SUSTAINED RELEASE OF DRUGS FROM ION EXCHANGE RESINS

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The development of preparations to give sustained release of drugs in the body when administered by mouth, has been recently reviewed[1]. Most of these preparations are based on physical methods for retarding the release of drug as, for example, by making tablets which disintegrate slowly or by coating pellets with slowly soluble films[2,3]. A more continuous and uniform release over a long period is likely to result if the drug is chemically bound to a solid carrier, from which it is slowly released by the action of the digestive fluids.

The slowness of the uptake and release of alkaloids from ion exchange resins has been noted by Saunders and Srivastava[4,5] and it was thought that these resins might provide suitable chemical carriers for drugs in sustained release preparations. Ion exchange resins are extremely insoluble in aqueous liquids and have no toxic effects unless they are given in large enough quantities to disturb the calcium content of the body fluids. When they are administered by mouth, they are likely to spend about two hours in the stomach in contact with an acid fluid of concentration of about 0·1N hydrochloric acid. They will then be moved to the intestine where they will be in contact with a fluid of approximately neutral pH and ionic strength of about that of 0·1N sodium chloride, for several hours.

An outline of the properties and structures of ion exchange resins has been given in a review by Saunders[6]. The common cation exchangers contain either carboxyl or sulphonic acid groups distributed throughout the resin particles. Both types in the hydrogen form (the "form" of a resin is named after the exchangeable ion contained in it) absorb alkaloids from solution, forming resin salts, in which the alkaloid is chemically combined with the exchanger anion.

$$R\mathrm{SO_3^-H^+} + \mathrm{Alk} = R\mathrm{SO_3^-AlkH^+}$$

($R\mathrm{SO_3^-}$ represents the resin anion; Alk and $\mathrm{AlkH^+}$, the alkaloid and the alkaloidal cation, respectively.)

We have found that the ephedrine form of the carboxylic acid type of resin releases its ephedrine very rapidly in acid solution and is therefore not likely to be of much use for oral, sustained release preparations, since nearly all of the alkaloid would be eluted in the stomach. On the other hand, the sulphonic acid resins give a more moderate release in acid solution and release occurs at almost the same rate in neutral salt solutions; for example, in sodium chloride solution the alkaloid ion on the resin exchanges with the sodium ion in solution. The release of dexamphetamine was also studied.

Experimental Methods

Sulphonated, cross-linked polystyrene resins of varying divinyl-benzene content, were cycled twice between the sodium and hydrogen forms, and the final hydrogen forms were thoroughly washed with distilled water and surface dried at 40° C. until their moisture content was about 25 per cent. They were then sieved to give a series of fractions whose mean swollen particle sizes were measured by miscoscopic examination, of about 250 particles from each fraction. Those used are described in Table I.

TABLE I

Resin fractions

Resin	Nominal per cent. divenylbenzene	Fraction B.S.S.	Mean diameter	Moisture Per cent.	Mg. equiv. (110° C. dried form) capacity
			mm.		
a	4·5	30–36	0·70	28	5·25
b	9*	20–30	0·71	26·4	5·08
c	9	40–60	0·45	26·2	5·08

* This is the usual degree of cross-linking in the commercial cation exchangers of this type.

To prepare the ephedrine form, the resin in hydrogen form, was rotated in a closed tube with an aqueous ephedrine solution containing the required amount of alkaloid until absorption was complete. To prepare the dexamphetamine form, 0·1N dexamphetamine sulphate solution was passed through a weighed amount of the resin, in hydrogen form, until the pH of the effluent was exactly that of the solution entering the column.

Release of Ephedrine from the Resin

Rates of release of alkaloid from the resins were studied by three different techniques.

Closed tube method. A series of equal quantities of the hydrogen form of the resin were weighed and converted to the alkaloid form. Each sample was transferred to a stoppered glass tube and 50 ml. of eluting solution was added. The tubes were clamped to arms attached to a shaft which caused them to rotate in a water thermostat bath, at 25° C. for most of the experiments, so that the resin granules fell through the solutions 24 times in a minute. After each interval, a tube was removed and a sample of the liquid in it was analysed for ephedrine by measuring its extinction at 257 mμ.

Replacement closed tube method. One tube was prepared for each resin-alkaloid system studied. At appropriate time intervals the contents of the tube were removed through a filter stick and replaced by fresh eluant. After removal from the tube, the solution was analysed.

Infinite bath method. A continuous stream of eluant was passed over a bed of the alkaloid form of the resin, one particle thick, placed on a sintered glass disc in a closed cell, surrounded by a jacket through which water from a thermostat was passed (see Fig. 1). The eluant flowed

through a spray bulb on to the resin at a controlled rate of 74–76 ml./min. A stop-clock was started when the flow of eluant from a large flask immersed in the thermostat, was commenced. The cell was half filled with liquid before the effluent was released from the bottom of the cell; throughout the elution the cell remained half full. Ten seconds before

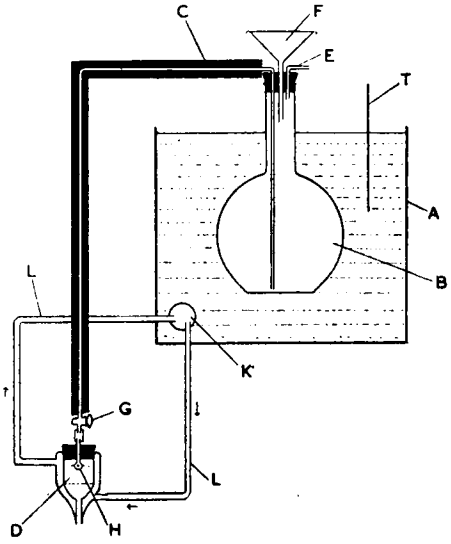

FIG. 1. Infinite bath apparatus.

A. Thermostat
B. Five litre flask
C. Glass siphon tube, insulated with asbestos tape
D. Elution cell with coarse sintered glass disc
E. Glass tube
F. Funnel
G. Stopcock
H. Spray bulb
K. Circulating pump
L. Thick walled rubber tubes
T. Thermometer

the scheduled end of elution the flow was stopped and the liquid in the cell drained. The resin was then washed free of eluant and analysed for alkaloidal content by one of the methods described.

With hydrochloric acid as eluant, the resin was transferred to a small column and a normal solution of sodium chloride was passed slowly through it for a period of several hours, until the pH of the effluent was exactly that of the original solution. The amount of acid in the combined effluent was determined by potentiometric titration with carbonate free 0·05N sodium hydroxide and this was equivalent to the amount of alkaloid released in the infinite bath experiment.

Infinite bath .. $H^+Cl^- + alkH^+RSO_3^- = alkH^+Cl^- + H^+RSO_3^-$

In column .. $Na^+Cl^- + H^+RSO_3^- = Na^+RSO_3^- + H^+Cl^-$

With sodium chloride or sodium bicarbonate as eluant in the infinite bath experiment the above method could not be employed since the

alkaloid released was replaced by sodium. The amount of sodium form of the resin present in the material taken from the elution cell was equivalent to the amount of alkaloid released and was determined by ignition of the resin and weighing as sodium sulphate[7].

Results

Figure 2 shows the results of elution experiments with 1 mg. equiv. of the ephedrine form of the resin (sample b, Table I) with 0·1N hydrochloric as eluant. When x, the percentage release of alkaloid is plotted against time of contact with eluant in hours, it is seen that there is a considerable difference between the closed tube method and the other methods, in which fresh eluant is brought into contact with the resin. This difference is believed to be due to the reversible nature of the elution reaction; in the closed tube method the released ephedrine remains in the eluting solution and re-absorption on to the resin occurs. According to the closed tube results, the rate of release of alkaloid falls off rapidly after two hours, whereas according to the other methods there is a sustained release for a period of more than six hours.

The differences between the results of the different experimental methods are accentuated when a mixture of ephedrine and hydrogen forms of the

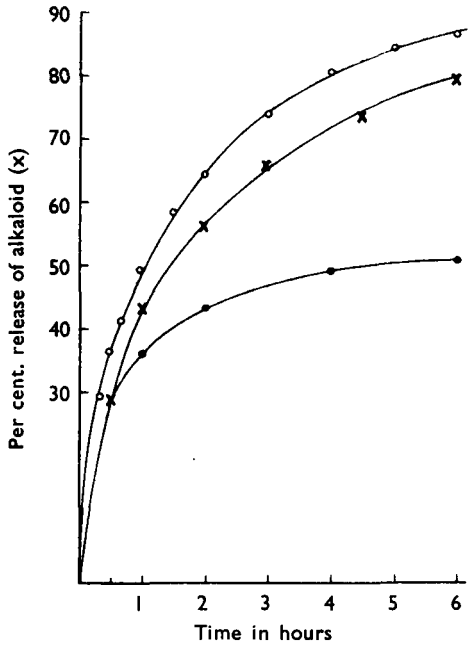

FIG. 2. Release of ephedrine using different techniques. 1 mg. equiv. of the ephedrine form of resin *b*; eluant 0·1N HCl.

- ● Closed tube.
- × Replacement closed tube.
- ○ Infinite bath.

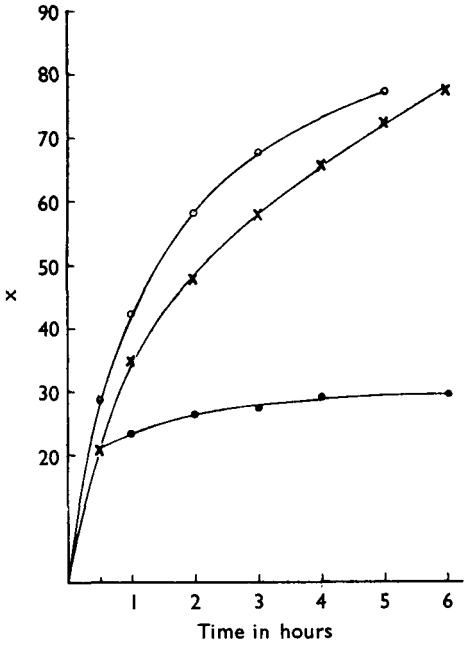

FIG. 3. Release of ephedrine from resin mixtures using different techniques.

- ● Closed tube.
- × Replacement closed tube.
- ○ Infinite bath.

resin is eluted. In Figure 3, the results by the three methods for the elution of a mixture of 1 mg. equiv. of ephedrine form and 1 mg. equiv. of hydrogen form with 0·1N hydrochloric acid, are shown (both are resin fractions *b*, Table I). The presence of the hydrogen form greatly increases the reversibility effect in the case of the closed tube method but the replacement closed tube method gives completely different results. In the latter, the presence of the hydrogen form reduces the amount of ephedrine released in the early stages of elution (compare with Fig. 2) and in consequence, increases the amounts liberated in the later stages. Addition of the hydrogen form therefore produces a straightening of the release curve. A similar result is obtained with the infinite bath method.

In view of these results a detailed study of elution with the closed tube method was not made. The effects of various factors on the rates of release of alkaloid were studied by each of the other methods.

Infinite Bath Method

The infinite bath elution measurements were interpreted by the theory of Boyd, Adamson and Myers[8] to give rate constants. The results obtained are summarised in the Appendix. Some values for the percentage elution of ephedrine and dexamphetamine from 1 mg. equiv. of resin *b* are shown in Table II.

TABLE II

PERCENTAGE RELEASE OF BASES BY THE INFINITE BATH METHOD

Time (hours)	Ephedrine		Dexamphetamine	
	0·1N HCl	0·1N NaCl	0·1N HCl	0·1N NaCl
0·5	37·0	31·2	31·3	30·5
1·0	50·1	45·7	43·9	42·1
1·5	59·1	56·0	52·5	50·6
2·0	64·9	62·9	59·4	57·2
4·0	81·0	77·9	74·1	71·2
6·0	86·8	85·8	83·0	81·0

Replacement Closed Tube Method

The infinite bath method is tedious and troublesome. To determine a single curve, about 75 litres of eluant are required and the experiment takes one week. For practical purposes, the replacement closed tube method is more useful. When a spectrophotometric method of drug determination is used, it is necessary to condition the resin thoroughly by cycling and copious washing, in order to ensure that no traces of impurity are released from the resin which might affect the extinction of the eluting solution. Throughout the spectrophotometric work, a continuous check on this possible source of error was maintained.

Using this method, some further studies of ephedrine release rates were made.

(*i*) *Incompletely converted resin.* The rate of elution from 1 mg. equiv. of resin *b* completely converted to the ephedrine form was compared with that obtained with 2 mg. equiv. of *b* (hydrogen form) only half converted to the ephedrine form. The half converted resin gave a slower rate of release in the early stages than the completely converted form and the

release curve was almost identical with that obtained with a mixture of 1 mg. equiv. of completely converted ephedrine form (*b*) plus 1 mg. equiv. of the hydrogen form (*b*). With 4 mg. equiv. of resin, one quarter converted to the ephedrine form, a further straightening of the release curve was obtained, but the total elution after six hours was reduced (see Fig. 4).

(*ii*) *Variations in the hydrogen form of the resin used* (Table III). In these measurements 1 mg./equiv. of ephedrine form of the resin (*b*) was mixed with different types of hydrogen form. The results are summarised in Table III. In each case the added hydrogen form is shown at the top of each column. The resin fractions *a* and *c* in the hydrogen form (Table I) are both more effective in reducing the initial release of alkaloid and hence in straightening the release curve, than the hydrogen form of *b*. This is to be expected, since both *a* and *c* absorb ephedrine at a considerably higher rate than *b*. An exceptionally uniform rate of release is achieved from the mixture of 1 mg. equiv. of ephedrine form of *b* plus 3 mg. equiv. of hydrogen form of *a* (see Fig. 4).

TABLE III

PERCENTAGE RELEASE (X) OF EPHEDRINE FROM RESIN MIXTURES

Time, hours	No. H form	1 mg. equiv. of H form of *b*	1 mg. equiv. of H form of *a*	1 mg. equiv. of H form of *c*	3 mg. equiv. of H form of *a*
½	29·1	21·1	15·5	16·4	8·0
1	43·9	34·9	29·3	29·9	15·6
2	57·1	47·6	42·9	43·1	24·2
3	66·4	57·7	54·4	54·1	32·5
4	72·6	65·8	63·8	62·9	40·1
5	77·1	72·3	71·4	70·0	46·9
6	79·4	77·6	77·5	75·9	53·1

DISCUSSION

A sustained release of ephedrine and dexamphetamine over a period of at least six hours can be achieved when the drug form of a sulphonic acid resin is put in contact with 0·1N acid and salt solutions. The most convenient method for studying the elution of drug from the resin is the replacement closed tube method.

If the drug form of the resin is given by mouth, the released base will probably be absorbed quite rapidly by the mucous membrane of the gastro-intestinal tract and so there is not likely to be any major effect due to the reversibility of the base release reaction. It is therefore to be expected that the infinite bath and the replacement closed tube methods may more nearly reflect the drug release *in vivo* than the closed tube method. In the body, the resin is unlikely to meet more drastic eluting conditions than those of the infinite bath method. The fact that a steady, continuous release of ephedrine is maintained in the infinite bath elution shows that the slow displacement of ephedrine from the interior of the resin particles is only slightly altered by the conditions of elution, when the eluted alkaloid is continuously removed. This conclusion provides an important safety factor for the possible use of these resins in medicine.

The release curves for ephedrine are very much the same with 0·1N hydrochloric acid, sodium chloride and sodium bicarbonate solutions as eluants (see Appendix). The curves can be appreciably straightened by using resins which are only partially converted to the ephedrine form or by using mixtures of the alkaloid and hydrogen forms of the resin. A mixture of equivalent proportions of these two forms gives the same total release after six hours as the ephedrine form alone, but the initial release rate is reduced. Higher proportions of hydrogen form cause a reduction in the alkaloid release over a six-hour period.

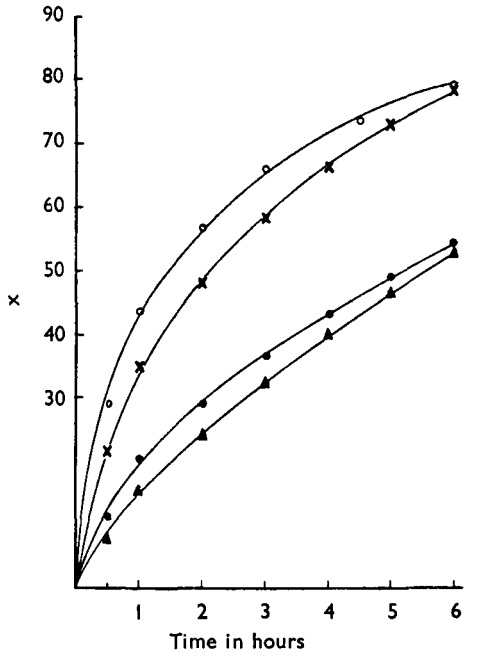

FIG. 4. Effect of hydrogen form on the release of ephedrine. Replacement closed tube method; 0·1N HCl as eluant.

- ○ 1 mg. equiv. of the ephedrine form of resin *b*.
- × 2 mg. equiv. of resin *b* (originally hydrogen form) half converted to the ephedrine form.
- ● 4 mg. equiv. of resin *b* (originally hydrogen form) one-quarter converted to the ephedrine form.
- ▲ Mixture of 1 mg. equiv. of the ephedrine form of resin *b* with 3 mg. equiv. of the hydrogen form of resin *a*.

APPENDIX

Infinite Bath Elution Results

The infinite bath elution results have been interpreted by the kinetic theory of Boyd, Adamson and Myers[8] and also by using the extended Table of functions given by Reichenberg[9]. The equation of this theory is shown below

$$F = 1 - \frac{6}{\pi^2} \sum_{n=1}^{n=\infty} \frac{\exp(-n^2 Bt)}{n^2}$$

Where n is an integer, $F = x/100$ i.e., F. is the fraction of alkaloid eluted from the resin in time t; B, the rate constant is defined as $B = \pi^2 D/r^2$ where D is the effective diffusion coefficient of the ion exchange process and *r* is the mean particle radius of the resin. F is dimensionless and B has the dimensions of reciprocal time, Bt is therefore dimensionless. Theoretical values of Bt for different numerical values of F can be computed from the above equation and numerical Tables of these quantities have been drawn up by Reichenberg. To calculate the rate constants B from the experiments, values of F are calculated from the measurements and the corresponding theoretical values of Bt are found from the Tables. These Bt values are plotted

against the experimental values of t and if the theory is correct a straight line passing through the origin, of slope B, should result. The value of B in sec.$^{-1}$ is found by measuring this slope. Deviations from the ideal Bt, t plot may arise if the rate of exchange is not controlled by the rate of diffusion within the resin particles; also, difficulty in deciding the exact time at which elution commences in a given experiment may give rise to a plot which although linear, does not pass exactly through the origin.

TABLE IV

ELUTION OF EPHEDRINE WITH VARIOUS ACID STRENGTHS

Normality of HCl	B in sec.$^{-1}$ $\times 10^5$	Time (min.) for half elution ($F = 0.5$)
0·025	—	112
0·05	—	73
0·075	—	62
0·1	8·7	60
0·25	13·3	38
0·5	19·4	26
0·75	24·8	20
1·0	28·6	18
1·5	32·5	15

TABLE V

PARTICLE SIZE EFFECT

Resin sample	Observed swollen diameter, mm.	B for 0·1N HCl Sec.$^{-1}$ $\times 10^5$	B for 1N HCl
b	0·71	8·7	28·6
c	0·45	27·7	75·9

The effects of various factors on the elution rate constant B, are summarised below.

(*i*) *Concentration of hydrochloric acid in the eluant* (Table IV). 1 mg. equiv. of resin sample *b* in the ephedrine form was used. The Bt, t plots were all linear but those for the lower acid concentrations below 0·075N did not pass exactly through the origin, the probable reason for this has already been mentioned. The uncertainty about the exact start of the experiment is likely to be greater when the rate of elution is slower as is the case with the more dilute acid solutions.

(*ii*) *Resin particle size* (Table V). 1 mg. equiv. of the ephedrine forms of resin samples *b* and *c*, were each eluted with 0·1 and 1·0N hydrochloric acid.

The value of B should be inversely proportional to the square of the particle radius, therefore the square root of the ratio of the values of B for a given acid concentration should equal the inverse ratio of the mean particle diameters. This inverse ratio of diameters is 1·6; for 0·1N acid the square root of the ratio of B values is 1·8 and for N acid it is 1·65. This represents a reasonable agreement with theory, considering the uncertainty of the mean particle diameter estimates.

(*iii*) *Cross linking of the resin.* The degree of cross linking of the resin is roughly measured by the proportion of divinyl benzene in the mixture which is polymerised to make the resin. By comparing the results for 1 mg. equiv. of the ephedrine forms of resins *a* and *b* with 0·1N hydrochloric acid as eluant, it was found that the more lightly cross linked resin gave a rate constant 5·9 times that of resin *b*.

(*iv*) *Temperature.* The effect of temperature on B is quite small; increasing the temperature from 25° to 35° C. increased B by a factor of 1·2, using 1 mg. equiv. of resin *b* and eluting with 0·1N hydrochloric acid.

(*v*) *Quantity of resin.* The value of B obtained using 2 mg. equiv. of ephedrine form of resin *b* was identical with that found with 1 mg. equiv.

(*vi*) *Flow rate.* The standard flow rate used was 75 ml./min. throughout these experiments. Increase of flow rate to 120 ml./min. did have some effect on B, increasing its value by a factor of 1·4.

(*vi*) *Eluant.* 0·1N sodium chloride solution and 0·1N sodium bicarbonate solution gave almost identical values of B when used to elute 1 mg. equiv. of the ephedrine form of resin *b*, showing that the anion in the eluant has no appreciable effect on the release rate. Both the sodium salts gave a B value which was slightly lower than that for 0·1N hydrochloric acid, the ratio being 0·86.

(*vii*) *Dexamphetamine.* The dexamphetamine form of resin *b*, when eluted with 0·1N hydrochloric acid gave a B ratio dexamphetamine/ephedrine of 0·72. With the more lightly cross-linked resin, *a*, the ratio was 0·81.

SUMMARY

1. The rates of release of ephedrine from sulphonic acid cation exchange resins in contact with 0·1N hydrochloric acid, sodium chloride and sodium bicarbonate solutions have been examined. Sustained release occurred over a period of more than six hours when a method involving removal of eluted alkaloid was used, even under the drastic conditions of the infinite bath method where a high continuous flow of eluant was employed. This provides an important safety factor for the possible use of these resin preparations in medicine. The release of dexamphetamine was also studied.

2. When the resin is only partly converted to the ephedrine form or when a mixture of the ephedrine and hydrogen forms of the resin is used, the initial release rate is reduced and the later rate is increased, producing a straightening of the release curve.

Our thanks are due to Professor W. H. Linnell for his interest in the work and to Clinical Products Ltd., for a grant.

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DISCUSSION

The paper was presented by MR. N. C. CHAUDHRY.

The CHAIRMAN asked whether any of the resin-bound drugs described had been tested clinically, and what were the classes of drugs which the authors had in mind for this type of preparation.

PROFESSOR W. H. LINNELL (London) said that in an American paper it was reported that in about 70 per cent. of some 300 or 400 cases the potency of resin-bound amphetamine was appreciably higher than amphetamine taken in the normal way. He had also seen thirty or forty clinical reports on an English preparation and they showed that there was an unexpected potency of the amphetamine-bound resin which might possibly be due to the slow release of the drug. The resins could be used with acidic or basic substances, but not for neutral compounds.

MR. D. JACK (London) said he was puzzled by the selection of 25° C. as the testing temperature. It was said that diffusion coefficient B increased by a factor of 1·2 for 35° C. as against 25° C. From the practical point of view one was really concerned with variations of F. It would be interesting to know what effect there was on the release in 2 hours when changing the temperature from 25 to 35° C. In Figure 4 the curve was straightened by adding the hydrogen form of the resin. A considerable straightening of the curve had been shown in the presence of hydrochloric acid. In the *in vivo* conditions in the stomach and intestine one would not expect such great changes in the shape of the curve with large quantities of cations and hydrogen ion, especially when the hydrogen form was introduced on a separate granule. That was important, because ideal sustained release forms should have a release curve which was linear with time. It would be interesting to have information on *in vivo* tests.

MR. A. AXON (Dartford) asked whether the authors would comment on (i) the difficulties of storage of a resin containing 25 per cent. moisture, (ii) the choice of preservative to prevent mould and fungal growth, and (iii) the release of drug from a dry resin.

DR. G. E. FOSTER (Dartford) asked how much of the resin had to be administered to give a dose of ½ grain of ephedrine and whether the quantity would be small enough in bulk to be prepared as a tablet.

MR. N. J. VAN ABBÉ (Loughborough) asked whether the authors felt that they had adequately characterised the resins. Some clarification would also be helpful of the statement on page 976 "At appropriate time intervals". As far as could be seen, the curves for the method under discussion in Figures 2 and 3 could be anywhere between the other two curves, according to the appropriate time intervals chosen.

DR. K. R. CAPPER (London) said that the interest shown suggested the possibility that this type of sustained release medicament might become a standard form of presentation and, if so, it would have to comply with performance tests. The manufacturer of such a drug was, to some extent, in the hands of the manufacturer of the ion exchange resin, and the importance of the degree of cross linking was shown in the paper. It would be very useful to know whether the authors had found any difference in performance between batches of the resin supplied as identical by the manufacturer.

MR. T. D. WHITTET (London) said that a quinine ion exchange resin compound was used for the diagnosis of achlorhydria. He had tried to

use ion exchange resins as a method of concentrating the pyrogens in tap water, but he had not been able to elute them. It was interesting therefore to note the release over quite a long period.

DR. J. C. PARKINSON (Brighton) asked whether the release of the alkaloid from the resin was dependent on the resin remaining in the stomach for the whole period. Did release cease when the resin passed out of the stomach into the less acid conditions further down the gastro-intestinal tract?

MR. S. G. E. STEVENS (London) said he was rather puzzled by the use of the words "sustained release". Examination of the graphs in Figures 2 and 3 showed, in his interpretation, that sustained release was not being obtained, but a gradually decreasing release. He also asked whether the authors proposed to follow their work with a study of less soluble drugs bound to ion exchange resins, because he would expect the pattern of release to be somewhat different, and the conditions of testing might have to be very severely modified to provide useful criteria. On what evidence was the rotating tube at 12 r.p.m. selected? The authors were careful initially to select material of a narrow range of particle size, and he wondered whether any sort of attrition effects came into play during the test. He was doubtful whether the simple *in vitro* test was sufficiently accurately reflecting the *in vivo* picture.

MR. N. C. CHAUDHRY, in reply, said they had not carried out clinical tests or studies of the release of drugs *in vivo*. The rate of release would depend, among other factors, upon the molecular size and dissociation constant of the individual drug. The temperature coefficient was small and the percentage release of ephedrine with 0·1N HCl after two hours (Table II) was 69 at 35° C. instead of 64·9 at 25° C. (F = 0·69 at 35° C. instead of 0·649 at 25° C.). The straightening of the release curve is due to the presence of the hydrogen form of the resin which exerts a reversible reaction of absorption of the ephedrine being released. As long as the resin granules remain in contact with gastric medium where hydrochloric acid predominates, the effect of reversibility will probably continue. However, on entering the intestine, this effect should cease and the rate of release would increase for the subsequent time intervals, i.e., third hour onwards; the net result should be a further straightening of the release curve. As is seen in Table III, column 2, percentage release after the first two hours is 57·1, and the purpose of the study of the mixtures for producing straightening effects was to decrease this initial high figure. Further experiments have been made on the release of ephedrine from a mixture of equal portions of resin (*b*) in the ephedrine form and resin (*a*) in the hydrogen form, by eluting in the first two hours with 0·1N HCl, followed by elution with 0·1N $NaHCO_3$ or 0·1N NaCl up to six hours. It was found that the release curve was further straightened and the percentage total release after six hours was 82 instead of 77·5 (Table III). The resins were air dried to about 25 per cent. moisture content (Table I). They were allowed to come to equilibrium with atmospheric humidity so that they were stable for quantitative work. These resins have been

stored for more than two years and no fungal growth has been observed. The release of drugs from an air dried resin had not been studied, but the release may be slightly slower in the first half hour. The release of drugs from anhydrous sulphonic acid resins could not be recommended because of the possibility of fracture of the resin granules due to rapid swelling. One grain of air dried resin would absorb ½ grain of dexamphetamine and 0·65 grain of ephedrine. The choice of time intervals was arbitrary and was made for experimental convenience. Two batches of the resin "Zeo-Karb 225" obtained in different years from the same manufacturer have shown identical performance, but variation between batches from different manufacturers is to be expected. A resin can be sufficiently characterized by determining its capacity and its volume expansion for a given exchange or change of solvent. This expansion measures the degree of cross-linking of the resin. The release of drugs from the sulphonic acid cation exchangers has been found to be almost independent of pH, and depends upon the cationic strength of the eluting solutions. Sustained release does not necessarily imply a uniform release. The rotation of tubes at 12 r.p.m. was selected because at this speed the rate of release was independent of the rate of rotation. Attrition in the tube did not seem to occur to any extent.

DR. L. SAUNDERS (London), in reply, said that the paper was of a preliminary nature. The temperature of 25° C. was chosen because the temperature coefficient was not very great. If one considered the volume of solution used in the infinite bath method it would be appreciated that considerable difficulty was experienced holding the temperature constant when working far from room temperature.