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Measurement of dissolution rates of potassium chloride from various slow release potassium chloride tablets using a specific ion electrode

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The *in vitro* rates of release of potassium ions from slow-release potassium chloride tablets from 12 sources have been compared. Dissolution rates were determined using a modified non-sink method and a modified sink method. Medicament release in both methods was continuously monitored using a potassium ion specific electrode. The release rate constants were derived and the applicability of the Noyes-Whitney equation, Hixson and Crowell's cube root law and Higuchi's equation was studied.

Slow-release preparations containing potassium chloride should be formulated with the aid of *in vitro* control methods, such as dissolution rate measurements, to ensure that the product releases the potassium slowly and shows uniform activity in the gastrointestinal tract thus avoiding high local concentrations with the concomitant hazard of ulceration.

The World Health Organization (W.H.O.), on advice from the Food and Drug Administration (F.D.A.), of the U.S.A., has recommended that potassium chloride preparations and all fixed combinations of thiazides and potassium chloride in tablet form for oral use be removed from the market (16:36, No. 75, 1970). The reason given is the incidence of serious toxicity, such as small bowel lesions that have caused ulcers, obstruction, haemorrhage and perforation. The W.H.O. points out that other less hazardous means of supplying potassium are available when potassium supplementation is required. The only dosage form available apart from the slow-release preparation is the liquid form but potassium chloride administration in this form is contraindicated since it causes gastric irritation and nausea.

My work suggests that the three types showing medium dissolution rates are safe, effective and make available the potassium chloride at a moderate rate unlikely to give rise to any adverse reactions such as ulceration of the gut.

Theory

Barlow (1965) used conductivity monitoring in a study of potassium release. I have used a potassium specific electrode under both sink and non-sink experimental conditions. Several theoretical approaches have been made to solute release and factors affecting dissolution from various dosage forms (Noyes & Whitney, 1897; Hixson & Crowell, 1931; Higuchi, 1963, 1964) and many experimental investigations have studied the course and factors affecting it.

The original equation for dissolution was that of Noyes & Whitney (1897):

$$\frac{dW}{dt} = \frac{DS}{h}(C_s - C) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where dW/dt is the total dissolution rate across the dissolving surface, D is the diffusion coefficient, S is the surface area exposed to the dissolution medium, h is the effective thickness film of diffusion-layer, C_s is the concentration of the solute at saturation and C is the solute concentration at time t.

Where the solid does not change shape during dissolution so that the surface area available for dissolution is proportional to (weight)$^{2/3}$, Hixson & Crowell (1931) postulated

$$W_o^{\frac{1}{3}} - W^{\frac{1}{3}} = K_R t \quad .. \quad .. \quad .. \quad .. \quad (2)$$

where W_0 is the weight of medicament at time $t = 0$, W is the weight of medicament at time t, and K_R is the release constant.

For non-disintegrating core tablets Higuchi (1963) gives (a) where the matrix is uniform:

$$Q = [Dt\,(2A - C_s)\,C_s]^{\frac{1}{2}} \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusivity of drug in the permeating fluid, A is the total amount of drug present in the matrix, per unit volume and C_s is the solubility of drug in the permeating fluid, and (b) for a non-homogeneous matrix

$$Q = \left[\frac{DE}{T}(2A - EC_s)\,C_s t\right]^{\frac{1}{2}} \quad .. \quad .. \quad .. \quad (4)$$

where E is the porosity of the matrix and refers to the volume fraction that is permeated by the solvent and available for diffusion in the already leached portion of matrix. T is the tortuosity factor of the capillary system (straight channel $T = 1$).

MATERIALS AND METHODS

Apparatus

The non-sink method of Levy & Hayes (1960). The apparatus is essentially a temperature controlled double walled vessel, with stirring device. The stirring rate was 10 rev min^{-1} to avoid turbulence and abrasion. The potassium ion electrode (A. H. Thomas 4923–Q 10) was introduced together with a reference electrode (A. H.

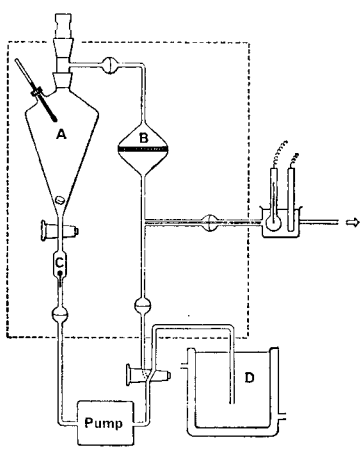

FIG. 1. Modified Marshall & Brook dissolution rate apparatus. Dissolution fluid was pumped from D through a one-way valve C into the dissolution flask A and then through a sintered glass filter B to trap any particles carried over. The fluid passed into a small reservoir before going to waste.

Thomas 4857–H 10 potassium free liquid junction electrode) and connected to an extended scale pH meter (IL pH/mV electrometer model 240) to measure the potential developed. A Sargent S.R.L. recorder was used to record automatically the potential versus time curve.

Modified Marshall and Brook sink method. The Marshall & Brook (1969) apparatus (Fig. 1) has been modified to include a Beckman pump flow = 20 ml min^{-1}), which pumps the dissolution fluid from receptacle D (a double walled temperature controlled vessel). The fluid was made to pass through a small reservoir before going to waste. This glass reservoir was made to accommodate the K^+ specific electrode and the reference electrode which were connected to an extended scale pH meter and the resulting potentials recorded automatically on a Sargent S.R.L. recorder. The amount of sample dissolving in the agitation zone at any given time was obtained by analytical measurements of the fluid passing over the electrodes. The apparatus attains perfect sink conditions if the sampling rate equals the pump rate, with fresh fluid continuously bathing the sample.

Non-sink method

For the calibration curve, standard solutions of 3, 30, 300, 3000, and 30 000 mg of potassium chloride (analytical grade), dried at 120° for 12 h, were prepared in a buffer solution of the following composition: 0·2M tris (hydroxymethyl) aminomethane (250 ml) 0·1N HCl (450 ml), and distilled water (to 1000 ml), adjusted to pH 6·8. All measurements were made for solutions at 37 $\pm$ 0·5°.

The potassium ion electrode performance specifications issued by the manufacturers allow for a concentration range of 1 to 10^{-4} mol of K^+ $litre^{-1}$, a pH range of 5 to 9 and a temperature range of 0 to 70°. Calibration was carried out before and after each run. This was done to allow the potential to stabilize within $\pm$0·1 mV. 15 min were allowed to elapse with the electrodes immersed in the buffer solution before the first readings were taken. Equilibration was usually complete in 5 min.

A plot of log potassium ion concentration versus mV was linear above 30 mg $litre^{-1}$ and had the Nernst slope (61·5 mV/pK^+). It served to obtain experimental concentrations from meter readings.

Modified Marshall & Brook (1969) *sink method*

Calibration curves were computed in the same way before each run. Tris/HCl buffer solution was again used as medium, but in larger quantities since it flows to waste. The apparatus was initially filled with the medium (300 ml) and the pump primed. The medium was circulated for 2–3 min, and the quantity of effluent was checked with the pump rate, which was set at 20 $\pm$ 0·2 ml min^{-1}. The tablets were then introduced into the dissolution vessel, A, and readings taken. Six runs of each sample were made for a minimum of 180 min each. On no occasion did the tablet or tablets break up into particles, thus indicating a non-disintegrating type of dosage form.

Simulation of gastric conditions

All the samples were subjected to the first stage of the B.P. 1968 disintegration test in a medium of 0·6% v/v hydrochloric acid. Dissolution studies were made on tablets before and after this test. Where tablets containing added diuretic were tested, it was established that there was no potassium response from the diuretic.

The tablets used were: hydrochlorothiazide 0·25 mg; cyclopenthiazide 0·50 mg; guanethidine sulphate 10·0 mg; trichloromethiazide 4·0 mg; methyldopa 250·0 mg; hydrochlorothiazide 15·0 mg; bendrofluazide 2·5 mg.

Comparative study

The performance of the potassium ion electrode was compared with flame photometric estimation of potassium on the same solutions to give a correlation coefficient of r = 0·99. The average percentage recovery values were 100·8% for electrodes and 99·8% for flame photometry.

RESULTS

Fig. 2 shows a typical graph of mV readings versus time, using the Levy & Hayes non-sink method. The potential readings were related to concentration by reference to the calibration curve.

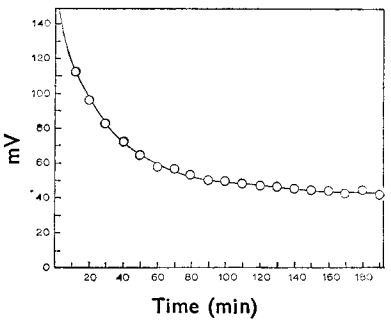

FIG. 2. A graph of mV readings *vs* time for a non-sink method of estimating dissolution rate.

Non-sink conditions

A plot of log % amount remaining undissolved at time t versus time was linear i.e.

$$\log 100 \frac{W_o - W}{W_o} = \text{constant} - K_1 t$$

where W is the weight of solute or tablet dissolved. Differentiation gives

$$\frac{dW}{dt} = (W_o - W)\, K_1 \times 2{\cdot}303$$

$$\text{and } \frac{dW}{dt} = K_R (W_o - W) \quad .. \quad .. \quad .. \quad .. \quad (5)$$

where $K_R = K_1 \times 2{\cdot}303$, the release constant.

Since the volume V remains constant equation 5 can be rewritten as

$$\frac{dC}{dt} = K_R (C_o - C) \quad .. \quad .. \quad .. \quad .. \quad (6)$$

i.e. the release of potassium chloride from tablets shows a first order dependence on the weight of potassium chloride remaining. This may be compared with the Noyes-Whitney equation (eqn 7) which requires a first order dependence on $(W_s - W)$ rather than $(W_o - W)$ and is in the form

$$\frac{dW}{dt} = \frac{DS}{Vh} (W_s - W) \quad .. \quad .. \quad .. \quad .. \quad (7)$$

dW/dt, D, S, and h have the same meanings as previously noted. V is the volume of dissolution medium, W_s is the weight of solute in the diffusion layer and W is the weight of solute in the bulk of the solution at time t.

First order rate constants obtained from the slopes K_R are listed in Table 1. The slopes were obtained by the least squares treatment. The plots indicate that the first portion of the potassium chloride was released immediately but at a very slow rate. The remainder was released exponentially. This initial time lag may be attributed to the presence of various thicknesses of sugar coatings on the tablet surface. Owing to this time lag, which varied from 0–45 min in most cases (but in the case of Product H and I was in the region of 200 min), the rate release constant (K_R) could not be ascertained during this phase. It was possible, however, to make a comparative study of the various release characteristics of the tablets by collating the release constants. It was not possible to determine the T50 values because of this initial time lag.

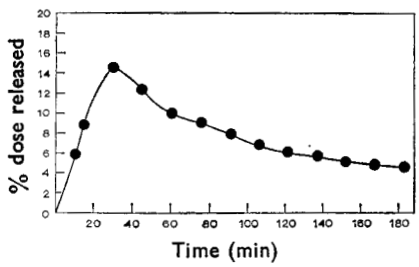

FIG. 3. Elution rate *vs* time using the forced convection sink method.

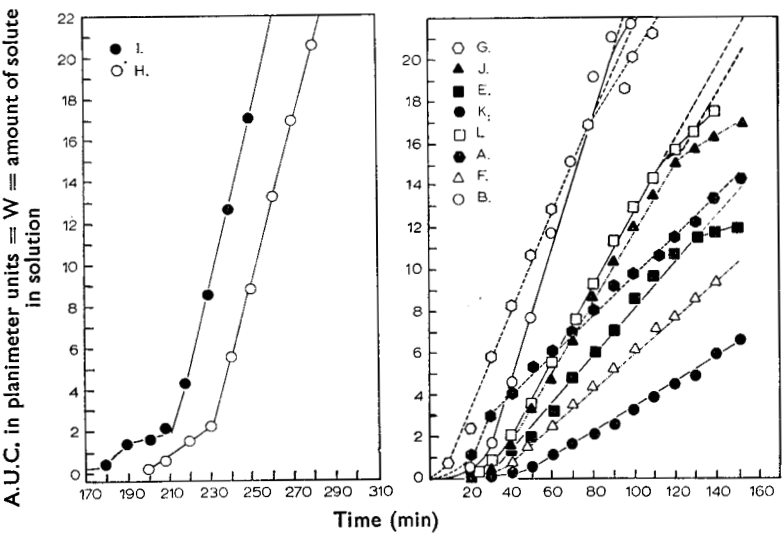

FIG. 4. Amount of drug eluted *vs* time using the forced convection sink method.

The Hixson and Crowell cube root law

The Hixson and Crowell equation was also applied to the experimentally measured values of release.

When values of $W_o^{\frac{1}{3}} - W^{\frac{1}{3}}$ were plotted against time, satisfactory straight lines resulted. The release rate constants obtained from their slopes are listed in Table 1

Table 1. *Products and collected data on dissolution rates.*

Product	Slow release mechanism	Active ingredient	Release constant min^{-1} non sink method	Slope Hixson-Crowell cube root law	T 50% values (Higuchi's equation)	Slope sink method	Release rate
G	Fat-wax KCl non-disintegrating core	Potassium chloride 400 mg, guanethidine sulph. 10 mg, cyclopenthiazide 0·15 mg	$5{\cdot}71 \times 10^{-2}$	$9{\cdot}75 \times 10^{-2}$	33·7 min	$30{\cdot}0 \times 10^{-2}$	Excessively fast dissolution rate
B	Cellulose acetate phthalate (C.A.P.) enteric coating	Potassium chloride 600 mg	$5{\cdot}04 \times 10^{-2}$	$9{\cdot}36 \times 10^{-2}$	40·0 min	$23{\cdot}3 \times 10^{-2}$	Excessively fast dissolution rate
K	Shellac enteric coating	Potassium chloride 625 mg, hydroflumethiazide 25 mg	$1{\cdot}08 \times 10^{-2}$	$3{\cdot}09 \times 10^{-2}$	110·0 min	$6{\cdot}0 \times 10^{-2}$	Moderate rate o release
E	Fat wax KCl non-disintegrating core	Potassium chloride 600 mg, hydrochlorothiazide 12·5 mg	$1{\cdot}00 \times 10^{-2}$	$2{\cdot}72 \times 10^{-2}$	90·0 min	$12{\cdot}3 \times 10^{-2}$	Moderate rate of release
J	Fat wax KCl non-disintegrating core	Methyldopa 250 mg, hydrochlorothiazide 15 mg, pot. chloride 200 mg	$0{\cdot}86 \times 10^{-2}$	$2{\cdot}56 \times 10^{-2}$	130·0 min	$17{\cdot}0 \times 10^{-2}$	Moderate rate of release
A	Insoluble wax coat on a non-disintegrating KCl core	Potassium chloride 600 mg	$0{\cdot}85 \times 10^{-2}$	$2{\cdot}47 \times 10^{-2}$	103·0 min	$9{\cdot}25 \times 10^{-2}$	Moderate rate of release
L	A non-disintegrating core containing ethyl cellulose, polyethylene glycol and C.A.P.	Potassium chloride 625 mg, bendrofluazide 2·5 mg	$0{\cdot}79 \times 10^{-2}$	$2{\cdot}32 \times 10^{-2}$	108 min	$17{\cdot}50 \times 10^{-2}$	Moderate rate of release
F	Fat-wax KCl non-disintegrating core	Potassium chloride 600 mg, cyclopenthiazide 0·25 mg	$0{\cdot}53 \times 10^{-2}$	$1{\cdot}66 \times 10^{-2}$	145 min	$9{\cdot}0 \times 10^{-2}$	Moderate rate of release
D	Fat-wax KCl non-disintegrating core with a C.A.P. plus insoluble wax coat	Potassium chloride 573 mg, bendroflumethazide 2·5 mg	$0{\cdot}11 \times 10^{-2}$	$0{\cdot}3 \times 10^{-2}$	Not achieved	Unattainable	Very slow release rate
C	As D	Potassium chloride 600 mg	$0{\cdot}09 \times 10^{-2}$	$0{\cdot}14 \times 10^{-2}$	Not achieved	Unattainable	Very slow release rate
I	KCl core plus C.A.P. coating covered with a gelatin and acacia Kaolin mix	Potassium chloride 300 mg, hydrochlorothiazide 50 mg	$13{\cdot}79 \times 10^{-2}$ after lag phase of 220 min	Not recorded	Not recorded	$22{\cdot}4 \times 10^{-2}$ after 170–200 min lag phase	Lag phase of 200 min followed by rapid release
H	Shellac enteric coated KCl core	Potassium chloride 500 mg, trichlor methiazide 4 mg, reserpine 0·1 mg	Not recorded	Not recorded	Not recorded	$36{\cdot}6 \times 10^{-2}$ after 170–200 min lag phase	As I

and show the same trend as these obtained from the other equations. The results obtained after subjecting the tablets to the first stage of the British Pharmacopoeia (1968) disintegration test were meaningless as the tablets became eroded and in some instances dissolved completely in the hydrochloric acid 0·6% v/v.

Higuchi's Equations

Some of the products tested were of the non-disintegrating fat-wax matrixed type of dosage form. Subject to the diffusion process being rate determining, it was assumed reasonable to apply Higuchi's equations (eqns 3 or 4). Plots of percent concentration versus (time)$^{\frac{1}{2}}$ should be linear. For comparison the results for other types of tablet were also plotted. All were substantially linear over much of the dissolution period, excepting the initial and final stages. The satisfactory agreement of experimental results with these markedly different equations is unexpected. It implies that the approaches, though different, are approximately equivalent; or that more precise methods of measurement are needed to distinguish between them.

Sink conditions

Dissolution rate-limited absorption indicates that there is no increase in drug concentration in the gastrointestinal fluids, i.e., the fluids function as a perfect sink, which is a necessary condition of agreement between *in vitro* and *in vivo* tests. Sink conditions are claimed to exist when $C \ll C_s$, usually $C \leqslant 0{\cdot}1\ C_s$. Equation 1 simplifies to:

$$dW/dt = K\ S\ C_s \quad .. \quad .. \quad .. \quad .. \quad (8)$$

indicating that if the surface area is held constant under sink and nonreactive conditions, then the rate of dissolution is constant, i.e., the kinetics are of zero order.

$$\text{Integration leads to } W = K\ S\ C_s t \quad .. \quad .. \quad .. \quad .. \quad (9)$$

A plot of W versus t will yield a straight line with slope = $K\ S\ C_s$ in mg min^{-1} litre^{-1}.

The percentage of original dosage released per time interval was computed from the calibration curve and is depicted in Fig. 3. The curve shows that a definite maximum dissolution rate was reached.

The total amount of drug eluted, W, at time t, i.e., the amount of solute in solution (the integral of dW/dt), can be calculated by measuring the area under this curve (A.U.C.) at various time intervals (e.g. 10 min) with a planimeter. A.U.C. units ($\equiv$W) versus time (t) were plotted, and, except for a slight deviation initially and at the end of the curve, gave a straight line (Fig. 4). The best fitting line was determined by the method of least squares. The slopes ($K\ S\ C_s$) of the curves are listed in Table 1; these give an indication of the varying dissolution rates.

(The peak concentration from C and D tablets was too small to measure.) The release constants obtained under sink conditions (zero order) bear a close relation to those obtained under non-sink (first order) experimental conditions.

The results obtained after subjecting the tablets to the first phase of the B.P. 1968 disintegration test are listed in Table 2. The results are not as well defined as the previous findings. There are deviations from the straight line relation, and in three instances there was not sufficient of the tablet remaining after the disintegration test to allow any further experimental work.

Table 2. *Values obtained after tablets were subjected to the disintegration test and forced convection sink method using the Marshall & Brook Apparatus.*

Product	Slope = KSC_s	Dissolution rate at peak elution (mg min^{-1})
C	$5{\cdot}7 \times 10^{-2}$	4·80
A	$7{\cdot}1 \times 10^{-2}$	6·60
G	$9{\cdot}2 \times 10^{-2}$	7·80
D	$9{\cdot}5 \times 10^{-2}$	8·00
F	10×10^{-2}	9·00
H	16×10^{-2}	16·00
K	22×10^{-2}	22·30
J	35×10^{-2}	30·00
I	46×10^{-2}	40·00
L, E, B	Not sufficient left after disintegration for estimation.	

DISCUSSION

Current U.S. Food and Drug Administration regulations require that all slow release preparations be regarded as new drugs. Thus, their safety and efficiency must be demonstrated before they may be introduced into clinical use.

The loss of potassium from the body and the amount of potassium necessary to prevent hypokalaemia vary greatly among different patients. The incidence of stenosis and ulceration of the gut is dependent on the dissolution characteristics of the dosage form. A slower release of potassium chloride should give a lower concentration of electrolyte in the boundary layer surrounding the dissolving tablet, resulting in a reduced likelihood of intestinal ulceration. It is therefore pertinent that formulation of a potassium chloride dosage form be such that the dissolution characteristics be quantitatively adequate and at a desirable rate.

The release constants derived by applying the apparent first order rate equation, the Hixson & Crowell cube root law and Higuchi's equations to the non-sink method of dissolution rate measurements and the apparent zero order release rate constant utilizing the sink method indicate that the twelve preparations listed in Table 1 can be grouped into four types: (1) G, B; (2) K, E, J, A, L, F; (3) D, C; (4) I, H.

The most satisfactory products appear to be those prepared from a fat-wax potassium chloride matrix, an insoluble wax coat on a non-disintegrating wax core and a combination of potassium chloride, C.A.P. ethyl cellulose and polyethylene glycol.

There are a few exceptions—Products G, I and K do not fit into this general picture: I and K appear satisfactory and G unsatisfactory—a reversal of expected results.

The methods used to measure the dissolution rates have proved of value in assessing the characteristics of slow-release preparations, and could be adopted as routine test procedures, but they are not really accurate enough for investigational studies.

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