J. Pharm. Pharmac., 1977, 29, 367

COMMUNICATIONS

An *in vitro* dissolution test for slow release potassium chloride tablets

A. C. CARTWRIGHT*, C. SHAH, *British Pharmacopoeia Commission Laboratory, Government Buildings, Honeypot Lane, Stanmore, Middlesex HA7 1AY, U.K.*

The need for control of release of potassium from slow release potassium tablets has been stressed by earlier investigators (Barlow, 1965; Thomas, 1972). Also, the Pharmaceutical Society's Council in its 1975 document 'Further observations on biological availability' emphasised particularly the requirements for adequate standards for sustained release products.

Although the amount of potassium released from slow release potassium preparations must be sufficient to treat or prevent hypokalaemia, the rate of release should be such that high localized concentrations of potassium are avoided thus reducing the likelihood of intestinal ulceration. In consequence an *in vitro* dissolution test is desirable as a pharmacopoeial control procedure.

Materials. Samples of four leading brands in Britain of slow release potassium tablets were obtained. These are referred to as Brands A, B, C and D. Brand B had a label claim of 750 mg of potassium chloride, the others a label claim of 600 mg.

Methods. Using a suitable pIon meter with a selective potassium electrode it was found possible to estimate the release of K^+ into solution using the procedure devised by Thomas (1972). Standard solutions containing 0·03, 0·3, 3 and 30 g litre^{-1} KCl (AR) were made up in pH 6·8 tris and HCl buffer (each litre contained 250 ml 0·2 M tris and 45 ml N HCl). The solutions were allowed to stand at 37° and the readings were determined on the expanded mV scale of a pH/pIon meter for each solution. A graph of the mV readings versus the logarithm of the concentration of potassium was plotted. Using this the amount of potassium released from any tablet at any time could be determined with a reproducibility of $\pm$ 2% of the concentration. The standard graph was prepared daily to allow for any slight drift in the response of the meter and/or the electrode.

The dissolution of brands A, B, C and D was evaluated using the British Pharmacopoeia 1973: Addendum 1975 apparatus for Determination of Solution Rate, which consisted of a 1 litre flat bottomed flanged flask fitted with a suitable lid. A variable speed motor caused a basket to rotate in the vessel. The basket was cylindrical stainless steel made of woven wire cloth with a nominal aperture size of 425 μm. The basket was attached to a drive shaft which passed through the lid via a stirrer guide to reduce basket vibration. The stirrer motor was driven through a tachometer drive control and maintained at the set speed of 100 $\pm$ 2 rev min^{-1}. The temperature was maintained at 37 $\pm$ 0·5° by immersing the 1 litre flask in an unstirred water bath. The dissolution medium was 900 ml of pH 6·8 tris/HCl buffer. A single tablet was placed in the basket which was then rotated at 100 rev min^{-1}. The glass selective ion electrode was lowered into the buffer to a point approximately mid-way between the basket and the wall and half-way up the basket. The mV reading was taken at 1 min intervals for the first 30 min, and every 15 min thereafter. The concentration of potassium in solution was determined by reference to the standard calibration graph.

Mean results from each brand of tablets (typical of 40 analyses) are given in Table 1 and shown graphically in Figs 1 and 2. To show the variation between tablets in a given batch the individual Brand A results are shown in Table 2.

All the brands tested showed a similar variation between tablets in their release rate. The variation in release of potassium chloride between tablets in a batch is probably due only in a small degree to potency variation or tablet weight variation. It is likely to be caused

* Correspondence.

Table 1. *Mean release of potassium chloride in mg from each brand of tablets.*

Brand of Tablets	Mg released after (min)													
	15	30	45	60	90	120	150	180	210	240	270	300	330	360
A	53	117	158	192	244	287	325	351	372	387	400	408	413	416
B	73	122	166	194	263	311	345	374	391	418	439	458	471	483
C	27	51	85	115	184	221	262	293	322	347	363	380	401	419
D	0	3	7	15	37	79	123	162	204	238	272	298	326	355

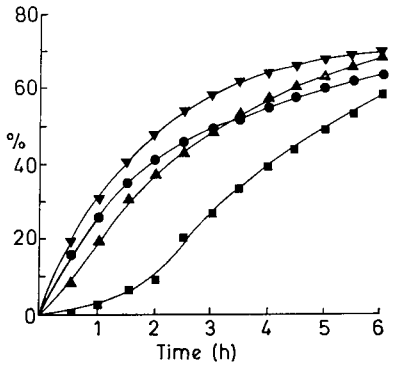

FIG. 1. Mean dissolution patterns of the four different brands. ▼——▼ Brand A, ●——● Brand B, ▲——▲ Brand C, and ■——■ Brand D. Ordinate—Mean percentage label claim released. Abscissa—Time after test start.

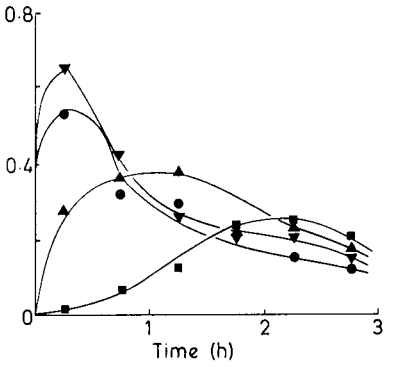

FIG. 2. Mean dissolution rates of the different brands versus time after start of the test. ▼——▼ Brand A, ●——● Brand B, ▲——▲ Brand C, and ■——■ Brand D. Ordinate—Dissolution rates—%KCl released per min. Abscissa—Time after test start.

Table 2. *Release of potassium chloride in mg from individual tablets of Brand A.*

	Mg released after (min)													
Tablet	15	30	45	60	90	120	150	180	210	240	270	300	330	360
1	48	115	160	195	240	285	325	360	380	380	400	415	430	430
2	38	96	145	175	223	255	300	325	350	375	380	390	390	390
3	60	120	165	195	290	325	350	370	370	375	385	390	400	404
4	62	120	160	195	253	300	335	357	365	395	405	405	405	415
5	56	133	160	199	255	303	339	365	395	410	430	440	440	445
Mean	53	117	158	192	244	287	325	351	372	387	400	408	413	416

by variation in the characteristics of the wax or plastic matrices from which the potassium is released.

In the pH 6·8 tris/HCl buffer, Brands A, B and C showed a similar pattern of release with approximately 50% of the label claim being released in 2 to 3 h. Brand D tablets showed a very much slower pattern of release.

It is suggested that control over the maximum amount of potassium chloride released in the first hour would give a reasonable assurance that the maximum dissolution rate is not too high. This control might be achieved by setting a 50% label claim limit on the amount found in solution at 1 h.

Two approaches are possible to designing a standard to define the release pattern of potassium chloride to control the total amount released. One approach would be to control the amount of potassium chloride in solution only at 6 h to say between 50 and 80% of label claim. All brands would comply with these limits including Brand D with its very much slower pattern of release. It may be desirable to obtain a higher percentage release at earlier times so that potassium is available for absorption more quickly to enable a possibly more complete absorption. In this case the criterion of acceptance might be that at 3 h between 40 and 65%, and at 6 h between 55 and 80% of label claim are released. The latter approach would exclude the slower Brand D.

No attempt has been made to correlate the *in vitro* data with the dissolution of the tablets *in vivo*. It has been reported that the dissolution of slow release potassium tablets is faster in alkaline pancreatin than in buffer at the same pH (Jouhar, Garnett & Wallington, 1968). This will be caused by the pancreatic lipase digestion of the wax matrix of some of the slow release cores. The use of pancreatin in this test is contra-indicated however by the fact that it coats the electrode surface and alters its response and sensitivity.

The procedure given here may enable the release pattern of potassium chloride in tablets to be checked, using simple equipment (a pH meter with an expanded scale). Suitable electrodes whether of the glass, solid state or liquid membrane types are available at reasonable cost. Modern ion selective electrodes show good selectivity for potassium over other ions including sodium and hydrogen, and the simplicity of the technique may well appeal over other reported methods (Engdahl, Karlberg & Thelander, 1976) involving expensive automated equipment.

February 16, 1977

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Bioassay by cascade superfusion using a highly sensitive laminar flow technique

H. BULT*, M. J. PARNHAM, I. L. BONTA, *Department of Pharmacology, Erasmus University Rotterdam, Rotterdam, The Netherlands*

Superfusion of tissues (Finkleman, 1930; Gaddum, 1953; Vane, 1964) is a widely used technique for the bioassay of biologically active substances. Recently, Ferreira & De Souza Costa (1976) described a sensitive superfusion method using a laminar flow technique. The tissues were superfused with Krebs at a low flow-rate and were protected from desiccation by suspending them in mineral oil. This technique permitted the detection of minute amounts of smooth muscle stimulating substances, such as prostaglandins (PGs), bradykinin and angiotensin II. The sensitivity of the technique was competitive with radioimmunoassays. However, the disadvantage of this method is that it is not possible to use a combination of different assay tissues arranged in a cascade (Vane, 1964) for simultaneous parallel bioassay. In this paper we describe a simple adaptation of the method of Ferreira & De Souza Costa (1976), which permits the use of at least two tissues, superfused in a cascade with the laminar flow technique.

A siliconized glass cylinder, with a sloping drain attached to the inside, was fitted into an organ bath surrounded by a water jacket at 37° (Fig. 1). The organ bath was then filled with gassed (95% O_2, 5% CO_2) Krebs, the level of which was adjusted with a syphon. The upper tissue was secured by knotting the lower thread in a small hole in the middle of the drain and the lower tissue was secured as described by Ferreira & De Souza Costa (1976). Both tissues were connected to Harvard heart/smooth muscle transducers and contractions were recorded on a Rikadenki pen recorder. Krebs solution was then delivered directly onto the thread above the upper tissue, at 0·3–0·4 ml min^{-1}, with a peristaltic pump (Verder, Vleuten, The Netherlands). The Krebs solution in the organ bath was replaced by prewarmed mineral oil, which was gently poured down the inside of the bath. The Krebs was displaced through the syphon until the oil-water boundary was below the lower tissue; the upper oil level was kept above the upper tissue by adjusting the syphon. To obtain a smooth flow over the tissues, the inner cylinder was carefully cleaned before each experiment and the tissues were tied to the transducers with thick threads (Leinenzwirn, 4, J. Phrimmer & Co., F.R.G.). In initial experiments, the upper tissue was secured by tying it to a small hook attached to the cylinder immediately above the drain. However, this was less satisfactory as, in some cases, the Krebs tended to run down the side of the bath instead of flowing completely over the lower tissue.

Test substances were dissolved in either Krebs or saline and injected in constant volumes with micropipettes (10–100 μl, Eppendorf or Finnpipette) directly

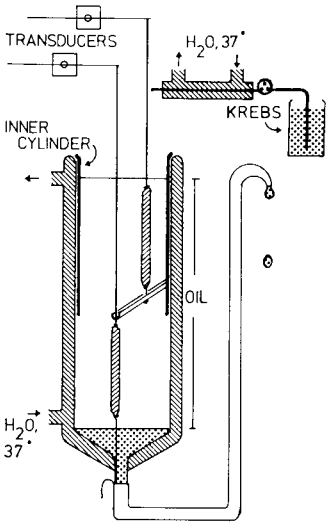

FIG. 1. Organ bath, containing an inner cylinder with a small drain. At the beginning of each experiment the level of the paraffin oil was adjusted with the syphon.

* Correspondence.