J. Pharm. Pharmac., 1971, **23**, 490–494 *Received December* 15, 1970

The drug release characteristics of various rectal suppositories as determined by specific ion electrodes

W. H. THOMAS AND R. MCCORMACK

Pharmacy Department, University of Otago, Dunedin, New Zealand

Suppositories containing sodium phenobarbitone (200 mg) were manufactured with the following bases; cocoa butter, cocoa butter plus beeswax, Dehydag and polyethylene glycols. The release of sodium ions through a dialysis membrane was conveniently measured with a sodium-specific ion electrode. The method facilitates evaluation and comparison of suppository bases and allows continuous monitoring of the release of active ingredient.

The release of a drug from a suppository is critically dependent on the physical characteristics of the base (Lesser, 1943). It follows that base and active ingredient must be considered together. Physical factors that affect drug release from a suppository include (i) particle size of the suspended drug, (ii) the effect of surface-active agents on the mucous fluids secreted over the absorbing surface, and (iii) the binding of the drug to components of the base. Diffusion of the drug to the surface for absorption is one of the rate limiting steps (Reigelman & Crowell, 1958).

The official quality control procedures for suppository bases may be considered inadequate. The B.P. (1968) stipulates only the usual chemical assay and a melting point determination for the base. The U.S.P. XVII states that the preparation (suppository) should melt, soften or dissolve at body temperature. Other tests include deformation of the suppositories at various temperatures below the melting point of the base (Tuma, 1963); a test for the disintegration rate of suppositories (Baker & Ranson, 1934) and an evaluation of the rate of drug release by microbiological cup methods (Buchi, 1944). Determination of the amount of a drug passing out from an immersed suppository at different times into an aqueous medium has also been suggested (Gross & Becker, 1953; Peterson & Guida, 1953).

Henning (1959) and Setnikar & Fantelli (1962) have endeavoured to reproduce the mechanical and physico-chemical conditions present in the human rectum. Setnikar & Fantelli used a glass cylinder in which the water at 37° circulates around a suspended length of moistened inflated cellulose dialysis tubing containing the suppository. Liquifaction time was determined. We have modified this apparatus to permit measurements to be made with specific ion electrodes.

MATERIALS AND METHODS

Apparatus

The modified Setnikar-Fantelli apparatus used is shown in Fig. 1. This, the primary part, is a double walled glass vessel with open ends, in the interior of which is supported a length of dialysis tubing (Union Carbide 36/36 membrane) previously tied with thread 5 cm from the lower end. The ends of the dialysis tubing are folded back over the open ends of the apparatus and securely tied. A small immersible

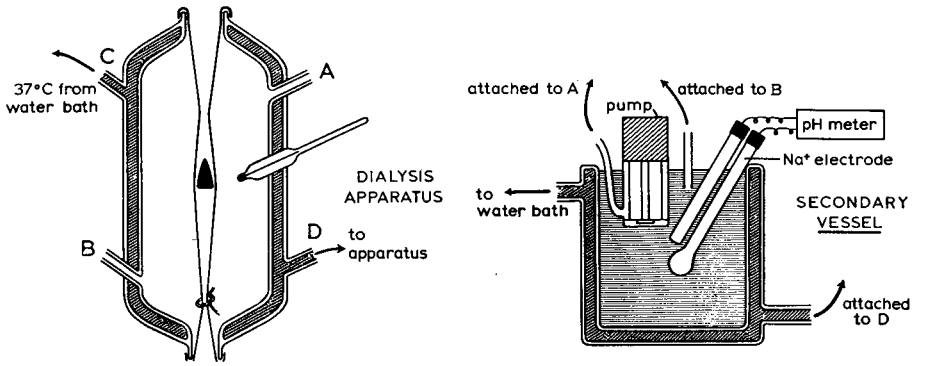

FIG. 1. Diagram of modified apparatus of Setnikar & Fantelli. See text for full description.

electric pump placed in the secondary vessel (Fig. 1) circulates the eluting fluid outside the dialysis membrane. Water at 37° is circulated through the walls of the dialysis apparatus and the secondary vessel which are interconnected (Fig. 1).

The sodium electrode (Arthur H. Thomas model 4923-L10) measuring the release was placed in the secondary vessel and a Radiometer pH meter with expanded scale was used to measure the potential difference between this and the reference electrode (a double junction model 90-01-Orion).

To provide calibration curves, solutions containing 5, 10, 50, 100, 200, 600, 1000 and 1400 mg of sodium phenobarbitone per litre were made in a tris buffer solution of composition: 0·2M tris (250 ml), 0·1N HCl (450 ml) and distilled water (to 1000 ml) adjusted to pH 6·8. All measurements were made at 37° ± 0·5°.

Suppositories

Using 1 g moulds sodium phenobarbitone (200 mg) was incorporated into the following bases: cocoa butter, cocoa butter plus 2, 3 and 5% beeswax, polyethylene glycol (PEG) type I (33% of PEG 1500, 47% PEG 6000, 20% water), PEG type II (33% PEG 4000, 47% PEG 6000, 20% water), PEG type III (30% PEG 1500, 40% PEG 4000, 30% PEG 400), PEG type IV (90% PEG 1000, 4% PEG 4000), PEG type V (70% PEG 1500, 30% PEG 6000), PEG type VI (30% PEG 1500, 50% PEG 6000, 20% water), Dehydag suppository base I and II (long chain fatty alcohols plus solid fats produced by Henkel International Germany), Suppositories for baseline measurements were made as above but without the sodium phenobarbitone.

The sodium phenobarbitone sample used was found to be 99% pure by non-aqueous titration (Beckett & Stenlake, 1964).

Method

The suppositories and suppository bases were prepared and stored for two days to allow the base to revert to the more stable crystalline state. The calibration curve was then plotted of potentiometric response in mV against the logarithm ($\log_{10}$) sodium ion concentration for sodium phenobarbitone solutions made up using tris buffer. This was done before each series of measurements to account for changing electrode characteristics such as change of junction potential. The wet dialysis tubing was secured firmly at the lower end of the apparatus and the upper end was left open until the inner chamber was filled with tris buffer solution (representing total body fluids). One litre (accurately measured) of tris buffer was used for each run;

its flow was regulated by varying the pressure of a clamp set between the electrical pump in the secondary vessel and the dialysis apparatus. By reducing the flow the dialysis tubing was made to open half way down its length. After the suppository had been dropped into the tubing, the clamp pressure was eased to refill the chamber, after which mV readings were taken every 2 min. At 5 min intervals the melted base was dispersed along the dialysis tubing by varying the clamp pressure. The melting time of each suppository base was also recorded.

RESULTS

The melting times for the various suppositories are recorded in Table 1.

Table 1. *Melting point* (°C) *and time for complete melting* (*at* 37°) *of suppository base containing* 200 *mg sodium phenobarbitone.*

Base	Melting point (° C)	Complete melting time (min) at 37° C ± 0·5°
Cocoa butter	32–34	4
Cocoa butter + 2% beeswax	35–37	35
Cocoa butter + 3% beeswax	39–44	50
Cocoa butter + 5% beeswax	42–47	80
Polyethylene glycol type 1 base	39–40	20
Polyethylene glycol type II	50–51	24
Polyethylene glycol type III	33–38	18
Polyethylene glycol type IV	33–38	20
Polyethylene glycol type V	38–43	20
Polyethylene glycol type VI	48–52	22
Dehydag base I	33–36	6–8
Dehydag base II	37·5–39·5	Does not melt at experimental temperatures

A calibration curve of log concentration of Na^+ (as mg sodium phenobarbitone per litre) versus potential gives in the linear region an experimental slope of 60 mV for each decade change of sodium ion concentration, a value approximating closely the theoretical Nernst slope (2·303 RT/F) of 61·5 mV at 37°. The concentration range recommended by the manufacturer is 1 to 10^{-5} mol of Na^+ per litre, but we found it more convenient to use standard solutions of 5 to 1400 mg/litre. Six runs of each suppository formulation were considered adequate.

Graphs of Na^+ (as mg of sodium phenobarbitone/litre) versus time were plotted and the time required for the suppository to release half of its contents to the medium was designated the T50% value, average values of which are in Table 2.

Fig. 2 shows the release of drug as assessed by Na^+ release from the cocoa butter suppositories and the Dehydag base I and base II suppositories. These are considered melting fat type bases. Fig. 3 shows the drug release characteristics of the dissolving type of suppository—the polyethylene glycol base.

No suppository base similarly treated released sodium ions.

DISCUSSION

The relation between the ion activity and electrode potential is logarithmic. Thus, the rate of release of sodium phenobarbitone from suppository bases is measured by reference to a calibration curve which is plotted before each set of measurements. This calibration curve is based on the potential produced by the electrodes as a function of sodium ion activity or $\log_{10}$ sodium ion concentration. This is expressed

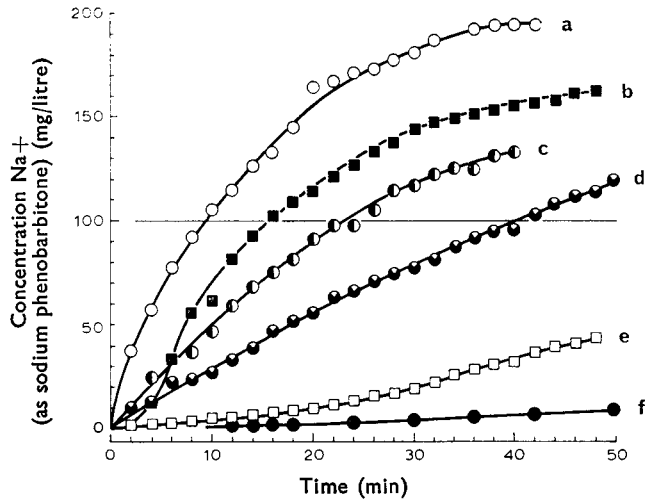

FIG. 2. The release of phenobarbitone sodium as assessed by Na^+ release from the cocoa butter and Dehydag based suppositories. a, cocoa butter Av.T50: 9·2; b, Dehydag base I Av. T50: 15·6; c, cocoa butter + 2% beeswax Av.T50 : 23; d, cocoa butter + 3% beeswax Av.T50 : 38·8; e, Dehydag base II Av. T50 : 92 min; f, cocoa butter + 5% beeswax: no T50 value.

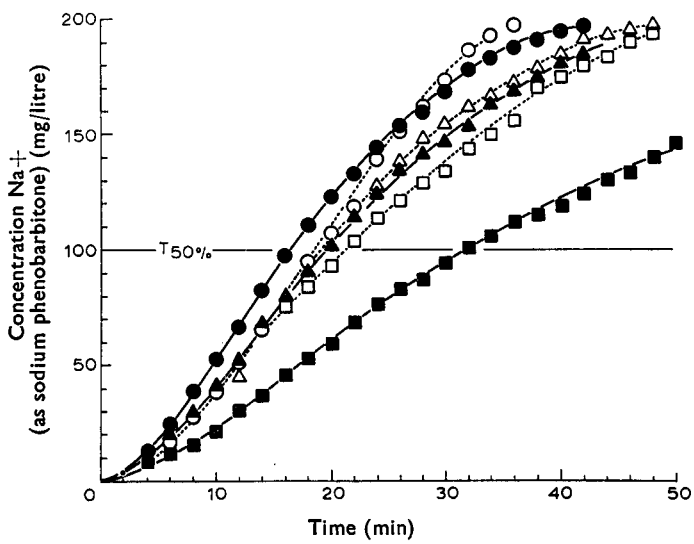

FIG. 3. The release of phenobarbitone sodium as assessed by Na^+ release from the PEG bases. ▲ PEG I T50 : 19; ○ PEG II T50 : 18·5; △ PEG III T 50: 19; ● PEG IV T50: 16·4; ■ PEG V T50: 31·6; □ PEG VI T50: 212.

by the Nernst equation: $E_{obs} = E_s + 2{\cdot}303\ (RT/nF) \log (A_{Na}+)$ where 2·303R/F = 0·1984 (Nernst factor). At 37°, T × 0·1984 = 61·5 mV, which is the theoretical slope of E_{obs} *vs* log (A_{Na+}). For each decade change in Na^+ activity over the range of 1 to 10^{-5}M concentrations, the potential changes by approximately 61·5 mV.

In addition to established routine quality control procedures for suppositories it is essential for effective quality control to estimate the rate and extent of release of medicament. The drug release rate of 37° is dependent on melting characteristics of the fatty suppositories so that melting point determination does give some indica-

Table 2 *T50% values (time required for suppository to release half of its contents to the medium).*

Base	T50% values (min)	Standard deviation
Cocoa butter	9·2	0·08
Cocoa butter with 2% beeswax	23	2·20
Cocoa butter with 3% beeswax	38·8	3·04
Cocoa butter with 5% beeswax	T50% value not reached at 37°	—
Dehydag base I	15·6	2·06
Dehydag base II	92	7·03
Polyethylene glycol type I	19·0	0·11
Polyethylene glycol type II	18·5	0·23
Polyethylene glycol type III	19·0	0·27
Polyethylene glycol type IV	16·4	0·77
Polyethylene glycol type V	31·6	5·76
Polyethylene glycol type VI	21·0	2·56

tion of release in this class of suppository. With water-soluble bases, quantitative measurement of release is the most desirable parameter of availiability of drug.

No easy method, as far as we are aware, is available for measuring quantitatively *in vitro* release rates of medicaments from suppository bases, nor a method to measure a continuous change with time.

The specific ion-dialysis membrane method described furnishes a means of measuring a continuous change in the amount of drug released from a suppository in conditions which approximate those *in vivo*, namely: (i) an average temperature of 36–37°, (ii) little or no peristaltic movement, (iii) minimal quantity of unbound water present in the liquid state, and (iv) a pressure of 0–50 cm of water. Furthermore this method can be easily modified to measure release under "sink" conditions.

The results obtained substantiate previous claims that the melting characteristics of fat-base suppositories influence drug release rate at 37° irrespective of other factors. This is adequately demonstrated by the T50% values, which increase as the melting point of base increases. Readings with all the water-soluble polyethylene glycol bases were recorded after 2 min but it appears—as is substantiated in the literature (Hassler & Sperandio, 1953)—that the duration of action is longer than with the fat-wax melting suppositories (Table 2). T50% values are about 20 min.

The results obtained and the ease and simplicity of operation of the apparatus indicate that specific ion electrodes can be used to evaluate drug release from dosage forms as long as the active ingredient is represented by free ion.

REFERENCES

BAKER, J. R. & RANSON, R. M. (1934). *J. Hyg., Camb.*, **34**, 474–485.

BECKETT, A. H. & STENLAKE, J. B. (1964). *Practical Pharmaceutical Chemistry.* University of London: Athlone Press.

BUCHI, J. (1944). *Pharm. Acta Helv.*, **19**, 171–174.

Dehydag Booklet. (Henkel International, Germany.)

GROSS, H. M. & BECKER, C. H. (1953). *J. pharm. Sci.*, **42**, 96–100.

HASSLER, W. H. & SPERANDIO, G. J. (1953). *J. Am. pharm. Ass. (Pract. Edn.)*, **1**, 26–27.

HENNING, W. (1959). *Ueber die rektale Resorption von Medikamenten*, Juris, Zurich, Switzerland.

LESSER, J. (1943). *Drug Cosmet. Ind.*, **53**, 32–34.

PETERSON, C. F. & GUIDA, A. J. (1953). *J. Am. pharm. Ass. (Sci. Edn)*, **42**, 96–101.

REIGELMAN, S. & CROWELL, W. J. (1958). *Ibid.*, **47**, 115–127.

SETNIKAR, I. & FANTELLI (1962). *J. pharm. Sci.*, **51**, 566–571.

TUMA, R. (1963). *Arch. Pharm.*, **8**, 137–140.