each rubber shows a high degree of uniformity between the two samples examined, thus pointing to a uniform distribution of phenol between water and rubber when the conditions of storage remain constant. The larger differences occurring in the phenol content of rubber are explained by normal limits of error which result from the fact that these calculations are obtained by difference and not by direct analysis as in the solutions.

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TABLE VII

PHENOL DISTRIBUTION BETWEEN RUBBER AND WATER AT POINTS OF EQUILIBRIUM

Concentration of original phenol solution = 0·5 per cent. w/v approx

Sample No.	Storage time in days							
	7 (37° C.)		7 (37° C.)		44 (2° C.)		44 (2° C.)	
	a	b	a	b	a	b	a	b
1	9·4	3·89	8·7	3·96	8·2	4·07	7·6	4·20
2	10·8	3·75	11·7	3·68	11·2	3·77	12·1	3·75
3	6·3	4·20	6·6	4·17	6·1	4·28	6·8	4·28
4	6·1	4·22	6·2	4·21	6·8	4·21	7·1	4·25
5	9·3	3·90	8·7	3·96	9·0	3·99	9·6	4·00
6	9·4	3·89	8·7	3·96	9·6	3·93	11·1	3·95
7	3·6	4·47	4·1	4·42	3·9	4·50	5·1	4·45
8	5·0	4·33	4·5	4·38	6·3	4·26	6·4	4·32
9	2·5	4·58	2·8	4·55	2·8	4·61	3·3	4·63

Concentration of original phenol solution = 4 per cent. w/v approx.

Sample No.	Storage time in days							
	12 (37° C.)		12 (37° C.)		10 (37° C.)		10 (37° C.)	
	a	b	a	b	a	b	a	b
1	76·0	31·7	78·0	31·5	63·0	33·7	72·0	32·8
2	86·0	30·8	82·0	31·1	79·0	32·1	83·0	31·7
3	52·0	34·1	45·0	34·8	51·0	34·9	56·0	34·4
4	53·0	34·1	50·0	34·3	54·0	34·6	56·0	34·4
5	66·0	32·7	64·0	32·9	64·0	33·6	—	—
6	68·0	32·5	71·0	32·2	63·0	33·7	54·0	34·5
7	42·0	35·1	35·0	35·8	39·0	36·1	47·0	35·3
8	55·0	34·9	38·0	35·5	41·0	35·9	51·0	34·9
9	11·0	38·2	17·0	37·6	18·0	38·2	29·0	37·1
10	75·0	31·8	82·0	31·2	—	—	—	—

a = mg. of phenol in rubber.
b = mg. of phenol per ml. of solution of phenol.

TABLE VIII

PHENOL DISTRIBUTION BETWEEN RUBBER AND WATER AT EQUILIBRIUM AFTER RUBBER
SAMPLES 1 TO 9 CONTAINING PHENOL HAD BEEN PLACED IN WATER AND STORED AT 37° C.

Sample No.	Stored in 0·5 w/v phenol solution before transfer to water		Stored in 4 w/v phenol solution before transfer to water	
	Phenol distribution		Phenol distribution	
	Rubber, mg.	Water, mg. per ml.	Rubber, mg.	Water, mg. per ml.
1	1·7, 1·2	0·65, 0·64	14·4, 14·6	6·21, 6·37
2	2·6, 2·9	0·86, 0·92	18·8, 15·6	6·68, 6·66
3	0·5, 1·2	0·56, 0·56	9·3, 3·6	4·28, 4·16
4	1·1, 1·1	0·57, 0·60	10·2, 7·7	4·25, 4·25
5	1·7, 2·1	0·73, 0·75	15·8, 14·0	5·05, 5·28
6	2·2, 2·2	0·74, 0·77	17·8, 18·7	5·05, 5·28
7	0·3, 1·3	0·36, 0·38	6·2, 1·8	3·59, 3·34
8	1·0, 0·8	0·53, 0·56	17·6, 1·5	3·70, 3·62
9	— —	0·37, 0·37	— —	2·78, 2·81

THE RELATIONSHIP OF ALKALINITY TO PHENOL ABSORPTION

Phenol under some circumstances acts as an acid, and rubber often contains alkaline fillers such as zinc oxide and alkali carbonates. In addition, ammonia is often added to latex. For this reason it was decided to examine all solutions, after being stored in contact with rubber to determine whether phenol absorption could be related to the alkaline reaction of the rubbers examined. From Table IX it is seen that, although there appeared a certain uniform variation between each series of

rubber examined, and the *p*H alteration of solution to the alkaline side in some cases bore a relation to phenol absorption, this was by no means consistent. The alkaline nature of the tubings might be interpreted to being one minor factor, out of several, which possibly influenced the main process of absorption of phenol.

TABLE IX

THE *p*H OF PHENOL SOLUTIONS AFTER RUBBER HAD BEEN STORED IN THEM

Strength of phenol solutions, per cent. storage time	4 16 hours	4 64 hours	4 10 days	4 10 days	4 10 days	0·5 7 weeks	0·5 7 weeks	A 13 days	B 13 days	C 14 days
Sample										
1	—	7·66	7·8	7·75	7·85	7·14	—	6·67	7·4	6·67
2	7·13	7·3	7·58	7·70	7·73	6·96	6·68	8·1	7·28	6·72
3	7·20	7·12	7·42	7·38	7·46	6·47	6·53	7·78	7·16	6·32
4	6·86	6·91	7·22	7·12	7·22	6·08	6·42	7·33	7·70	6·05
5	6·86	6·96	7·18	6·90	7·00	6·16	6·00	7·12	6·32	5·92
6	6·82	6·83	7·20	6·81	6·88	6·15	6·04	6·93	6·40	5·84
7	6·63	6·45	6·83	6·38	6·81	5·44	5·74	6·46	6·20	5·78
8	7·12	7·14	7·24	7·11	7·18	6·84	6·57	6·32	6·36	6·55
9	6·4	6·23	6·71	6·29	6·82	5·47	5·76	6·67	6·12	5·42
Phenol solution	6·45	5·16	6·42	6·66	6·77	5·48	5·48			

A and B = Water into which phenol had passed from rubber containing phenol.
C = Rubber immersed in water.

PHENOLIC SUBSTANCES IN RUBBER

Rubber samples were autoclaved in 10 ml. of water for 1 hour, auto-claved a second time, and again examined after 14 days storage at 37° C. to determine whether phenolic substances were transferred to the water, and whether that had any direct relationship to phenol absorption. The amounts, calculated as phenol, were very small but did indicate the possibility that phenolic substances used in manufacture had increased the phenolic absorption. On the other hand, this could not be regarded as the main factor. Also, it is noted that these substances can be removed by repeated treatment as shown in Table X.

TABLE X

THE AMOUNT OF PHENOLIC SUBSTANCE, CALCULATED AS MG. OF PHENOL, TRANSMITTED TO 10 ML. OF WATER BY 5 CM. OF EACH RUBBER TUBING

Sample	Autoclaved 1 hour	Again autoclaved 1 hour	14 days at 37° C.
1	0·210	0·104	0·128
2	0·246	0·065	0·155
3	0·055	Less than 0·020	0·078
4	0·103	0·040	0·061
5	0·261	—	0·156
6	0·280	—	0·167
7	0·090	—	0·045
8	—	—	0·186
9	—	—	Less than 0·020
10	0·125	—	0·137

A PARTITION COEFFICIENT FOR RUBBER

From the examination of the rubber specimens, it seemed that rubber acted as a solvent for phenol. Owing to the consistent results obtained by the examination of different samples of each specimen of rubber when

stored at the same temperature in the same strength of phenol solution, the conclusion was reached that as with other immiscible solvents, a partition coefficient of phenol between rubber and water was established. The results referred to were those obtained after long enough storage to ensure that a point of equilibrium had been reached.

The partition coefficients were calculated by dividing the concentration of phenol in rubber expressed as mg./ml. by the concentration of phenol in water expressed as mg./ml.

$$K_c^t = \frac{Cr}{Cw}$$ where K = partition coefficient at temperature t determined for rubber immersed in phenol solution of strength c expressed as percentage phenol w/v; Cr = concentration of phenol in rubber expressed as mg./ml.; Cw = concentration of phenol in water expressed as mg./ml.

TABLE XI
PARTITION COEFFICIENTS FOR SAMPLE 10 RUBBER FOR DIFFERENT CONCENTRATIONS OF IMMERSING SOLUTION AT 2°C. AND 37° C.

Initial strength per cent. of phenol solution w/v	Partition coefficient at	
	2° C.	37° C.
0·5	2·16	1·87
1·0	1·78	1·70
2·0	1·81	1·70
4·0	1·62	1·52

From Table XI it will be seen that a slightly higher concentration of phenol in rubber is obtained at lower temperatures, and a slightly lower concentration of phenol in rubber compared with that in water is obtained as the concentration of immersing solution increases. Thus the partition coefficient decreases with rise of temperature and strength of phenol solution used.

In Table XII are given the partition coefficients calculated for rubber samples 1 to 9. These show the same general picture, at the same time providing the general impression that a low value of K links lower phenol absorption with the more desirable type of rubbers for use with injections. This combination of properties is desirable in the making of suitable closures for containers of injectable solutions.

It is seen from Table XII that samples 3 and 7 which are latex tubings intended for intravenous infusions, sample 8 which is a mixed latex and silicone tubing and sample 9 which is a silicone tubing all show K values of less than 1. All the red rubber tubings show K values greater than 1. Sample 4 which is an anti-static tubing containing carbon has a relatively low K value.

DISCUSSION

The problem of the removal of certain substances from injections, particularly the bactericides employed in multiple dose containers, appears to be mainly physical in nature. Although certain rubbers are alkaline in reaction or contain certain basic or basic carbonate substances as fillers it does not appear that there is any chemical interaction between them and phenol, at least, not sufficient to explain the process involved. It appears that rubber acts as a solvent and that phenol divides itself between water and rubber, which act essentially as two immiscible solvents.

The reactions have also been considered in relation to the amount of

TABLE XII

PARTITION COEFFICIENTS FOR RUBBER SAMPLES 1 TO 9

Sample	Specific gravity of rubber	K 2° C. 0·5		K 37° C. 0·5		K 37° C. 4	
		Readings	Mean	Readings	Mean	Readings	Mean
1	1·37	1·16 1·06	1·11	1·41 1·27	1·34	1·36 1·41 1·09 1·28	1·28
2	1·22	1·70 1·83	1·76	1·62 1·78	1·70	1·58 1·49 1·41 1·48	1·49
3	0·994	0·93 1·03	0·98	0·96 1·01	0·98	0·98 0·84 0·95 1·06	0·96
4	1·176	0·87 0·90	0·88	0·76 0·81	0·79	0·82 0·78 0·84 0·92	0·84
5	1·112	1·21 1·26	1·23	1·22 1·16	1·19	1·10 1·07 0·99	1·05
6	1·125	1·31 1·48	1·39	1·36 1·17	1·27	1·12 1·13 0·99 0·84	1·02
7	0·923	0·52 0·69	0·61	0·48 0·55	0·52	0·73 0·59 0·64 0·80	0·69
8	0·915	0·95 0·97	0·96	0·75 0·66	0·71	1·04 0·71 0·79 1·01	0·89
9	1·176	0·38 0·46	0·42	0·35 0·39	0·37	0·18 0·29 0·29 0·50	0·31

rubber in the rubber mixes. The results do not show any consistent agreement between phenol absorption and the rubber content of the rubber mix. Neither is there any clear relation between the amount of phenol absorbed and the filler content. The physical state of the rubber mix possibly explains the difference between the various samples in phenol absorption. There are several factors which may cause this, such as the influence of fillers, activators and accelerators in altering the physical state of the rubber. However, it does appear that whatever the explanation, the process is consistent for particular rubber mixes, to the extent that a partition coefficient can be determined which is capable of being used as a standard for determining the suitability of certain rubbers for making closures of multiple dose containers of injections. It must not be presumed that the results obtained for phenol are equally applicable to other substances employed as bacteriostatic agents, and that aspect requires further investigation. Indeed the work of Wiener, which was mentioned earlier indicates the possibility of a different type of absorption when dealing with thiomersalate.

It is suggested that the partition coefficient of phenol, for rubber in contact with aqueous solutions, under definite conditions of concentration and temperature can be used as a basis for the selection of rubber used for pharmaceutical purposes.

SUMMARY

1.   The absorption of phenol from aqueous solutions by rubber has been found to proceed to a state of equilibrium under controlled conditions of storage, the process being reversible.

2.   The amount of phenol absorbed has been shown to bear a direct relation to the concentration of phenol in the solution in contact with the rubber.

3.   The rate of absorption was found to increase with rise of temperature up to the point of equilibrium.

4.   The amount of phenol absorbed varies with the type of rubber.

5.   A partition coefficient for rubber may be calculated which is suitable for use as a method of controlling the standard of rubber for pharmaceutical purposes.

REFERENCES

1.   Wiener, *J. Pharm. Pharmacol.*, 1955, 7, 118.
2.   Burrell, *ibid.*, 1953, 5, 1019.
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4.   Berry, *J. Pharm. Pharmacol.*, 1953, 5, 1014.

DISCUSSION

The paper was presented by the AUTHOR.

MR. G. SYKES (Nottingham) said it seemed that absorption of a preservative by rubber was a two-stage process, adsorption on the surface followed by diffusion through the body of the rubber.   In view of statements made at the London conference two years ago he doubted whether any one rubber could be used as a standard, as it was not possible to guarantee that the mix of two batches of a rubber would be identical.

Would the author comment on the pharmacopœial method of preparing rubber caps for use?   On page 651 of the paper it was stated that "After equilibrium is reached this sample of rubber did not continue to absorb phenol, contrary to the inference of the Pharmacopœia".   However, the conditions were different.   In the case of a rubber closure a continuous diffusion of the phenol could take place, first into the rubber from the solution and, then by volatilisation to the air from the outer surface.

MR. F. G. FARRELL (London) said he had been studying the same problem using chlorocresol, and employing a spectrophotometric method of assay. Using immersed silicone rubber strips the results were similar to those obtained by the author, equilibrium being reached in a few days. With rubber caps on multidose containers where only one surface was in contact with the solution, equilibrium was not obtained for many weeks. Rubber caps subjected to the B.P. treatment of storing in 0·2 per cent. chlorocresol solution for 48 hours when used on multidose containers containing 0·1 per cent. chlorocresol solution, continued to take up chlorocresol after four months. Two samples of preserved physiological saline solution lost over 50 per cent. of chlorocresol in one year. It would seem that the surface area exposed was a very important factor and it would be interesting to know the diameter and thickness of the rubber tubes used by the author. The concept of a partition coefficient was very interesting and implied that the phenol was distributed in a homogenous manner. Had the author cut the rubber tubing and examined the innermost and outermost parts for phenol content?

PROFESSOR H. BERRY (London) said that the Pharmacopœia was interested only in the rubber used for closures for multidose containers, and such rubber should not contain fillers. Alkaline fillers were a source of danger if the solution in the container had an acid reaction. The author referred to a carbon filler, but he did not consider that a carbon filler should be used in rubber caps because of the difficulty of piercing such caps with a needle. Factors affecting the absorption of phenols into rubber were the area exposed and the presence of other substances in the solution which would alter the partition coefficient. If the medicament were a salt, the solubility of the phenol in the solution would be less and more phenol would go into the rubber. If the medicament was a substance which solubilised phenol such as soap, then less phenol would go into the rubber. The suggestion that if silicone rubber were used all the hazards in connection with rubber would disappear was not true from his own experience, and the author had confirmed that silicone rubber did absorb phenol. Further, when a closure of silicone rubber was pierced with a needle the hole remained wide open, and it was therefore useless as a material for closing multidose containers. He suggested that the author should extend his experiments with a view to obtaining information on the effect of medicaments on rubber.

MR. T. D. WHITTET (London) said that in contrast to the experience of the author, who found that phenols were distributed throughout the rubber he had found that when caps were soaked in metabisulphite solution they became bleached; but if cut open the inside of the rubber did not appear to be affected at all.

DR. L. SAUNDERS (London) commented on the rather loose use of the word "equilibrium" by the author in connection with the results at 2° C. Table II did not show that any equilibrium was reached. The curves in Fig. 1 did not appear to be the curves that one would draw from the results given without assuming that equilibrium was being reached. Had

the author made any attempt to calculate the diffusion coefficients for phenol in the rubber?

MR. W. T. WING, in reply, agreed with the remarks made by Mr. Sykes concerning absorption and diffusion. In the first instance his intention was to establish the conditions under which phenol was absorbed. He agreed that, in the case of a closure, phenol was absorbed and could diffuse through the rubber into the air. He had not intended to imply that one rubber should be used as a standard.

He was about to examine the British Pharmacopœia method of boiling in twice the strength of phenol more closely. Rubber might absorb too much phenol by boiling it in a double strength solution, it was possible that it should be boiled only in the strength of phenol to be used in the injection. He had done no work on chlorocresol. There was a possibility of chlorocresol and phenol behaving differently. Rubber would react with chlorine and form a definite chemical compound. It would also react with sulphites although probably only on the surface of the rubber. The tubings used were roughly $\frac{1}{4}$ in. in diameter and of 1/16 in. thickness. He had not examined the inside and outside of the tubings for their phenol content. He agreed with Professor Berry that fillers should not be present in the rubbers which were used as closures for containers. The purpose of his examination of several rubbers was to establish the differences between rubbers of varying composition. It would be seen from the tables that rubbers which were free from fillers absorbed less phenol than other types. Silicone rubber absorbed phenol but it had been shown to absorb less than any other type of rubber. It appeared that after sterilising the silicones gave off toxic substances and the dangers in its use had resulted in the withdrawal of silicone tubing for use in transfusions of electrolyte solutions. He had not dealt with diffusion coefficients.