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The determination of thermodynamic activity by gas chromatography head space analysis and its use in studying release rates of drugs from topical preparations

K. Al-Khamis, S.S. Davis, J. Hadgraft * and S. Mills

Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD (U.K.)

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Summary

Gas chromatographic head space analysis has been used to estimate the thermodynamic activity of methyl salicylate in polyethylene glycol bases. The release rate of methyl salicylate from these bases has been studied and the results show that the main factor determining the release characteristics is the thermodynamic activity of the salicylate.

Introduction

Previous work (Hadgraft et al., 1973) has shown that the thermodynamic activity is an important parameter in controlling the in vivo percutaneous penetration of methyl nicotinate. Further work (Albery et al., 1979) extended the theories of percutaneous absorption and showed the effects of simple physicochemical properties on penetration rates. It seems probable that the two dominant effects in considering release from topical bases are those of thermodynamic activity and viscosity (Davis and Khanderia, 1972). By considering a simple series of polyethylene glycols an attempt is made to demonstrate which of these two effects dominates. The thermodynamic activity of a solute in a semi-solid ointment base can be determined by measurement of the partition coefficient between the base and a

* To whom correspondence should be addressed.

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suitable non-miscible second phase (usually aqueous in nature). However, this is a tedious process and subject to problems in analysis.

Head space analysis by gas chromatography is an indirect method for the determination of volatile constituents in liquids or solids. The sample is allowed to come to equilibrium in a sealed container and the vapour phase analyzed. In this way a measure of the thermodynamic activity of the volatile component in the solid phase may be estimated (Ackerberg et al., 1977). For this study a model drug (methyl salicylate) was investigated in a series of polyethylene glycol bases.

Experimental

All materials were laboratory grade and supplied by BDH, Poole, Dorset.

Head space analysis

Samples of PEG bases containing known concentrations (ranging from 1% to 15% w/w) of methyl salicylate were prepared in glass vessels with PTFE-lined screw caps. The vessels were shaken at 55°C for 72 h to ensure that the salicylate was homogeneously dissolved in the base. The containers were then stored at 37°C for 40 days over which period of time thermodynamic equilibrium had been established. At the end of this period 100 µl vapour samples were withdrawn from the vessels and the methyl salicylate concentration analyzed by gas chromatography (Pye Unicam GCD). The column used at an operating temperature of 150°C contained 10% PEG on 100/120 diatomite CAW.

Release rates

The release of methyl salicylate from the PEG bases was studied by conventional techniques (Billups and Patel, 1970). A polydimethylsiloxane membrane was used as an inert support for the base and provided no contribution to the overall rate of release which was found to be diffusion-controlled, giving a linear relationship between the amount of drug released and the square-root of time (t). This is as predicted by Eqn. 1 (Higuchi, 1961).

$$Q = 2\,D^{1/2}\pi^{-1/2}t^{1/2}C_0 \qquad (1)$$

where Q is the amount of methyl salicylate released per unit area, D is the diffusion coefficient of methyl salicylate in the base, and C_0 is the initial concentration of methyl salicylate in the base. Eqn. 1 was used to calculate values of the effective diffusion coefficients in the different bases.

Results and Discussion

The in vitro release data of methyl salicylate from various PEG bases are shown graphically in Fig. 1. The results follow Eqn. 1 and show that the release rates are

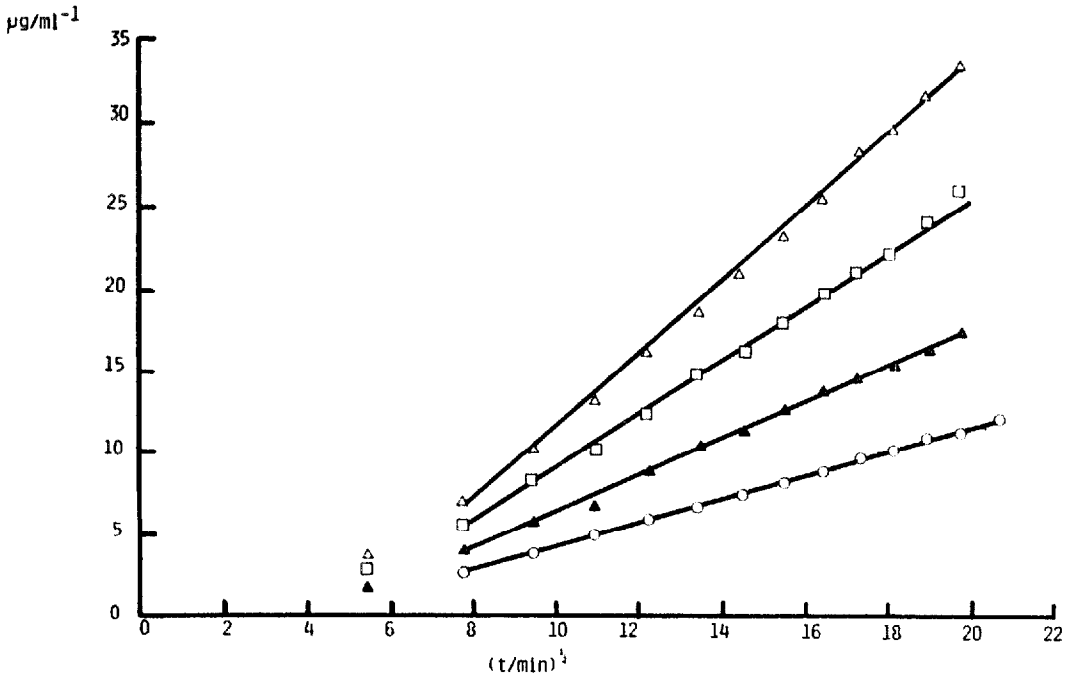

Fig. 1. The release of 10% w/w methyl salicylate from PEG systems at 30°C. △, PEG 600; □, PEG 850 *; ▲, PEG 1500; ○, PEG 2000; * = 20% PEG 200 plus 80% PEG 1000.

dependent on the base used. The higher the molecular weight fraction, the slower the release rate. From the gradients of the lines it is possible to calculate the effective diffusion coefficient of methyl salicylate in the different bases; these are summarized in Table 1. The diffusion coefficients are calculated on the basis that the drug concentration is the driving force for release. In reality the effect of thermodynamic activity should be considered and Eqn. 1 should be modified by multiplication by an activity coefficient.

This correction can be made by considering the results of the head-space analysis. Table 1 shows the concentration of methyl salicylate present in the vapour phase

TABLE 1

APPARENT DIFFUSION COEFFICIENTS FOR THE RELEASE OF 10% w/w METHYL SALICYLATE FROM POLYETHYLENE GLYCOL VEHICLES

PEG	Effective D ($cm^2\ sec^{-1}$) ($\times 10^{-7}$)	Head space concentration ($\mu g\ ml^{-1} \times 10^{-2}$)	Corrected D ($cm^2\ s^{-1}$) ($\times 10^{-7}$) (taking PEG 200 as arbitrary standard state)
200	-	5.97	-
600	1.80	4.11	3.79
850	1.05	3.33	3.37
1500	0.48	2.67	2.40
2000	0.20	2.01	1.76

when a *fixed* concentration of the salicylates has been dissolved in the different PEG bases and allowed to equilibrate. The different concentrations thus reflect the relative activity or escaping tendency of the methyl salicylate from the PEG. Consequently it is possible to correct the values calculated for the diffusion coefficient to allow for any changes in thermodynamic activity. These are also given in Table I. It is apparent that the spread of the diffusion coefficient has been considerably reduced by taking the thermodynamic activity into account. It is apparent that there is still a gradual decrease in the value of D as the molecular weight is increased and this may be attributed to viscosity effects (Davis and Khanderia, 1977) and to a lesser extent, the mechanical blockage of the diffusional process—the so-called obstruction effect (Mackie and Meares, 1955).

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