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Drug release from non-disintegrating hydrophilic matrices: sodium salicylate as a model drug

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Summary

Tablets containing different concentrations of sodium salicylate in a (hydroxyethyl)methylcellulose matrix swelled without disintegration or attrition. The release rate of the drug from the whole tablet was shown to conform with a model diffusional equation for two-sided release from a slab maintaining a constant surface–volume ratio on swelling, and the rate constant was linearly dependent on the drug dosage, as predicted by this equation, when the polymer concentration was kept constant. With varying polymer concentration, correction of the rate constants for their dependence on drug content of the matrix yielded constants dependent on the polymer concentration only. Such rate constants observed a semi-logarithmic relation to polymer content and extrapolated to give reasonable diffusion coefficient values for hypothetical low and high polymer content matrices. The temperature coefficient yielded a high value (9.15 kcal · mol^{-1}) for the activation energy of the diffusion process, consistent with the energy barrier in a polymer matrix. Such treatment of rate constants and component concentration variables offers a valuable method of correlating formulation and release parameters in non-disintegrating hydrophilic matrices.

Introduction

In previous work (Touitou and Donbrow, 1981) it was found that different methylcellulose-based compositions displayed extreme differences in disintegration behaviour and drug release mechanism according to the nature of the drugs or additives included. Certain drugs acted as anti-disintegrating agents, which maintained the integrity of the hydrated hydrophilic matrix tablets and enabled drug

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release to be sustained over a long period during which the kinetics followed a diffusional square-root of time dependence. This is in contrast to the relatively short diffusional release period reported previously (Lapidus and Lordi, 1968). It was therefore considered important to study one of these drug–matrix systems (sodium salicylate–methylcellulose) as a model for release kinetics from this type of non-disintegrating hydrophilic matrix tablet. Bamba et al. (1979) recently proposed a third-power equation for treatment of the release of drug from gel forming tablets. Solution of their equation requires the estimation of 3 parameters by a least-squares procedure. The present work offers a simpler approach to estimation of the parameters determining the drug release kinetics.

Materials and methods

Materials

Some of the materials and preparation methods have been described previously (Touitou and Donbrow, 1981).

The polymer Tylose MH [1] (a methylcellulose submitted to a minor ethoxylation process) had a viscosity of 4000 centipoises at 25C; degree of substitution (DS) 1.5; degree of polymerization (DP) 760; mean mol. wt. 140,000 and methoxyl content 23%. Lactose [2] and sodium salicylate [2] were USP grade.

Methods

Tablet preparation

Tablets were made by direct compression. The drug and the additive were first sifted (no. 60 sieve), then blended with the polymer and compressed in a KBr die [3] at high pressure to form flat tablets 13 mm in diameter.

Tablet dimensions

Tablet diameter and thickness were measured using a diameter rule divided into 0.1 mm sections. Areas and volumes were calculated using standard geometric equations for a cylinder, the average of 5 measurements being taken.

Determination of release rates

Measurements were made either by a closed circuit method or by removal of samples at regular intervals from the release medium.

The tablets were inserted in a rotating basket (Donbrow and Touitou, 1977) consisting of a perspex disc containing four cylindrical compartments with the exterior covered by 10 mesh perspex netting in the present work. The basket was rotated at constant speed [4] in a covered beaker at 90 rpm, using 1400 ml solvent at

[1] Hoechst AG.
[2] Merck.
[3] Research and Industrial Instruments.
[4] Fisher 'Stedi-speed' Adjustable Stirrer.

$37 \pm 0.5°C$ in standard work, conditions being changed only where specified for testing the influence of special parameters. A flow rate of 16 ml/min in the closed circuit, obtained by means of a peristaltic pump[5], was found optimal for direct lag-free spectrophotometric measurement in a flow cell, with print out at 30-min intervals. Where it proved impossible to work at a dilution allowing direct reading, 5 ml samples were removed and replaced by the same volume of water.

Results and discussion

Tablets containing only the hydrophilic polymer swelled, maintaining their cylindrical shape, but underwent slow attrition in water. When sodium salicylate in concentrations between 10 and 30% was used as the drug, the tablets swelled but neither disintegrated nor underwent attrition.

Swelling was progressive but the surface/volume (S/V) ratio changed rapidly only in the first 15–20 min undergoing little alteration (< 15%) during the subsequent 4 h period. This result is important, allowing the ratio S/V to be treated as a constant parameter after a short initial swelling period for tablets of a given size. Typical values of the radius, r, and thickness, h, together with the corresponding surface area, S, and volume, V, are given in Table 1 for two non-disintegrating compositions before and after swelling in water at various temperatures.

The sharp fall in r/h, a measure of the ratio of the areas of the flat to the curved surfaces, and also in S/V as compared with the initial values evidently results from differential expansion in the radial and thickness axes. The decrease in r/h is a reflection of tablet shape, the flat broad profile of the cylinder, approximating to slab form, evidently offering a large surface for water penetration and uptake by the polymer as compared with the narrow curved surface.

Models for diffusional drug release from hydrophilic matrices

For cylindrical bodies, release might be expected to follow Eqn. 1:

$$F = M_t/M_\infty = 4(Dt/r\Pi^2)^{1/2} - Dt/r^2 \qquad (1)$$

where F is the fraction released, M_t and M_∞ the quantities released at times t and infinity, respectively, D is the diffusion coefficient and r is the radius of the cylinder (Roseman and Higuchi, 1970). This model assumes infinite length and a constant radius, hence its application requires a correction for the change in radius during the swelling process (Akkapeddi et al., 1974).

However, there is a serious objection to the above treatment. The systems studied here, far from being in the form of cylinders of infinite length, are truncated. Furthermore, as water penetration occurs predominantly through the planar faces, it is postulated that drug release follows the same path and hence is better described

[5] H.R. Flow Inducer, Watson-Marlow.

TABLE 1

TABLET DIMENSIONS

S/V (cm^{-1})	V (cm^3)	S (cm^2)	r/h	r (cm)	h (cm)	T (h)	temp. (°C)	tablets (batches)
7.73	6.57	4.41	1.51	0.65	0.43	0	25	1
4.54	1.97	8.95	0.82	0.80	0.98	4		
7.73	0.57	4.41	1.51	0.65	0.43	0	37	
4.33	2.22	9.62	0.75	0.81	1.08	4		
7.73	0.57	4.41	1.51	0.65	0.43	0	45	
4.18	2.49	10.41	0.78	0.86	1.10	4		
9.09	0.44	4.00	1.97	0.65	0.33	0	37	2
4.60	1.91	9.10	0.95	0.86	0.82	4		

1 = 25% sodium salicylate in 75% methylcellulose (mean tablet weight 700 mg).
2 = 10% sodium salicylate in 90% methylcellulose (mean tablet weight 500 mg).

by planar geometry. Baker and Lonsdale (1974) give a diffusional equation (Eqn. 2) for release of a dissolved drug from the two sides of a slab of thickness ℓ up to 60% release ($0.6 > F > 0$):

$$F = M_t/M_\infty = 4(Dt/\Pi\ell^2)^{1/2} \quad (2)$$

where the terms are defined as for Eqn. 1.

Between 40 and 100% release, the behaviour is described by an exponential equation in place of the above.

Eq. 2 gives double the values yielded by Higuchi's equation (1962) developed for release from a single surface of matrix tablets, which may be written as:

$$Q = 2C_0(Dt/\Pi)^{1/2} \quad (3)$$

where C_0 is the initial concentration of the drug in the matrix. This equation is valid over the period during which C_0 in the concentration gradient term can be treated as constant, hence ℓ is not relevant.

For methylcellulose tablets giving two-sided release and not suffering attrition in water, the following equation is proposed for the readily water-soluble sodium salicylate:

$$Q' = 4A\left(\frac{S}{V}\right)\left(\frac{D't}{\Pi}\right)^{1/2} \quad (4)$$

In this equation, Q' is the quantity released in time t ($Q' = Q/S$), A is the initial quantiy of drug in the tablet ($A = C_0V$), S and V are the effective surface area and volume,, respectively, in the hydrated tablet and D' is the effective diffusion

coefficient in the matrix, the value of which is $D_0\varepsilon/\tau$; D_0 is the diffusion coefficient in water, τ is the tortuosity and ε the porosity of the hydrogel matrix. The equation may be expressed in the form:

$$Q' = K_1 t^{1/2} \tag{4a}$$

where

$$K_1 = 4A(S/V)(D'/\Pi)^{1/2} \tag{4b}$$

Although S and V vary with time, their ratio was shown earlier to be relatively constant in intact tablets after the initial hydration period. D′ and A will be treated as constant parameters in a given system.

Dosage dependence of release rate

Cumulative drug release profiles from whole tablets in which the polymer concentration is held constant at 65% by lactose addition are shown in Fig. 1 for a range of sodium salicylate concentrations. Rates fall with time, in conformity with the diffusional matrix model. The appropriate $Q' - t^{1/2}$ plots (Fig. 2) do not deviate from linearity during the test period, i.e. up to 60% drug release, a quantity considered sufficient to test the validity of Eqn. 2 and the correlation coefficients of these lines are 0.998–0.999. This was the case at all concentrations at which the tablets remained intact. The absence of both negative deviations appropriate to a cylindrical diffusion model and positive ones as observed by Lapidus and Lordi for hydroxypropylmethylcellulose tablets is noteworthy. The period of integrity of the tablets was longer than that observed by Lapidus and Lordi.

Whereas no intercept term is included in Eqn. 4, Fig. 2 shows the presence of a negative intercept the value of which is constant through these formulations. The lag-period derives from the time required by the system to reach a steady state. Similar phenomena were reported by Lapidus and Lordi (1968).

The slopes of the $Q'/t^{1/2}$ plots give the apparent release rate constants (K_1). They are related linearly to the initial dose in the tablet (Fig. 3) as expected from Eqn. 4 up to 200 mg, representing 30% w/w. The deviation of the last point is explained by the attrition of the tablet at higher drug concentrations, at which, unlike at lower ones, it was seen to dissolve in the course of time. A reason for this could be that the polymer concentration is insufficient to maintain matrix coherence (Lapidus and Lordi, 1968).

Dependence of release rate on polymer concentration

Release studies were also performed on matrices containing only the drug and polymer in different ratios, excipients having been excluded to prevent additional factors being introduced into the system. Here, too, the $Q' - t^{1/2}$ plots were linear.

Whereas at constant polymer concentration, it was found that slope K_1 showed a linear dependence on the initial dose of drug A, with a zero intercept, the matrices were here composed only of methylcellulose and sodium salicylate, the absolute

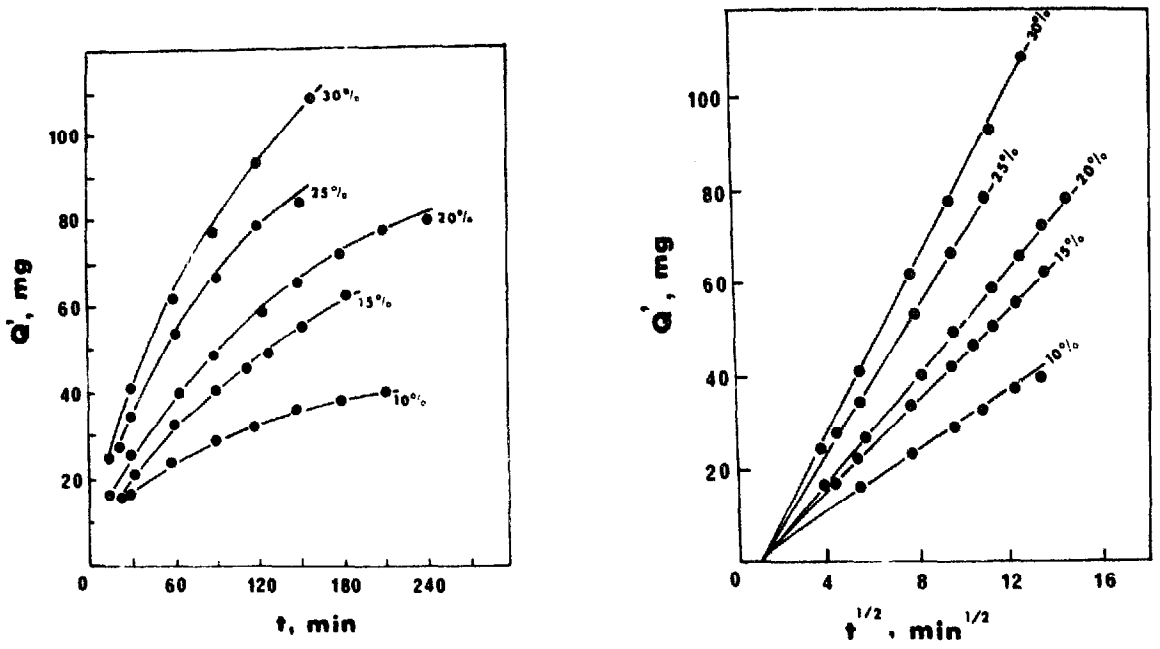


Fig. 1. Release profiles for sodium salicylate from methylcellulose whole tablets containing a constant concentration of polymer and varying concentration of drug (10–30%).

Fig. 2. Release rate profiles of Fig. 1 replotted as $Q'/t^{1/2}$.

concentrations of both components being variables. The existence of direct proportionality between release rate and initial drug dosage at constant polymer concentration permitted calculation of relative release rates corresponding to a given constant sodium salicylate dosage for each of the matrices in which the polymer concentration differed. In Table 2, K_1' represents the relative release rate for 50 mg of drug in the matrix, obtained by multiplying K_1, the experimental release rate, by the factor

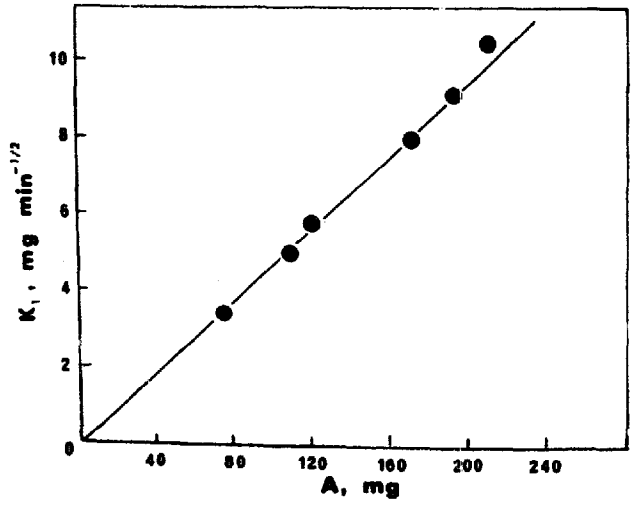


Fig. 3. Effect of sodium salicylate dose on the release rates, K_1.

TABLE 2

RELATIVE RELEASE RATES (K'_1) OF SODIUM SALICYLATE FROM TABLETS CONTAINING VARYING CONCENTRATIONS OF POLYMER [a]

F_P	A (mg)	K_1 ($mg \cdot min^{-1/2}$)	K'_1 ($mg \cdot min^{-1/2}$)
0.95	25	0.69	1.38
0.90	50	1.57	1.57
0.85	75	2.51	1.67
0.80	100	3.67	1.83
0.75	125	5.25	2.10

[a] For a constant dose of 50 mg sodium salicylate.

$50/A_n$ where A_n is the dose (in mg) of sodium salicylate in each 500 mg tablet. The assumption is made that the release rate dependence on sodium salicylate dosage is the same when the drug dosage is balanced with lactose to maintain a fixed proportion of polymer as it is in the absence of lactose when the polymer concentration varies. If this is true, correction of the release rates by use of the above factor gives a relative rate constant K'_1 which then depends only on the polymer concentration.

The results in Table 2 show that reduction in the concentration of the polymer raises K'_1 values significantly.

Borodkin and Tucker (1975) demonstrated a linear relation between the hydrophilic polymer concentration and the log of the drug release rate, in membranes containing mixtures of hydroxypropyl cellulose and polyvinyl acetate, described by the equation:

$$\log(K'_0) = K_R F_P + (\log K'_0)_P \tag{5}$$

in which F_p is the fraction of the hydrophilic polymer in the membrane, K_R is the characteristic slope of the specific drug–polymer system and K'_0 is the experimental release rate for a given F_P value. $(K'_0)_P$ is the release rate using a pure polyvinyl acetate membrane and is obtained by extrapolation. Donbrow and Samueloff (1980) found such a relationship to hold for 4 drugs in hydroxypropylcellulose–ethylcellulose films when the hydrophilic component content was considerable or predominant.

The validity of a semilogarithmic law was examined for the above two-component sodium salicylate-methylcellulose tablet matrices, expressed in the form:

$$\log(K'_1) = K_R F_P + \log(K'_D) \tag{6}$$

K'_1 is the release rate as previously defined, and K_R is the specific slope value for the sodium salicylate–methylcellulose system, assumed to have fixed A and S/V values. K'_D represents the release rate from a hypothetical tablet free of hydrophilic polymer.

The $\log(K'_1)/F_P$ plot is in fact linear (Fig. 4) indicating that the equation is observed by this compressed hydrophilic matrix in the range of compositions which could be studied, limited to $F_P > 0.6$, as attrition occurred at lower polymer fractions. Extrapolation shows that release rates should rise rapidly with fall in polymer content and yield a log K'_D value (Eqn. 6) of about 0.95 corresponding to K'_D 8.9 mg · $min^{-1/2}$. Using this value in Eqn. 4 together with 4.6 for S/V and 50 mg for A, the effective diffusion coefficient D′ may be calculated for release of the drug from a pure sodium salicylate tablet hypothetically maintaining diffusional release behaviour in conformity with tablets containing high fractions of the polymer, as used in plotting Fig. 4. The D′ value is 4.9×10^{-6}, which is not far from the value 1.53×10^{-5} for water calculated by means of the Stokes-Einstein equation using theoretical parameters for the molar volume of sodium salicylate and literature values for water viscosity. Bearing in mind the long extrapolation involved, this suggests that the line drawn through points representing high polymer content may in fact be valid for characterization of the general diffusional behaviour of methylcellulose matrices and its slope may be related to parameters of the diffusional pathway of solutes through this hydrated polymer.

Extrapolation to $F_P = 1$, on the other hand, will yield parameters for a hypothetical 100% polymer matrix and indeed the log K'_1 value obtained (about 0.1) is as expected very low, corresponding to $K'_1 \approx 1.26$.

Influence of temperature

Release rates of sodium salicylate from the methylcellulose matrix at a concentration level of 25% w/w were measured at 25, 37 and 45°C. $Q'/t^{1/2}$ plots were linear and the rate was enhanced as the temperature rose (Fig. 5), slopes being 4.8, 6.6 and 8.0 mg · $min^{-1/2}$, respectively.

Should there be diffusional control in the matrix, the effective diffusion coefficient D′ would be determined by the activation energy of the diffusion process in the

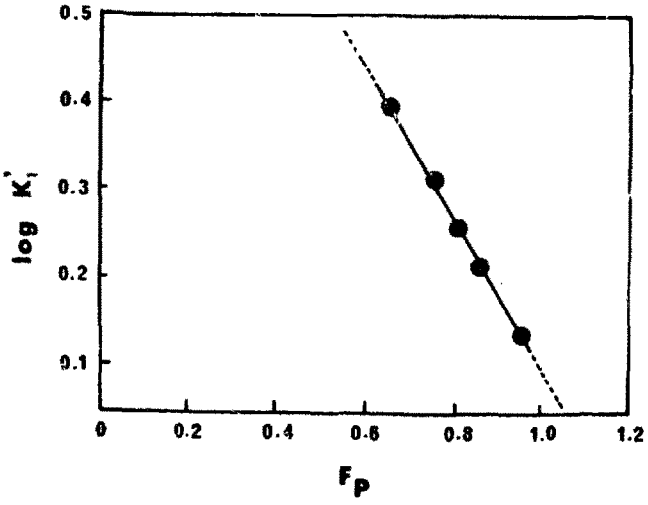


Fig. 4. Plot of sodium salicylate relative release rates, K'_1 against methylcellulose fraction, F_P.

matrix E_a, which may be estimated by an Arrhenius equation treatment:

$$D' = D_0 \exp(-E_a/RT) \tag{7}$$

It is convenient to carry out the Arrhenius plot directly on the release data by use of the logarithmic form of Eqn. 4:

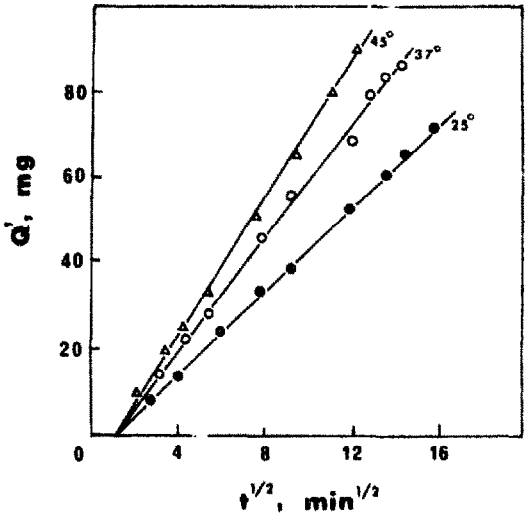
$$\log(Q'/t^{1/2}) = \log(4AS/V) + 1/2 \log D' - 1/2 \log \Pi \tag{8}$$

If the composition is held fixed, A is constant. Furthermore, over the experimental temperature range used, the surface/volume ratio of the tablet during swelling remains within the range 4.3 ± 0.16 ($\bar{X} \pm$ S.D.). This change, being small and negligable in the logarithmic term may be treated as constant. Substitution for D' in Eqn. 8 utilizing Eqn. 7 yields the form:

$$\log(Q'/t^{1/2}) = \text{constant} - 1/2(E_a/2.303R)1/T \tag{9}$$

The plot of log $Q'/t^{1/2}$ against $1/T$ is linear (Fig. 6), with E_a 9.15 kcal · mol^{-1} this value being relatively near that of 7.71 obtained by Chien and Lau (1976) for the diffusional release of norgestomet from methacrylate hydrogel. The experimental value for the sodium salicylate–methylcellulose tablet lies within the range of activation energies of similar diffusants in various polymers (6–20) (Crank, 1968).

These high values, arising from the elevated energy barrier to diffusion in polymers, may be compared with an estimated value of 4.57 kcal · mol^{-1} for



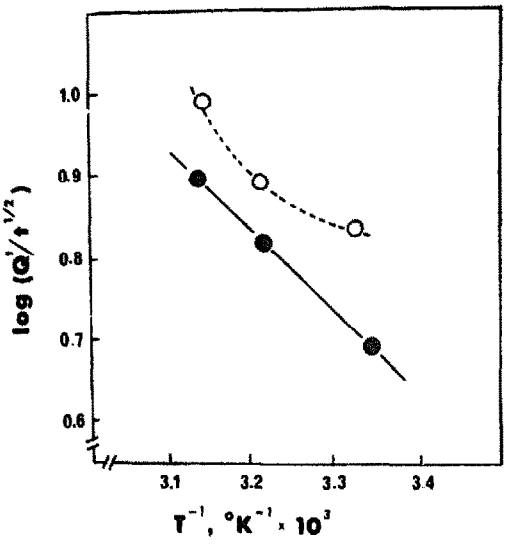


Fig. 5. Plots of cumulative amounts of sodium salicylate released, Q' against $t^{1/2}$ at 25, 37 and 45°C from tablets containing 25% drug and 75% polymer.

Fig. 6. Arrhenius plot of release rate ($Q'/t^{1/2}$) of sodium salicylate in the temperature range 25–45°C. ●, 25% sodium salicylate, 75% methylcellulose; ○, 25% sodium salicylate, 10% lactose, 65% methylcellulose.

diffusion of salicylate in water, obtained conveniently by means of an Arrhenius plot of the Stokes-Einstein diffusion coefficients; this value is close to those of most of the aqueous diffusion processes cited (about 5).

Conclusion

The release rates of sodium salicylate from the methylcellulose compositions which maintained tablet integrity observed diffusional equations for two-sided release of soluble drug from slabs having an apparently constant surface–volume ratio. The rate constants were linearly related to drug content and semi-logarithmically to polymer content. These correlations quantitatively expressed the dependence of release rate on matrix composition, furnishing a valuable method for treatment of this type of sustained-release formulation.

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