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IN-VITRO RELEASE OF DIAZEPAM FROM CONVENTIONAL AND DOUBLE-LAYER POLYETHYLENE GLYCOL SUPPOSITORIES

A.A. Deshmukh and P.M. Thwaites*

Dept. of Pharmaceutics,

The School of Pharmacy,

University of London.

*Present address:

Smith, Kline and French Laboratories Ltd,

Welwyn Garden City, Herts AL7 1EY

ABSTRACT

A dissolution cell of simple design has been devised specifically for the assessment of hydrophilic suppositories. The measured total percentage release of three conventional diazepam formulations has been measured and interpreted in terms of appropriate kinetic microconstants. The desirability of assessing such tests in terms of a dissolution half-life is discussed.

A novel hydrophilic double-layer suppository has been formulated and its measured dissolution profile is described both mechanistically and in terms of suitably derived kinetic equations. The initial total percentage release of this formulation was significantly greater than that of the conventional suppositories which were tested. It is suggested that a double-layer suppository of this type could be therapeutically advantageous in the treatment of epilepsy.

INTRODUCTION

Although drug release from suppositories can only be assessed adequately by tests in man, in-vitro dissolution studies are of value during the development of a formulation and for quality control. Hence there is considerable interest in the possible regulatory and compendial use of suppository dissolution tests. In-vitro dissolution tests using membranes prevent mixing, emulsification or dissolution of the base in the receptor phase and are a means of controlling the interfacial area of the dissolution medium. However their use is associated with a number of disadvantages which have been well documented in the literature[1]. In particular, Tukker and de Blaey[2] have emphasised the importance of monitoring the total rather than the apparent release of drug in such an experiment. Unofficial methods of suppository dissolution testing using aqueous receptor phases, have been developed by simple modification of the USP tablet

dissolution tests[3,4,5]. Experiments of this type might be satisfactory to study the release of drugs from lipophilic (fatty) suppository bases as their immiscibility with an aqueous receptor phase presents a natural interface between the bulk of the base and the dissolution medium. This simulates the in-vivo process in which the drug diffuses through the melted base before partitioning into the rectal fluid. However, such tests would fail to mimic the in-vivo release from a hydrophilic suppository which involves partitioning of active principle from a dissolving or dissolved basis, diffusion through the viscous rectal polymer solution and subsequent partition into the rectal membrane. A new dissolution cell has been devised for the assessment of release from water-soluble suppository bases in a more realistic manner. It has been used to measure the release of diazepam from three conventional suppository formulations which have a polythylene glycol basis and from a novel double-layer suppository in which the drug is dissolved in a thin outer layer of polyethylene glycol 1000 (PEG 1000) coated on a drug-free core of polyethylene glycol 6000 (PEG 6000). Equations have been derived to describe the in-vitro release from such a formulation in terms of total percentage release of drug.

EXPERIMENTAL

Materials: Diazepam, Valium(R) 5 mg suppositories (Batch B5152, Roche Products, Welwyn Garden City), Polyethylene Glycol 1000 and

6000 (Koch-Light Laboratories, Suffolk), Octan-1-ol (East Anglia Chemicals, Ipswich) and double distilled water. All materials were BP or analytical grade and were used without further purification. In the dissolution studies octan-1-ol pre-saturated with double distilled water and double distilled water pre-saturated with octan-1-ol at the temperature of measurement were used.

Instrumentation: The absorbance of diazepam in the octan-1-ol phase was continuously monitored using a Cecil CE 202 variable wavelength U.V. spectrometer. The melting point behaviour of the suppository bases containing 0.4% of diazepam was measured with a Du Pont Series 99 thermal analyser equipped with a 910 differential scanning calorimeter system.

Preparation of conventional suppositories: Suppositories were manufactured consisting of 5 mg of diazepam in PEG 1000 or PEG 6000. The suppositories were prepared by fusion using a 12 cavity "1 g" mould. All products used for testing weighed between 1.15 and 1.18 g. Valium(R) 5 mg suppositories which are known to have a polyethylene glycol base[6] were used for comparison in the dissolution tests. These had a weight range of 1.43 to 1.45 g.

Preparation of thin layer suppositories: A suitable weight of PEG 6000 was warmed carefully until it was just molten. This melt was poured into a specially designed brass mould (Fig. 1) and allowed to cool to room temperature. The cylindrical cores were then

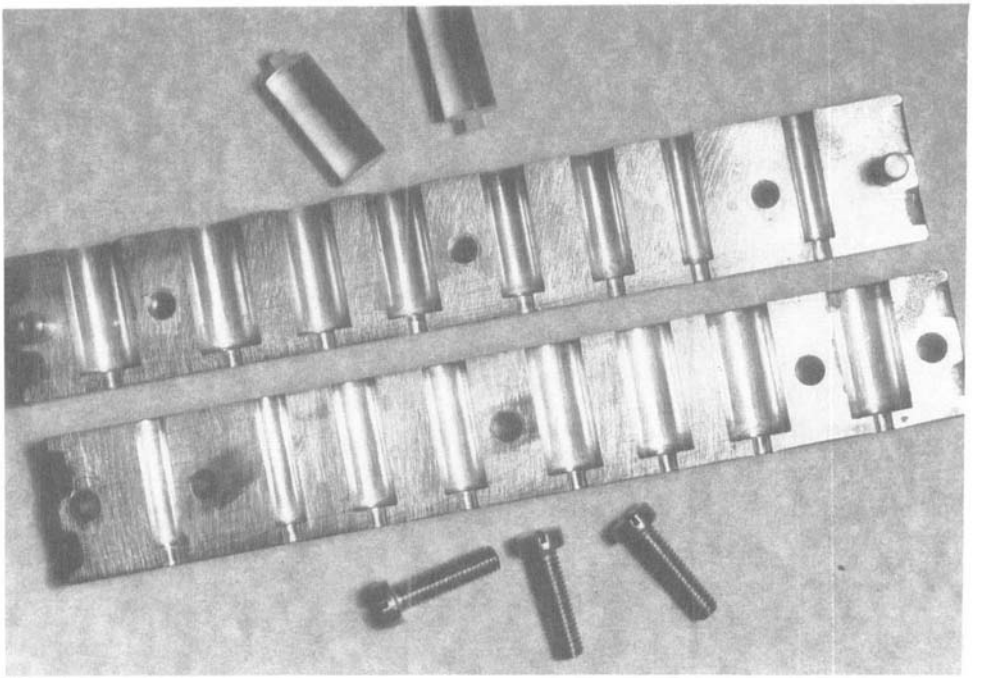


FIGURE 1

Brass mould used for the preparation of the core of the double layer suppositories.

trimmed and removed from the mould avoiding damage to the locating stub. The mould was capable of producing cores of various diameters but in this study those of 9 mm diameter having a weight range of 1.59 to 1.62 g were used for subsequent coating. Such cores were located in a further stainless steel mould (Fig. 2) by means of the locating stub and molten PEG 1000 containing diazepam in solution was slowly injected into the outer annulus using a glass syringe, taking care to avoid the incorporation of air

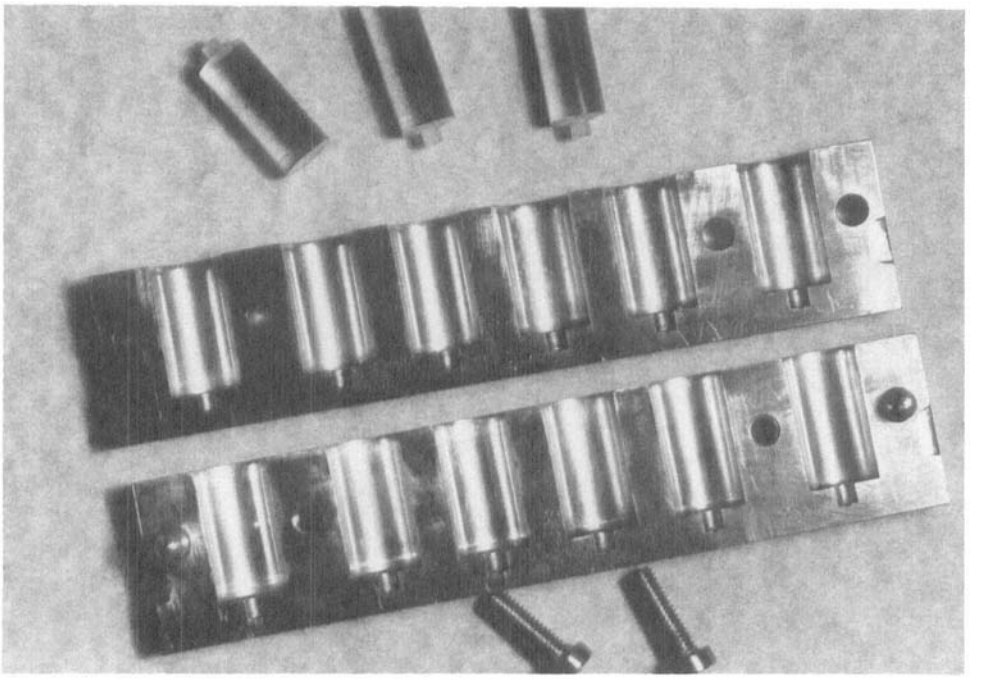


FIGURE 2

Stainless steel mould for the preparation of outer layer of the double layer suppositories.

bubbles. The coating had a weight range of 0.81 to 0.85 g equivalent to a diazepam content of 4.97 to 5.12 mg. In addition, a coating of identical thickness and composition was deposited upon 9 mm diameter perspex cores. This set was used to evaluate the rate of dissolution of the outer coating in the absence of PEG 6000. The nominal diazepam content of 5 mg was used in all the calculations.

Design of Dissolution Cell: The apparatus, which is of simple construction and inexpensive to produce, consists of a 200 ml tall-form pyrex glass beaker with a close fitting lid containing access holes for a stirrer, thermometer and dissolution pipework. The suppository dissolves within the small volume of aqueous fluid and apparent release is determined by measuring the appearance of the drug in the octan-1-ol layer. Such a dual phase system in which the suppository base is preferentially soluble in the aqueous medium and the drug is readily soluble in the organic medium results in retention of the base within a defined volume of dissolution medium of known cross-sectional area. By making the aqueous volume minimal, those physical parameters likely to influence the in-vivo release of the formulation can be studied in a discriminatory manner.

Dissolution Measurement: The dissolution apparatus is shown in Fig. 3. 170 ml of octan-1-ol were carefully layered on top of 40 ml of double distilled water in a tall-form beaker and the whole apparatus was thermostated in a water bath at 37^{o} C. When both phases had reached this temperature, the suppository under test was introduced via a glass tube which was then withdrawn. This technique avoided coating the suppository with octan-1-ol prior to immersion in the aqueous phase. Each phase was stirred separately at 60 r.p.m. This stirring rate was adequate to produce a homogeneous aqueous phase containing dissolved base without causing undue disturbance at the octanol/water interface. The

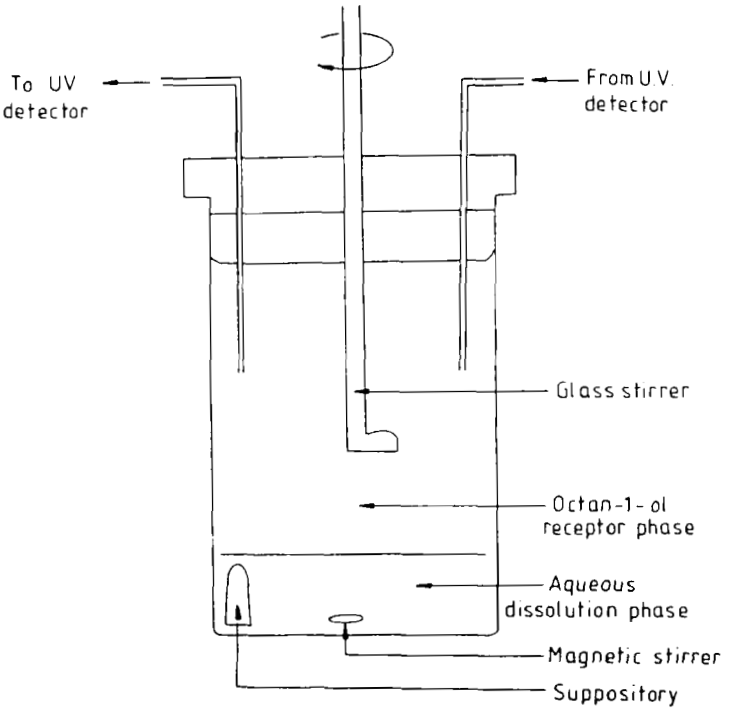


FIGURE 3

The partition dissolution cell

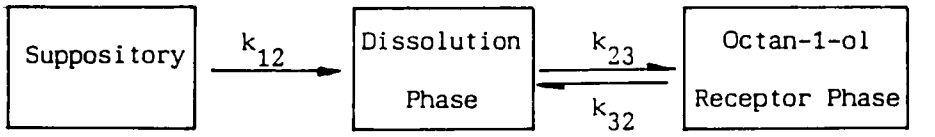
times for complete dissolution of the suppository bases under test were also noted.

THEORY

1: Conventional Suppositories

Kinetic rate constants which describe the release of diazepam from the suppositories into the octan-1-ol layer have been evaluated by fitting the data to the following kinetic models.

Model 1



The suppository dissolves in the aqueous phase at a rate represented by the linear first order constant k_{12}. It would be envisaged that the dissolving suppository base would progressively influence the viscosity and lipophilicity of this dissolution phase. The subsequent partitioning of the drug into the octan-1-ol receptor phase is described in terms of linear rate constants k_{23} and k_{32}. The percentage release of drug P_c at any time t in the octan-1-ol layer is given by

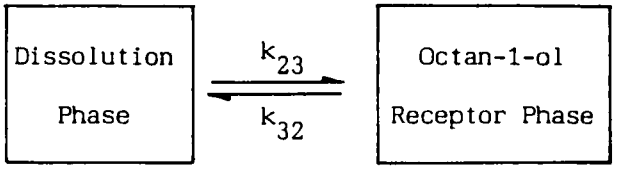
$$P_c = 100k_{23}\left[\frac{(1}{A} - \frac{\exp(-k_{12}t)}{(A-k_{12})} + \frac{k_{12}\exp(-At)}{A(A-k_{12})}\right] \quad 1$$

where $A = k_{23} + k_{32}$

Moreover the total percentage release of the dosage within both phases is

$$P_{TOTAL} = 100\{1 - \exp(-k_{12}t)\} \quad 2$$

At time Γ, the drug content of the suppository is completely and uniformly distributed in the dissolution phase and the apparent release into the octan-1-ol may now be represented by model 2.



If the mass of drug in the octan-1-ol compartment at time Γ is M_Γ, the percentage release of drug in the organic layer is given by

$$P_c = \frac{100k_{23}}{A}\{1-\exp(-A\theta)\} + \frac{100\ M_\Gamma \exp(-A\theta)}{M_\infty} \qquad 3$$

where M_∞ is the initial mass of drug in the suppository and

$$\theta = (t-\Gamma) \qquad 4$$

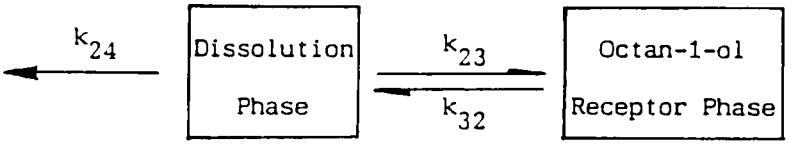
The apparent partition coefficient K of drug between receptor and aqueous donor phase is equal to

$$K = \frac{P_c}{P_B} = \frac{k_{23}}{k_{32}} \qquad 5$$

2: Double Layer Suppository

Although the initial release of the outer coating of the double layered suppository can be described adequately using model 1 the subsequent dissolution behaviour may be more complex. Consider the case where the dissolved core material has a significant affinity for the drug in the aqueous layer and/or the core material is markedly viscous in solution. In this instance, the consequent retardation of drug transfer into the organic phase

after the outer coating has dissolved would be better represented by model 3



In this case, when $t \geq \Gamma$,

$$Pc = \frac{100\, M_{\Gamma}}{M_{\infty}(\beta-\alpha)} \{(\beta-k_{24}) \exp(-\beta\theta) + (k_{24}-\alpha) \exp(-\alpha\theta)\} + \frac{100\, k_{23}}{(\beta-\alpha)} \{\exp(-\alpha\theta) - \exp(-\beta\theta)\} \quad 6$$

where

$$\alpha = \tfrac{1}{2}\{(k_{24} + A) - \sqrt{(k_{24} + A)^2 - 4k_{24}\, k_{32}}\} \quad 7$$

and

$$\beta = \tfrac{1}{2}\{(k_{24} + A) + \sqrt{(k_{24} + A)^2 - 4k_{24}\, k_{32}}\} \quad 8$$

and M_{∞} is the initial drug loading of the suppository. Finally, when the core has dissolved completely ($t = \Gamma^*$), the subsequent diffusion of drug into the organic layer is represented by a modification of model 2 in which the apparent partition coefficient K of diazepam between the organic phase and the aqueous phase containing both PEG 1000 and PEG 6000 is equal to the ratio $\frac{k_{43}}{k_{34}}$

and $\theta = t - \Gamma^*$ 9

NUMERICAL TREATMENT OF DISSOLUTION DATA

The data for percentage release P_C versus time were fitted using a non-linear least squares program. The rate of transfer of diazepam was sufficiently rapid to permit measurement of changes in concentration within the organic phase at early times. For each formulation, the data were partitioned into sets corresponding to the calculated dissolution times and the equations were solved using a combination of suitable functions. Microconstants derived from this procedure were then used to calculate P_B and P_{TOTAL} using the appropriate equations. A suitable starting value for the microconstant k_{12} for the double layer suppository was deduced from experiments in which the dissolution from a perspex core coated with a thin layer of PEG 1000 was studied. Initially, the data from the dissolution of the double layer suppository were fitted to models 1, 3 and 2. However, this analysis showed that under these experimental dissolution conditions, $k_{24} = 0.009\ h^{-1}$ and the retardation effects on the transport of diazepam due to the dissolving core could in this case be neglected. Therefore, in subsequent analysis models 1 and 2 were fitted to the data.

RESULTS AND DISCUSSION

The release of diazepam (mean $\pm$ s.e.) into the octan-1-ol phase for the conventional formulations under test is represented by figure 4, which indicates satisfactory between assay reproducibility. The solid curve in Fig 4 represents the rate profile

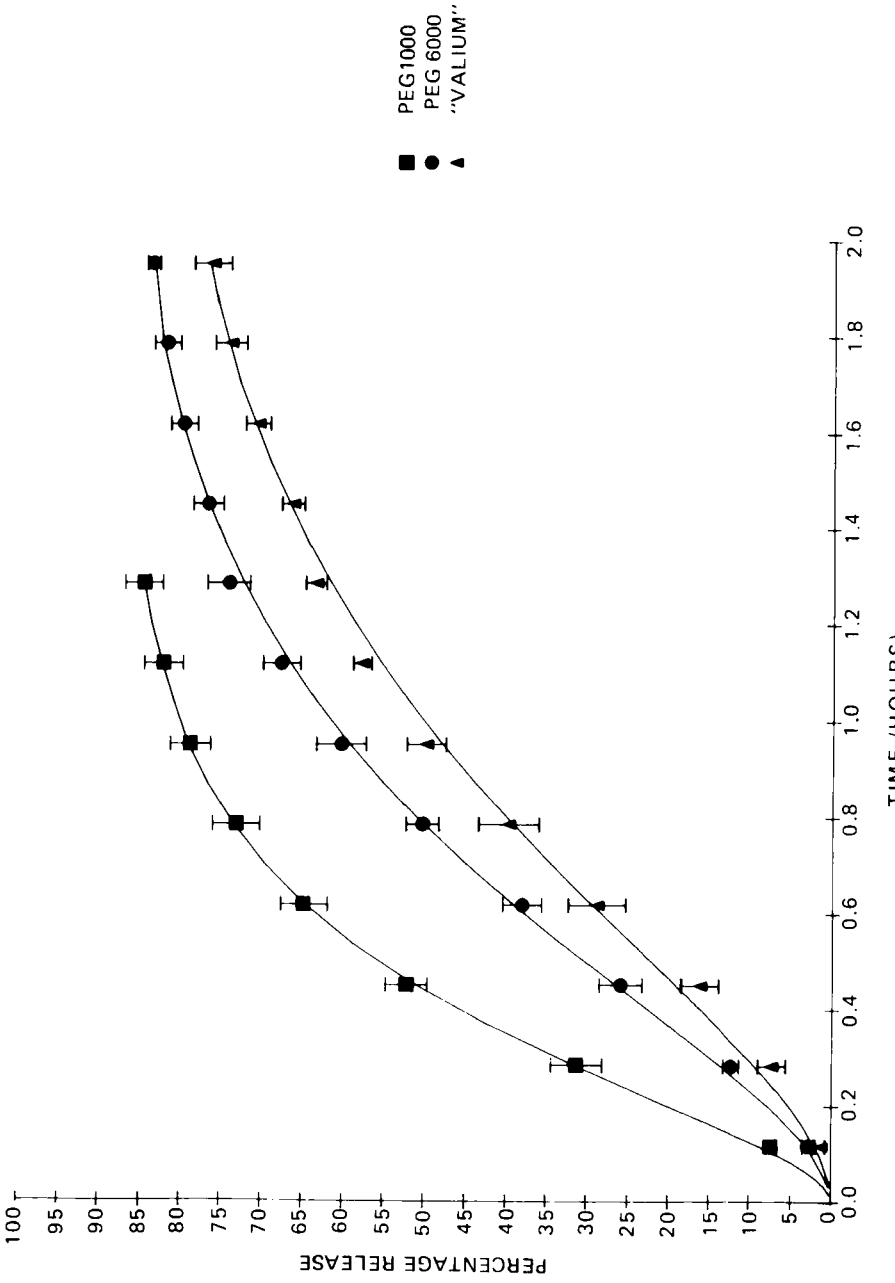


FIGURE 4

The apparent release of diazepam from "1g" polyethylene glycol suppository formulations, and from the commercial formulation "Valium 5".

TABLE 1

Rate Constants k_{ij} and Apparent Partition Coefficients K for the in-vitro Dissolution of the Suppositories.

	Rate constant (h^{-1}) (± standard error)		K	
Double-layer suppository	k_{12} k_{23} k_{32}	51.85 (4.25) 1.59 (0.02) 0.22 (0.02)	K_{23}	7.2
	k_{43} k_{34}	1.56 (0.03) 0.20 (0.02)	K_{43}	7.8
PEG 1000	k_{12} k_{23} k_{32}	7.36(0.31) 2.58(0.04) 0.34(0.03)	K_{23}	7.6
PEG 6000	k_{12} k_{23} k_{32}	3.05(0.15) 1.72(0.03) 0.26(0.02)	K_{23}	6.6
Valium 5 mg	k_{12} k_{23} k_{32}	2.54(0.08) 1.32(0.02) 0.18(0.01)	K_{23}	6.5

predicted by the kinetic models, both polyethylene glycol formulations showing a significantly better release of diazepam when compared with the commercially available formulation. Numerical values for the rate constants k_{ij} (± s.e.) generated by the regression procedure are given in Table 1 for the conventional and thin-layer suppositories. The value of determining these rate constants is twofold. Firstly, it offers a numerical basis by

which the release from different formulations may be compared and secondly it permits the evaluation of the relative proportions P_B and P_C of drug in the aqueous and organic phases at a given time t. The total percentage release of drug released P_{TOTAL} can thus be calculated which is an apparatus independent measure of the release of the suppository. Fig. 5 shows the total percentage release of diazepam from the all dosage forms which were tested.

Tukker and de Blaey[2] measured the in-vitro release from a lipophilic suppository using a cell in which an artificial membrane was used to separate aqueous dissolution and receptor phases whose polarity remained essentially unchanged during the test. Although they quantified the release of drug using compartmental models similar to those proposed here, their method of analysis avoided the computation of rate constant k_{12} and assumed that the ratio k_{23}/k_{32} was large and directly proportional to the inital volumes of water in the two compartments of their cell.

In this study, when the drug-loaded base had dissolved the concentration of polymer in the aqueous phase was between 2 and 4% w/v depending on the formulation. For the double-layer form at the temperature of measurement, dissolution of the PEG 6000 core is not influencing the solubility or transport characteristics of diazepam since $k_{23} \simeq k_{43}$.

If the values of k_{12} are substituted into equation 2, the dissolution half life and the time for 95% of the drug to be released can be calculated. These values are given in Table 2 together with the observed time of dissolution of the suppository bases.

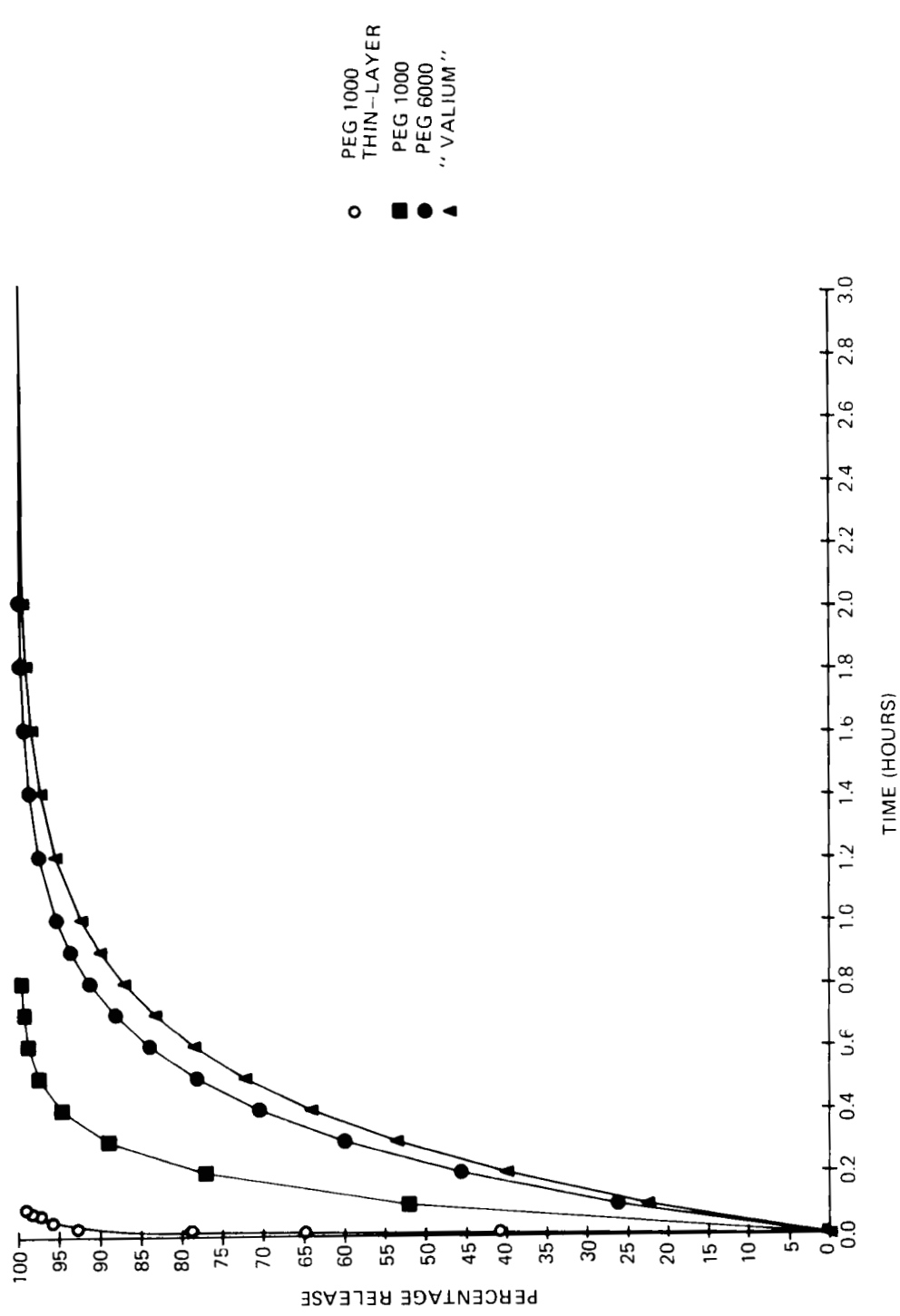


FIGURE 5

The total release of diazepam from the suppository formulations.

TABLE 2

Surface Area, Drug Concentration Melting Point and Release Times of Suppositories.

Formulation	Initial Surface area cm^2	Initial concentration of drug % $\%^{w/w}$	Melting point Range ^oC	Base dissolution time min	Dissolution half life (min)
PEG 1000	4.4	0.4	25-38	9	6
PEG 6000	4.4	0.4	57-63	50	14
Outer coating of double layer	9.3	0.6	25-38	4	0.8
Valium 5 mg	7.6	0.4	35-50	30	16

It is clear from the calculated dissolution values for 50% release that the rate constant k_{12} is a measure not only of the dissolution rate of the base but also of the diffusive transfer of the drug across the viscous dissolution phase, and is thus a particularly informative parameter. Since these effects are likely to influence the in-vivo efficacy of these dosage forms it is suggested that the dissolution tests of hydrophilic suppositories should be described in terms of a dissolution half life rather than an observation of the time at which the basis completely dissolves.

In-vivo, it has been shown that convulsive episodes in young epileptic children may be treated using a rectal solution of diazepam[7]. However, administration of such solutions may lead to such rapid absorption that respiratory depression can occur making

them unsuitable for domiciliary use. Conversely, conventional suppositories cannot be used because they release the drug too slowly[8]. In a study using human subjects, Marvola et al.[9] showed that the bioavailability of 5 mg diazepam suppositories made from polyethylene glycol was significantly greater than that in which similar suppositores were formulated using a fatty base. These observations imply that whilst diazepam is readily transported across the rectal membrane the inherent physico-chemical properties of the drug/base combination are rate-limiting.

In this study, the geometry, drug loading and nature of the coating on the double layer suppository is such that diazepam will be delivered to the rectal membrane so rapidly that the core properties are not likely to retard release. However, by modifying these parameters it should be possible to produce a set of suppositories with a range of release rates which could be quantified using the proposed kinetic analysis. It would be useful to establish clinically whether formulations of this type could release diazepam at such a rate that the clinical problems associated with the use of diazepam solutions or conventional suppositories could be avoided.

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REFERENCES

1. D.J.W. Grant, G.G. Liversidge, J. Bell, Int. J. Pharm. 14, 251 (1983).
2. J.J. Tukker, C.J. De Blaey, Drug Dev. Ind. Pharm. 9, 383 (1983).
3. S.N. Pagay, R.I. Poust, J.L. Colaizzi, J. Pharm. Sci. 63, 44 (1974).
4. A.J.M. Schoonen, F. Moolenar, C. Haverschmidt, T. Huizinga. Pharm. Weekbl. III, 585 (1976).
5. E.L. Parrott, J. Pharm. Sci. 60, 867 (1971).
6. Oral Communication.
7. Knudsen, F.U., Arch. Dis. Child. 54, 855 (1979).
8. Knudsen, F.U., Acta Paediatr. Scand. 66, 563 (1977).
9. Marvola, M., Jokila, P. and Komulainen, M. Acta Pharm. Fenn. 90, 211 (1981).