Release of potassium chloride from tablets

SIR,—The occurrence of characteristic obstructive ulceration of the small intestine apparently associated with potassium supplemented thiazide therapy has recently been reported (Baker, Schrader & Hitchcock, 1964; Lindholmer, Nyman & Räf, 1964; Aberuzze & Gooding, 1965; Bennett & Davy, 1965; Buchan & Houston, 1965; Morganstern, Freilich & Panish, 1965).

Boley, Schultz, Krieger, Schwartz, Elguezebal & Allen (1965), working with dogs, and Diener, Shoffstall & Earl (1965), using olive baboons, have shown that tablets containing potassium chloride can give rise to the lesion, whereas controls without the salt gave no reaction. These workers suggest a correlation of the high local concentration of potassium chloride and the reported lesions.

Because large oral doses of potassium chloride can give rise to nausea and gastric irritation, its availability is usually modified to prevent or limit irritation in the stomach. We have measured the rate of release of potassium chloride from nine commercially available tablets containing the salt (either alone or in combination with diuretics (Table 1) by an *in vitro* method.

Method. Tablets were agitated by means of an apparatus conforming to the B.P. specification for disintegrating tests (B.P. 1963a) in beakers containing 1·0 litre of test solutions designed to simulate gastrointestinal environment. Acid pepsin solution or alkaline pancreatin solution (B.P. 1963b) freshly prepared for each determination was used. Solutions were stirred at a constant slow speed and maintained at 37 $\pm$ 0·1° in a thermostatically controlled water-bath.

Release of potassium chloride was measured by monitoring the conductivity of the solution continuously, using an immersion conductivity cell (Radiometer CD 104). Calibration curves of conductivity versus potassium chloride concentration were prepared using known increments of potassium chloride. The curves obtained were linear over the range studied.

Tablets equivalent to 10–12 g of potassium chloride were placed in the tubes of the disintegrator and a record of change in conductivity of the solution with time obtained. Experiments were run for 2 hr or to completion in the simulated gastric fluid, or to completion in the simulated intestinal fluid. Graphs of % total potassium chloride released versus time were prepared. Where potassium chloride was released, 100 $\pm$ 3% of the theoretical content was found in solution at completion of release, indicating that excipients and coating materials did not interfere with the measurements.

TABLE 1. DETAILS OF TABLETS AND MAXIMUM VALUES OF DW/DT* IN ACID PEPSIN AND ALKALINE PANCREATIN SOLUTIONS

Product	Remarks	Declared KCl content (mg)	No. of tablets used for test	dW/dt max.		Time from start at which dW/dt max. occurred	
				Pepsin	Pancreatin	Pepsin	Pancreatin
A	Manufacturer states "Slow release"	630	16	100	150	5 min	10 min
B	Manufacturer states "Enteric coated"	573	18	0	450	0	10 min
C	No statement	500	20	—†	—†	—†	—†
D	No statement	572	18	0	405	0	20 min
E	No statement	600	17	0	315	0	10 min
F	No statement	625	16	235	230	20 min	20 min
G	Manufacturer states "Slow release core"	600	17	80	115	10 min	10 min
H	Manufacturer states "Enteric sealed"	325	30	0	225	0	20 min
J	Manufacturer states "Slow release core"	400	25	65	70	10 min	10 min

* dW/dt = Average wt of potassium chloride in mg released by one tablet in time increment of 5 min.
† Lack of between tablet uniformity prevents valid assessment.

Results. These are expressed as the average amount of potassium chloride dW (in mg) released from one tablet in consecutive time increments dt (5 min), values for dW being read off % versus time curves. Histograms of dW/dt versus time were prepared, representative results being shown in Fig. 1. Maximum values of dW/dt are shown in Table 1 together with the time at which they occurred. This enables a comparison to be drawn between products which allows for inherent differences in tablet content. Reproducibility was assessed on an enteric coated tablet (Product D) and a controlled release tablet (Product G). Standard Error of the Mean for dW/dt max. was 5·4% for Product D and 6·2% for Product G.

From Table 1 it can be seen that products B, D, E and H can be classified as enteric coated and products A, F, G and J as controlled release preparations. Release from C was too erratic to allow evaluation.

The method measures the rate at which potassium chloride is released into solution from a tablet under standard conditions, results being expressed as the amount released in a given time, giving an indication of the local concentrations likely to arise. Thus, tablets showing higher values of dW/dt should give rise to higher local concentrations than those showing lower values, as more is released in a given time. Enteric coated tablets showed high values for dW/dt in the simulated intestinal fluid, and are therefore likely to give rise to high local concentration of potassium chloride. Controlled release tablets show appreciably lower values of dW/dt in simulated intestinal fluid, indicating that they are less likely to cause high local concentrations under the same conditions. In addition, these tablets showed release in simulated gastric fluid, further reducing the possibility of high dW/dt values occurring later under alkaline conditions.

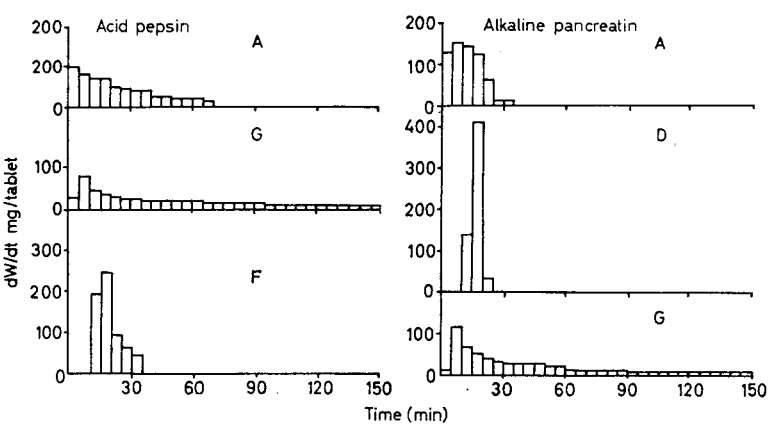

FIG. 1. Average wt in mg (dW) of potassium chloride released in 5 min increments (dt) versus time in acid pepsin solution and in alkaline pancreatin solution for products A, D, F, G.

Release patterns obtained using other simulated gastrointestinal fluids and buffer solutions gave a qualitatively identical overall picture, although different dW/dt max. values were found with different solutions.

A recently published report on experiments with olive baboons (Lister, 1965), shows that although enteric coated tablets gave rise to iatrogenic ulceration, a slow release preparation showed no lesions of the digestive tract. This suggests

a correlation between ulceration and rate of release of potassium chloride, and the method described here can be used as a comparative measure of this tablet parameter.

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Note: A key to products studied is available from the author on request.