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SUSTAINED RELEASE FROM INERT MATRICES I. EFFECT OF MICROCRYSTALLINE CELLULOSE ON AMINOPHYLLINE AND THEOPHYLLINE RELEASE

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SUMMARY

The release of aminophylline and theophylline embedded in a matrix composed of different ratios of microcrystalline cellulose and glyceryl monostearate (or propylene glycol monostearate) was investigated. The result indicated that drug release within a certain period follows a diffusion-controlled matrix model, where the drug quantity released was proportional to the square root of time. The release rate was found to increase with increasing microcrystalline cellulose–glyceryl monostearate ratio. The logarithm of the rate constant was proportional to the fraction of microcrystalline cellulose in the matrix. The tablets prepared using solvent-evaporated matrix showed quicker release than those prepared from fused ones. Propylene glycol monostearate achieved similar, but somewhat quicker release, than glyceryl monostearate.

INTRODUCTION

Many compositions have been suggested for sustaining release over a long period. A method of adequately maintaining a desired plasma drug level is to incorporate the drug in a sustained-release wax matrix. The mechanism of drug release from wax matrices involves the leaching by intestinal fluid that contacts the embedded drug (Dakkuri et al., 1978). In other systems (Goodhart et al., 1974), the release from a typical wax matrix occurred by a diffusion mechanism. In the last case, diffusion was attained by mild agitation conditions, so as to avoid erosion of the tablet. Drug release from the wax matrix results from channels through which the intestinal fluid penetrates the tablet and leaches out the drug. Surfactants (Dakkuri et al., 1978), and povidone (Dakkuri et al., 1978) were used as channeling agents to improve the release from a wax matrix.

It is the purpose of this paper to evaluate microcrystalline cellulose as a channeling agent to improve the release of aminophylline and theophylline from an inert compara-

TABLE 1
Formulae used for preparing tablets:

	1	2	3	4	5	6	7	8
Drug								
Aminophylline [a]	345	345	345	345	–	–	–	–
Theophylline [a]	–	–	–	–	300	300	300	300
Matrix								
Glyceryl monostearate [b]	147	191.1	227.85	257.25	147	191.1	227.85	257.25
Microcrystalline cellulose [c]	147	102.9	66.15	36.75	147	102.9	66.15	36.75
Lubricant								
Magnesium stearate [d]	6	6	6	6	6	6	6	6
Total weight	645	645	645	645	645	600	600	600
Surface free for release: 113.09 mm^2								

[a] E. Merck AG, Darmstadt, Germany.
[b] FMC Co., Pennsylvania, U.S.A.
[c] Hopkin and William, Essex, England.
[d] BDH, Poole, England.

tively low melting point fatty matrix; glyceryl monostearate or propylene glycol monostearate. The work was aimed at determining the mechanism of release of drugs from this system.

MATERIALS AND METHODS

Matrices were made according to formulations shown in Table 1. Two methods of incorporating the drug and the matrix were carried out, i.e. fused matrix and solvent-evaporated matrix (dissolving the fat in hot ethanol and mixing with the other ingredients, then evaporating the solvent). The fused drug matrix mixture was prepared by melting glyceryl monostearate (65°C) or propylene glycol monostearate (60°C). Aminophylline or theophylline, after passing through a 60-mesh screen, was mixed with microcrystalline cellulose and their mixture was added gradually to the melted mass while the whole was mixed. The mixture was allowed to cool slowly, with constant stirring. The congealed mass was crushed and granulated (14-mesh), and magnesium stearate was added before compression into tablets. Solvent-evaporated matrices were prepared by dissolving glyceryl monostearate or propylene glycol monostearate in hot ethanol (60°C). The drug–microcrystalline cellulose mixture was then added to the ethanolic solution, and after thorough mixing, the solvent was evaporated and subsequently, the solidified mass was crushed, granulated and tabletted. The tabletting [1] was carried out by direct compression on a single punch machine at 600 mg using a 12 mm diameter flat-faced punch. The

[1] Erweka Heanson Stamn, Kr, Offenboch, Main., G.F.R.

hardness of the tablets was in the range of 10–15 kg (measured on Erweka [1] hardness tester). The friabilities [1] were all below 1.2%.

Dissolution studies were carried out at 37°C in U.S.P. dissolution tester [1]. The whole surface of the tablets was coated with a thin layer of silicone [2], but leaving one surface uncoated. Using an adhesive, the tablet was kept closed to the lower part of the basket of the dissolution tester, leaving the uncoated surface free for release. The basket was immersed in 600 ml of a pH 7.4 phosphate buffer and rotated at 50 rpm for 3 h in the case of aminophylline tablets and 10 h in the case of theophylline tablets. At the specified time intervals, a 2-ml sample was withdrawn and filtered through millipore [3] filter (0.5 μm) and immediately replaced with an equivalent volume of dissolution medium. Two to 3 runs were made for each batch and the average was calculated. Absorbance [4] was measured at 275 nm. Drug concentration in withdrawn solution was calculated from a constructed standard Beer's law plot.

RESULTS AND DISCUSSION

The cumulative amounts of aminophylline and theophylline released from tablets made of drug in a matrix of microcrystalline cellulose and glyceryl monostearate at a ratio of (1.25 : 8.75) using the fusion and the solvent techniques are given in Table 2. Aminophylline tablets showed 95% dissolution within 3 h, whereas theophylline tablets achieved 94% release within 9 h.

To explore the mechanism of release it was assumed to be either a first-order or a diffusion-controlled process. On plotting the logarithm of the drug remaining in the matrix, a monolinear curve was obtained, indicating the lack of first-order kinetics. Accordingly, an attempt was made to determine whether the drug release could be described according to the equation proposed by Higuchi, 1963:

$$Q = \left(\frac{D\epsilon}{\tau}(2A - \epsilon Cs)\,C_s t\right)^{1/2} \tag{1}$$

where Q is the amount of the drug released per unit area of the tablet exposed to the solvent, D is the diffusion coefficient of the drug in the permeating fluid, ϵ is the porosity of the matrix, t is the tortuosity of the matrix, A is the concentration of solid drug in the matrix, Cs is the solubility of the drug in the dissolution medium, and t is the time. In this case, 2A exceeds Cs, therefore justifying the use of this particular equation. Also, this includes porosity due to air- and water-soluble ingredients including the drug if:

$$k = \frac{D\epsilon}{\tau}(2A - \epsilon Cs)\,C_s^{1/2} \tag{2}$$

then

$$Q = kt^{1/2} \tag{3}$$

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[2] Dow Corning, Midland, MI, U.S.A.
[3] Millipore, Bedford, MA, U.S.A.
[4] Varian techtron, UV-VIS. Model 635, U.S.A.

TABLE 2
Release of aminophylline and theophylline from fatty matrix tablets

Hours	Tablet [a] position		Cumulative amount released			
	Aminophylline	Theophylline	Aminophylline		Theophylline	
			%	Q/113 mm^2	%	Q/113 mm^2
0.025	Stationary		30	90	15	45
0.5	Stationary		45	135	23.3	70
1.0	Stationary		63.3	100	30.66	92
1.5	Stationary		80	240	39.3	118
2	Stationary		90	270	45	135
3		Stationary	95	285	53.3	160
4		Slight elevation			64	192
5		Slight elevation			70	210
6		Partial erosion			80	240
7		Considerable erosion			90.6	272
8		Considerable erosion			93.3	280
9		Considerable erosion			94	282

[a] Tablets prepared using formula no. 4 (Table 1).

Treatment of the experimental data on the basis of the diffusion-controlled model indicated that the drug released increased linearly with the square root of time up to 7 h in the case of theophylline.

Fig. 1 shows typical Q–$t^{1/2}$ plots obtained from tablets containing 345 mg of aminophylline or 300 mg of theophylline with 294 mg matrix microcrystalline cellulose and

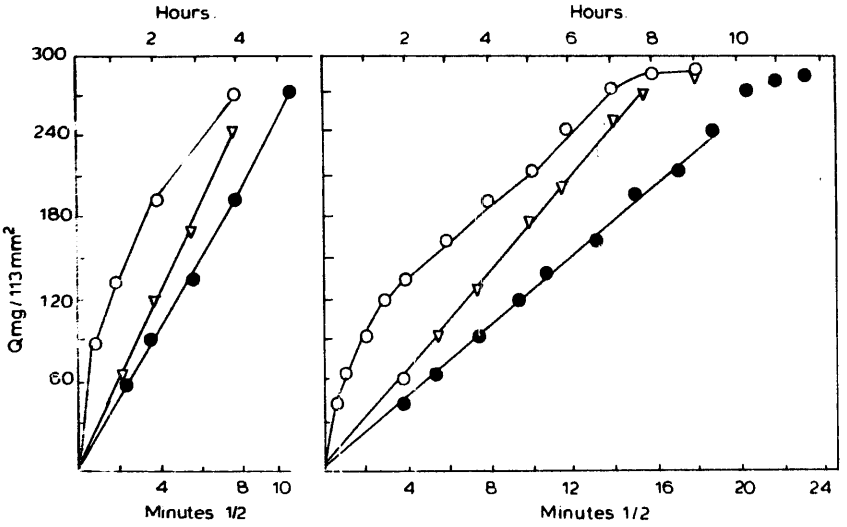

Fig. 1. Aminophylline (A) and theophylline release from fatty matrix (microcrystalline cellulose–glyceryl monostearate, 1.25 : 8.75) tablets. Symbols: fused matrix – ○, Q vs t and ●, Q vs $t^{1/2}$; and ▽, solvent-evaporated matrix.

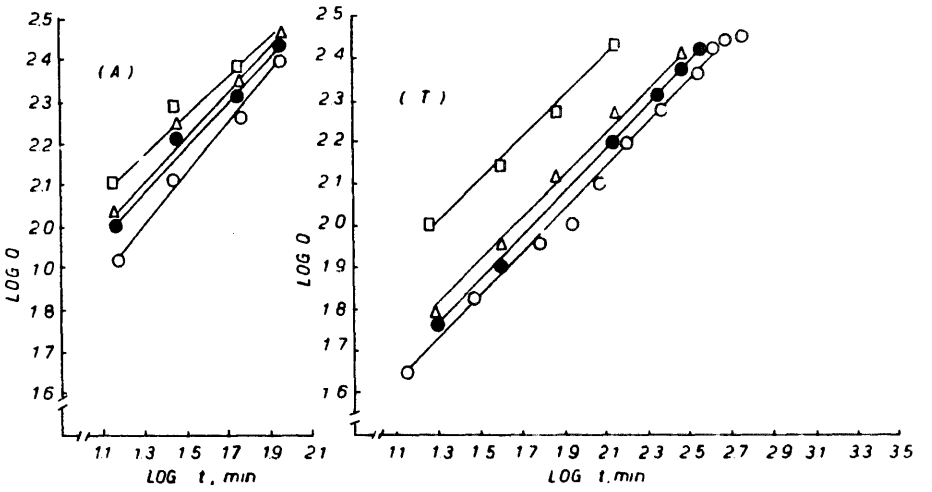

Fig. 2. Relationship of log Q to log t for tablets of aminophylline cellulose–glyceryl monostearate. Symbols: ○, 1.25 : 8.75; ●, 2.5 : 7.5; △, 3.75 : 6.25; and □, 1 : 1.

glyceryl monostearate in the ratio 1.25 : 8.75. For theophylline tablets, the release does not follow the Higuchi equation after 7 h. Table 2 shows the position of the tablet during dissolution within the first 6 h of dissolution, the tablets were stationary and showed no erosion, after which time the erosion starts. This indicates that the drug dissolution after that time (6–7 h) results from the continuous erosion in which new surfaces are being exposed (Choulis and Papadopoulous, 1975).

A further evidence to show that the release within the first 6–7 h is diffusional (Samuelov et al., 1979) is provided by plots of log Q against log t, based on the logarithmic form of the diffusional Eqn. 3 (Fig. 2). Aminophylline and theophylline tablets prepared using a matrix of microcrystalline cellulose–glyceryl monostearate (1.25 : 8.75) studied gave slopes of 1.8 and 1.04 respectively, during the periods of diffusional release.

Microcrystalline cellulose content. The effect of increasing the microcrystalline cellulose content at constant drug concentration led to a marked increase in the release rate for both aminophylline and theophylline (Fig. 3). The slopes of the linear Q–$t^{1/2}$ plots give the diffusional release rate constants (k, Eqn. 3) for the individual tablets (Table 3). Microcrystalline cellulose underwent rapid leaching out, with about 45 and 85% of theophylline being recovered from the dissolution medium within 120 min from tablets prepared using matrices of microcrystalline cellulose–glyceryl monostearate at ratios of 1.25 : 8.75 and 1 : 1 respectively. It is worth noting that the increase in the content of microcrystalline cellulose enhances the time for start of erosion of the tablet. The presence of the drug and microcrystalline cellulose gave pores on leaching. The increase in content of microcrystalline cellulose, and consequent increase in porosity of the tablet would be expected to be occupied by external solvent diffusing in the tablet (Samuelov et al., 1979). Accordingly, the release rate constants increase markedly with an increase in microcrystalline cellulose content in the tablet. A plot of log k against microcrystalline cellulose fraction was linear. Borodkin and Tucker (1974) gave the following equation for the release of methapyrilene and other drugs from a system containing hydroxypropyl

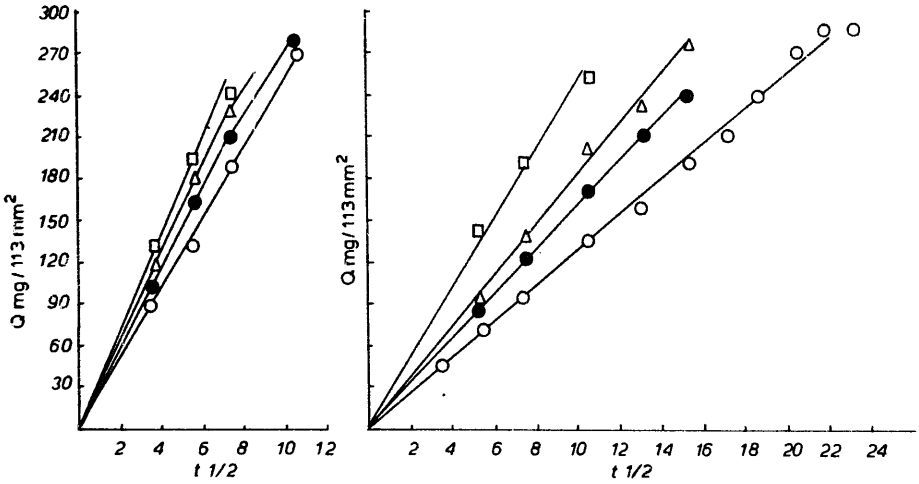

Fig. 3. Aminophylline (A) and theophylline (T) release from fatty matrix tablets. Symbols: see Fig. 2.

cellulose and polyvinyl acetate and ethylcellulose:

$$\log k_H = K_R F_H + \log K_p \quad (4)$$

where K_R is a constant specific for each drug concentration, F_H is the fraction of hydroxypropyl cellulose in the matrix, and K_p approximates K in pure polyvinyl acetate. With the present work, the same equation could be applied, considering microcrystalline cellulose instead of hydroxypropyl cellulose glycol and glyceryl monostearate instead of polyvinyl acetate. Fig. 4 shows graphically the linear relationship of log k to the fraction of microcrystalline cellulose in the matrix.

Effect of matrix-forming technique. Fig. 1 shows that the rate of release of aminophylline and theophylline from tablets prepared by solvent-evaporated matrix is somewhat

TABLE 3

Effect of microcrystalline cellulose content on the release rate constant (k) for aminophylline and theophylline prepared from fused matrices

Microcrystalline cellulose–glyceryl monostearate ratio	Aminophylline	Theophylline
5 : 5	2.33	1.52
3.75 : 6.25	2.00	1.047
2.5 : 7.5	1.66	0.78
1.25 : 8.75	1.33 (1.31) [a] (1.33) [b]	0.428 (0.583) [a] (0.54) [b]

[a] k for tablets whose matrix was prepared by evaporated solvent technique.

[b] k for the tablets prepared using propylene glycol monostearate instead of glycerol monostearate, fused matrix.

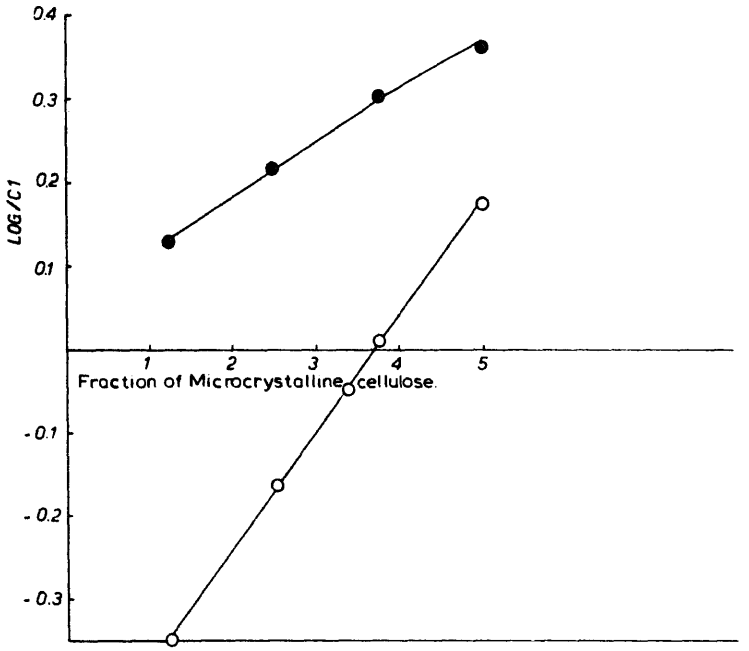

Fig. 4. Relationship of log K (release rate constant) to fraction of microcrystalline cellulose. Symbols: •, aminophylline; ○, theophylline.

quicker than those prepared from the fused matrix. Table 3 illustrates k (release rate constant) for the tablets prepared by the two techniques. The enhancement in release is probably due to the regular distribution of the channeling agent inside the tablet.

Effect of propylene glycol monostearate. Figs. 1 and 5 illustrate the release of aminophylline and theophylline from their tablets prepared using the respective formulae nos. 1 and 4 shown in Table 1. The same pattern of release achieved by glyceryl monostearate

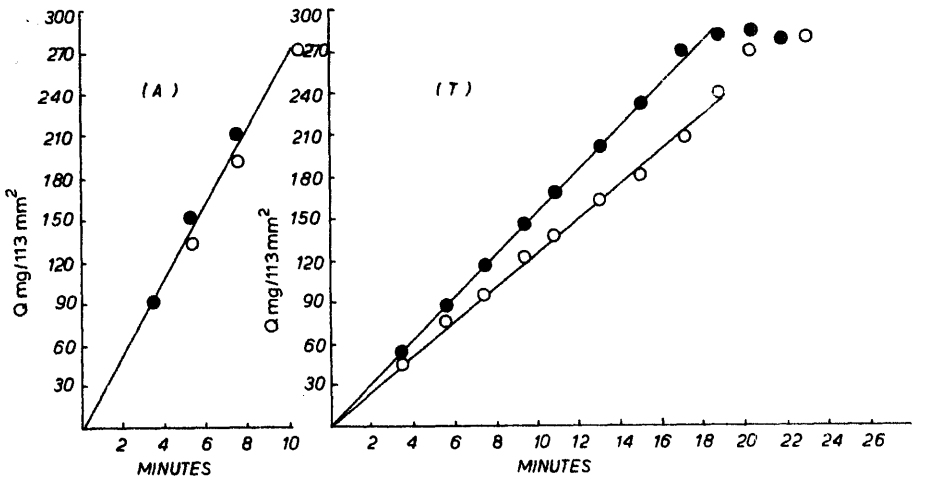

Fig. 5. Aminophylline (A) and theophylline release from fatty matrix tablets. Symbols: ○, prepared using glyceryl monostearate; •, prepared using propylene glycol monostearate.

was obtained with propylene glycol monostearate, with the sole difference being that the latter slightly hastens the rate of release. Table 3 illustrates the release rate constants of the two drugs prepared using a matrix of a microcrystalline cellulose monostearate at a ratio of 1.25 : 8.75. It is worth noting that the release follows the Higuchi equation, for the first 7 h, after which excessive erosion of the tablets alters this sequence.

These results indicate that the release of drugs such as aminophylline and theophylline from the matrix prepared by fusion or solvent-evaporation follows a diffusion mechanism for a certain period after which the release starts to be via erosion. Needless to say, the period of diffusional release might be affected by the area of the tablet exposed for release. The proposed matrix could be used for sustaining the release of other drugs.

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