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The effect of the aqueous solubility of xanthine derivatives on the release mechanism from ethylcellulose matrix tablets

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Abstract

Release data from ethylcellulose (EC) matrix tablets was analyzed to determine which release equation provides the best fit to the data and to observe the effect of drug solubility on the release mechanism(s). Tablets were prepared by direct compression of drug, EC, and lubricant in an appropriate mass ratio to achieve a high and a low drug loading. Theophylline, caffeine, and dyphylline were selected as non-electrolyte xanthine derivatives with solubilities from 8.3 to 330 mg/ml at 25°C. Drug release studies were conducted in 37°C water with UV detection at 272 nm. Several equations to characterize release mechanisms were tested with respect to the release data. Drug diffusion, polymer relaxation, and tablet erosion were the mechanisms considered. Parameters were generated and ANOVA data presented by WinNonlin Pro® software. The Akaike Information Criterion was also considered to ascertain the best fit equation. At high drug loading, drug was released by a diffusion mechanism with a rate constant that increased with an increase in aqueous solubility. At low drug loading, polymer relaxation also became a component of the release mechanism. However, its contribution to drug release was less pronounced as solubility decreases, becoming negligible in the case of theophylline.

Keywords: Caffeine; Drug release equations; Dyphylline; Ethylcellulose; Release mechanism; Theophylline

1. Introduction

Ethylcellulose (EC) is an inert, hydrophobic polymer that has been studied substantially for its application as a matrix forming material in direct compression tablets. Direct compression is the

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preferred method of manufacture for producing tablets intended for immediate or sustained release. There have been reports on the compressibility and compactibility of EC (Shlieout and Zessin, 1994; Upadrashta et al., 1994; Katikaneni et al., 1995a; Shlieout and Zessin, 1996) and on its use as a matrix forming material in direct compression tablets for delivery of soluble and poorly soluble drugs (Shaikh et al., 1987a,b; Upadrashta et al., 1993, 1994; Katikaneni et al., 1995a,b; Pollock and Sheskey, 1996; Shlieout and Zessin, 1996; Pather et al., 1998).

Tablet hardness (Katikaneni et al., 1995b; Pollock and Sheskey, 1996; Shlieout and Zessin, 1996), the particle size of the polymer (Katikaneni et al., 1995b; Dabbagh et al., 1996; Pollock and Sheskey, 1996), and the viscosity grade (Upadrashta et al., 1993; Katikaneni et al., 1995b) were observed to directly affect the drug release rate. It was noted that tablet hardness affected the dissolution half-life more profoundly than did the viscosity grade (Upadrashta et al., 1993). Lower viscosity grades were more compressible and allowed a wider range of tablet hardness, and thus dissolution rates, for theophylline and indomethacin (Upadrashta et al., 1993). It was found that there is apparently a limit to the tablet hardness that could be obtained by an increase in compression force when a particular viscosity grade is employed (Katikaneni et al., 1995b; Pollock and Sheskey, 1996). One of the major problems associated with hydrophobic matrix tablets is the reduction in the terminal release rate. The erosion of the EC matrix over time can serve to lessen this problem (Pather et al., 1998).

The mechanism of drug release appeared to be simple diffusion from an ethylcellulose matrix tablet and the data could be adequately described by the Higuchi square root of time relationship for water-soluble pseudoephedrine hydrochloride at 12.5–25% drug loading (Katikaneni et al., 1995a). Release of slightly soluble theophylline or practically insoluble indomethacin from such tablets at 50% or 25% drug loading, respectively, was described by diffusion with polymer relaxation and erosion contributions to the release mechanism (Upadrashta et al., 1993).

The focus of this study was to systematically examine the differences in release mechanism of three non-electrolytes of varying aqueous solubility from direct compression EC matrix tablets. By limiting the study to non-electrolytes, water being drawn into the tablet by an osmotic effect of a salt form of the drug is eliminated. By using xanthine derivatives as model drugs, differences due to the effect of drug molecular size, shape, and volume should be minimized. The objectives, then, were: (1) to prepare EC matrix tablets with high or low drug loading, using a consistent EC viscosity grade, (2) to analyze the drug release data to determine which of several release equations provides the best fit to the data, and (3) to observe the effect of drug solubility on the release mechanism(s) as determined by the best-fit equation.

2. Experimental

2.1. Materials

Dyphylline (Knoll), caffeine (Pfizer), and theophylline (Sigma) are xanthine analogs (Fig. 1), with solubilities of 330, 20.0 and 8.3 mg/ml,

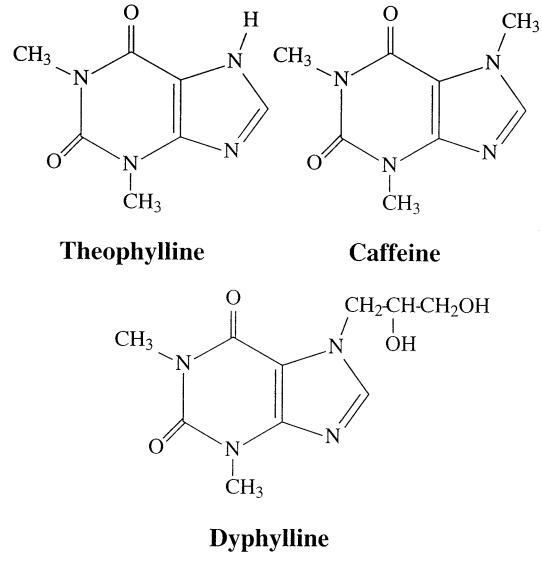

Fig. 1. Chemical structures of the xanthine derivatives in this study.

respectively, at 25°C (Gennaro, 1990). Dyphylline has a relatively high solubility, such that it was not necessary to resort to a salt form to achieve a high solubility. These drugs are weak bases with pK_b values between 13 and 14 (Gennaro, 1990) and theophylline has a reported pK_a of approximately 8.6, such that ionization under the dissolution conditions will be negligible.

Ethylcellulose (Ethocel NF, 10 cps viscosity grade, standard grade) was a gift from Dow Chemical Company, Midland, MI. This viscosity grade has been shown to be highly compressible and produced a harder tablet than did the 20, 45, and 100 cps viscosity grades of EC (Katikaneni et al., 1995b).

2.2. Methods

Tablets of 202 mg average mass were prepared by direct compression of powder blends of drug, the 80/100 mesh fraction of EC, and magnesium stearate in the mass ratio of 49.5:49.5:1 or 9.9:89.1:1 to achieve a high or low drug loading, respectively. Tablets were compressed at 3000 psi for a dwell time of 0.1 s using an automated Carver Press and a standard 5/16″ flat-faced punch and die set. Release studies in 37°C purified water, USP, were conducted with six replicates using a Distek dissolution apparatus with a paddle stirring rate of 100 rpm and UV detection at 272 nm. The suitability of several equations, which are reported to define the release mechanism(s), was tested with respect to the release data. Drug diffusion, polymer relaxation (some refer to it as polymer swelling (Huang and Schwartz, 1995)), and tablet erosion were the mechanisms considered.

2.3. Data analysis

The diffusion models are expected to be valid only up to approximately 75% cumulative drug released (Carstensen, 1993) and the data analysis will be limited to the 0.80 fraction of drug released. Data obtained from each set of six experiments were pooled for non-linear least-squares regression analysis (Gauss–Newton with Levenberg–Hartley modification) using WinNonlin Pro® version 1.5 software (Scientific Consulting, Cary, NC). The model that best fit the data was chosen by the following criteria:

1. examination of the fit of the predicted curve to the data and the sum of the squared residuals (SSR),
2. comparison of the Akaike information criterion (AIC) determined for each model fit, and
3. examination of the validity of the final parameter estimates (including magnitude and confidence intervals).

The AIC is defined by $n[\ln(SSR)] + 2p$ where n is the number of experimental data points, SSR is the sum of the squared residuals (which can be weighted), and p is the number of parameters to be estimated (Yamaoka et al., 1978). The lower the value of the AIC, the better the model describes the data. However, since the AIC is based on both the fit to the data and the number of estimated parameters, if two models both fit the data well, the AIC will be lower for the model with fewer estimated parameters.

2.4. Release equations

The following models were considered. In each case, F refers to the fraction of the total drug released at time t. Each term on the right-hand side, then, must have no units. The units associated with the time factor must therefore cancel out the time units. Time in each case was measured in minutes. Model 1 is based on drug diffusion through the matrix (Higuchi, 1963):

$$F = k_1 t^{1/2} \quad (1)$$

Model 2 is similar to Model 1 except that the exponent is not fixed at 0.5 (Ritger and Peppas, 1987):

$$F = k_1 t^m \quad (2)$$

The magnitude of the exponent m allows the general indication of Fickian diffusion, Case II transport, or anomalous transport as the release mechanism. For disk-shaped matrix tablets, m should be in the range 0.425–0.50 (Ritger and Peppas, 1987). Peppas and Sahlin (1989) noted that contributions to drug release could be considered additive, and this allowed the development of

several other models for drug release from matrix tablets. Fickian diffusion is represented in Model 3 by the square root of time term, with the polymer relaxation contribution acknowledged in the linear time term (Harland et al., 1988):

$$F = k_1 t^{1/2} + k_2 t \quad (3)$$

Model 4 is based on Model 3 without exponents fixed at $m = 0.5$ (Peppas and Sahlin, 1989):

$$F = k_1 t^m + k_2 t^{2m} \quad (4)$$

Model 5 includes diffusion, polymer relaxation, and tablet erosion contributions (Upadrashta et al., 1993):

$$F = k_1 t^{1/2} + k_2 t + k_3 t^2 + k_4 t^3 \quad (5)$$

where the diffusion component is again represented by the first term on the right-hand side, with polymer relaxation contributing to the second term. Tablet erosion contributes to the last three terms in Model 5 (Upadrashta et al., 1993). Model 6 is the release model based on tablet erosion alone (Bidah and Vergnaud, 1990):

$$F = 1\text{-}(1\text{-}k_1 t)^3 \quad (6)$$

Katzhendler et al. (1997) introduced Model 7 as a general mathematical model to describe drug release from an erodible matrix in the form of a tablet:

$$F = 1 - \left(1 - \frac{k_a t}{C_0 a_0}\right)^2 \left(1 - \frac{2k_b t}{C_0 b_0}\right) \quad (7)$$

In this expression, C_0 equals the initial drug concentration, where a_0 and b_0 are the initial radial and vertical dimensions of the tablet, and k_a and k_b represent the erosion rate constant in the radial and vertical directions, respectively. The model therefore differs from Model 6 in that it takes into account the possibility that erosion rates in the radial and vertical directions are different. Note that if $a_0 = b_0/2$, and $k_a = k_b$, this model reduces to Model 6 with $k_1 = k_a/C_0$. For tablets in this study, a_0 essentially equals $b_0/2$, since the initial diameter and the thickness of the tablet are comparable. This model therefore could reveal a difference between k_a and k_b.

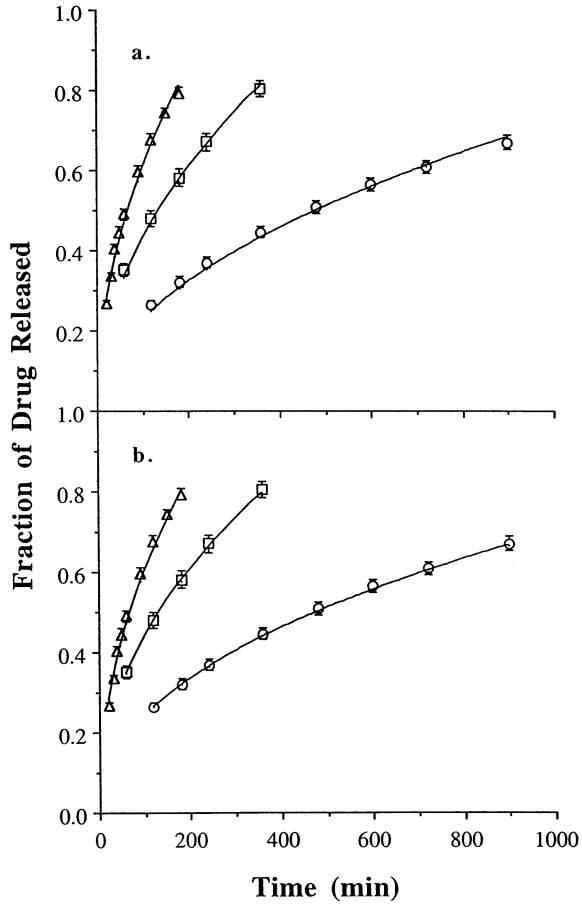

Fig. 2. Drug release profiles from tablets with high drug loading. Triangles represent the dyphylline data, squares the caffeine data, and circles the theophylline data. Error bars present the standard deviation. The curves present the fit of: a, Model 1; and b, Model 2 to the release data.

3. Results and discussion

For the results presented here, time is in minutes. The coefficients, therefore, bear the units appropriate for the model in question.

At high drug loading, the release mechanism in each case is drug diffusion through the matrix, as shown by the excellent fit of Model 2 to the data (Fig. 2) and the confirmation by the exponent m in the range of 0.425–0.50 (Table 1). Ritger and Peppas (1987) have determined that m should be in the range 0.425–0.50 for disk-shaped matrices when diffusion is the release mechanism. The use

of flat-faced punches produced disks in this study. Model 1 also provides a good fit to the data (low SSR) because it is based on the assumption of drug diffusion as the primary release mechanism. Forcing the time exponent to 0.5, however, does not allow as good a fit as Model 2 has. Models 3 and 4 were ruled out because k_2 converged to zero, or the second term offers less than 0.3% of the drug released at any time. This is obvious if one considers the magnitude of k_2 in these models, and compares the SSR with that of the similar model that has no second term (Table 1). The 95% confidence intervals for k_2 in each case included zero, thus providing no confidence in the existence of the second term. Model 2, then, provides the best fit to the release data for tablets with high drug loading, and Fickian diffusion describes the release mechanism.

At low drug loading, Model 2 still provides a better fit, as indicated by the AIC and SSR (Table 2), but m exceeds the range defined by Ritger and Peppas. If m exceeds 0.5, it indicates that there is a mechanism other than diffusion that contributes to drug release (Peppas and Sahlin, 1989). Model 4 again collapses to Model 2 in each case. Model 3 provides a better fit than does Model 1 as judged by the AIC (Table 2) and the fit to the data (Fig. 3). Thus, at low drug loading, polymer relaxation is also contributing to the drug release mechanism. Its contribution, however, becomes less pronounced as solubility decreases.

The solubility of the drug in water is expected to influence the release rate from a matrix tablet, as evidenced by the equation derived by Higuchi (1963) which forms the basis for Model 1:

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \tag{8}$$

where Q is the mass of drug released per unit exposed surface area (mg/cm^2), ε is the porosity, and τ is the tortuosity of the matrix system, A is the drug loading (mg/cm^3), and C_s is the solubility of the drug in the release medium (mg/cm^3). D is the diffusion coefficient of the drug in the release medium (cm^2/min), and t is the exposure time for the tablet in the release medium (min). Converting the left-hand side of the equation to the fraction of drug released gives:

$$F = \sqrt{\frac{S^2 D\varepsilon}{\tau V^2 A^2}(2A - \varepsilon C_s)C_s t} \tag{9}$$

where S is the exposed surface area of the tablet (cm^2) and V is the volume of the tablet (cm^3). According to this equation, if the drug loading is assumed to be much greater than the drug solubility in the release medium ($A \gg C_s$), the release rate

Table 1
Parameter and statistical estimates for drug release from tablets with high drug loading (100 mg/202 mg tablet)

Model no.	$k_1 \times 10^2$ ($\pm$ cv%)	$k_2 \times 10^2$ ($\pm$ cv%)	m ($\pm$ cv%)	AIC	SSR $\times 10^2$
Dyphylline					
1	6.05 (0.45)	–	–	−216	1.76
2	6.84 (3.1)	–	0.473 (1.4)	−229	1.33
3	6.05 (1.8)	0.00 (23K)	–	−214	1.76
4	6.84 (11)	0.00 (260K)	0.473 (11)	−227	1.33
Caffeine					
1	4.27 (0.70)	–	–	−124	1.50
2	5.22 (6.5)	–	0.463 (2.6)	−131	1.13
3	4.27 (3.3)	1.00 (7.3K)	–	−122	1.50
4	5.22 (28)	8.00 (13K)	0.462 (20)	−128	1.13
Theophylline					
1	2.27 (0.55)	–	–	−198	1.56
2	2.99 (4.9)	–	0.456 (1.7)	−220	0.934
3	2.27 (2.5)	2.00 (1.2K)	–	−195	1.60
4	2.99 (23)	0.00 (150K)	0.456 (13)	−218	0.934

Table 2
Parameter and statistical estimates for drug release from tablets with low drug loading (20 mg/202 mg tablet)

Model no.	$k_1 \times 10^2$ ($\pm$ cv%)	$k_2 \times 10^6$ ($\pm$ cv%)	m ($\pm$ cv%)	AIC	SSR $\times 10^2$
Dyphylline					
1	3.31 (1.2)	–	–	−126	6.93
2	1.70 (5.2)	–	0.620 (1.5)	−202	1.37
3	2.47 (3.1)	507 (8.6)	–	−189	1.78
4	1.67 (22)	1.00 (5.2K)	0.623 (9.3)	−199	1.39
Caffeine					
1	2.90 (0.91)	–	–	−137	5.49
2	1.74 (6.6)	–	0.585 (1.8)	−179	2.21
3	2.36 (3.3)	253 (14)	–	−170	2.65
4	1.73 (27)	0.00 (16K)	0.586 (12)	−177	2.21
Theophylline					
1	2.80 (0.50)	–	–	−199	1.52
2	2.42 (4.9)	–	0.524 (1.6)	−205	1.26
3	2.67 (2.1)	65.0 (39)	–	−203	1.34
4	2.42 (22)	1.00 (13K)	0.525 (11)	−204	1.27

constant in Model 1, k_1, should be directly proportional to the square root of the drug solubility, if all other factors are constant:

$$k_1 = \sqrt{\frac{2S^2 D\varepsilon}{\tau V^2 A} C_s} \tag{10}$$

Confirmation of this can be seen most readily for caffeine and theophylline data shown in Fig. 4, where the best fit line through the origin and Model 1 release rate constants for high drug loading tablets is presented. The drug loading, even at high drug loading, does not dramatically exceed the solubility of dyphylline, and this contributes to the deviation of dyphylline data (at $\sqrt{C_s} = 18.2$ (mg/ml)$^{1/2}$) from that linearity. Eq. (10) nevertheless indicates that dyphylline should be released at the fastest rate, and this was indeed observed at both the high and low drug loading. Since caffeine and theophylline are less soluble, drug release is intrinsically slower. For cases where the drug is the only soluble component in a matrix tablet and the volume fraction of the drug is large in comparison to the initial tablet porosity, ε can be estimated by the product of the drug's specific volume (cm^3/mg) and the concentration of that component in the tablet (mg/cm^3) (O'Connor and Schwartz 1993). In the case of caffeine, this would equal 0.468. The tortuosity, τ, for most matrix systems is assumed to be approximately 3 (Higuchi 1963). Based on these two estimates, and using Eq. (10) and the slope of the line presented in Fig. 4, the diffusion coefficient for caffeine and theophylline can be estimated to be 2.4×10^{-5} cm^2/s. Diffusion coefficients in liquids tend to cluster about 10^{-5} cm^2/s and deviations from that value of more than an order of magnitude are unusual (Cussler 1985). Therefore, this is a reasonable estimate of a diffusion coefficient for these xanthine derivatives in water.

The low drug loaded tablets, which have a higher polymer content, require a longer time to hydrate and swell, which leads to slower release rates. The influence of the polymer relaxation term on the fraction of drug released from tablets with low drug loading can be seen to increase with a increase in drug solubility and with an increase in time (Fig. 5) where the fraction of drug released due to Fickian diffusion was calculated for the Model 3 fit using (Peppas and Sahlin, 1989):

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^m}$$

The results are not surprising since the more soluble drugs will more likely encourage water penetration into the core of the tablet. With time,

EC can hydrate and swell and this, in turn, provides a less tortuous pathway by which the drug can exit the tablet. This indicates that drug solubility can influence the release mechanism if EC is allowed to hydrate and swell. Release at high drug loading did not require the additional mechanism of polymer relaxation.

Model 5 provided a good fit to the data for both high and low drug loading tablets, as judged by the AIC, but it was ruled out because in each case two or more of the model parameters converged to zero. This model introduced erosion as an additional drug release mechanism. Although erosion occurs slowly, EC matrix tablets can erode in water due to separation of surface particles (Pather et al., 1998). According to Upadrashta et al. (1993), the term involving k_1 in Model 5 is expected to represent only the influence of Fickian diffusion; the k_2 term reflects a combination of polymer relaxation and erosion influences, based on Models 3 and 6; and k_3 and k_4 terms represent contributions solely from erosion, as given by Model 6. Model fitting indicates that only k_1 could be reliably predicted. In all cases k_4 converged to zero, indicating that erosion is not a component of the drug release mechanism. At low drug loading, and for dyphylline at high drug loading, k_3 also converged to zero. For caffeine and theophylline at high drug loading, k_2 converged to zero, indicating that polymer relaxation did not contribute to the drug release mechanism. Convergence of select rate constants to zero when fitting Model 5 to the release data serves to indicate the unimportance of certain release mechanisms. By ruling out those mechanisms, Model 5 fitting confirms the previously selected best-fit models.

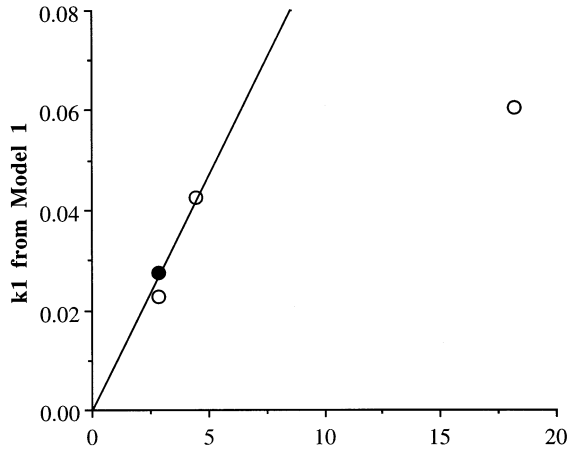

Fig. 4. Release rate constants for Model 1 from high drug loading data as a function of the square root of the drug solubility in water. Error bars present the coefficient of variation but are obscured by the symbols. The filled circle represents literature data (Upadrashta et al., 1993) for theophylline under comparable conditions. The data point not on the line is for dyphilline. The line represents Eq. (10) if all factors under the radical, with the exception of C_s, are constant.

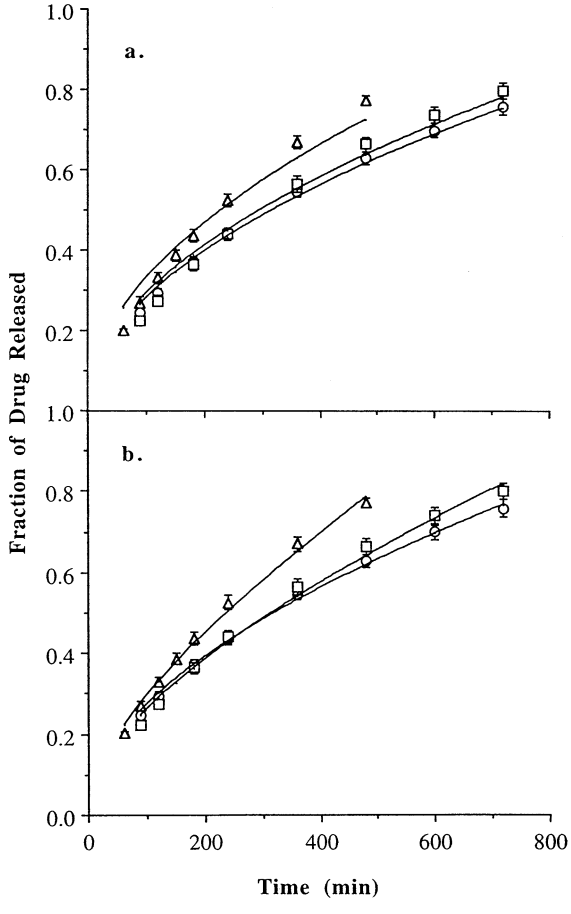

Fig. 3. Drug release profiles from tablets with low drug loading. Triangles represent the dyphylline data, squares the caffeine data, and circles the theophylline data. Error bars present the standard deviation. The curves present the fit of: a, Model 1; and b, Model 3 to the release data.

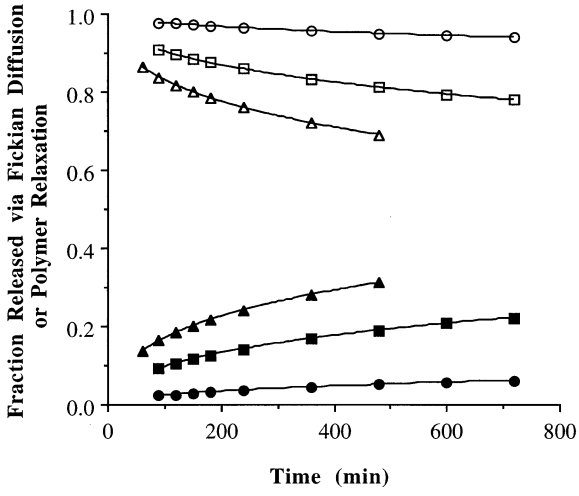

Fig. 5. Fraction released due to Fickian diffusion and polymer relaxation as a function of time for Model 3 fit to low drug loading release data. Triangles represent the dyphylline data, squares the caffeine data, and circles the theophylline data. Open symbols present the fraction due to the Fickian diffusion term; closed symbols present the fraction due to the polymer relaxation term.

Due to poor fit, the results for Models 6 and 7 are not presented. It is not surprising that Models 6 and 7 did not provide a good fit since drug diffusion is likely to be a contributing mechanism for release from these matrix tablets. In addition, it was concluded from visual observation that the tablets remained intact through the course of the drug release profiles, thus making it unlikely that erosion was the sole drug release mechanism.

4. Conclusions

At each drug loading, an increase in drug solubility resulted in an increase in the dissolution rate, but did not change the best-fit release model. At high drug loading, drug is released by a diffusion mechanism. The exponent in Model 2 confirmed the existence of Fickian diffusion through a disk-shaped matrix. At low drug loading, the release mechanism is still primarily drug diffusion through the matrix, but polymer relaxation or swelling is also contributing to the release mechanism. The solubility of the drug in water did not influence the release mechanism at high drug loading. At low drug loading, however, as drug solubility decreases, the contribution of polymer relaxation to the release mechanism substantially diminishes.

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