



# A Re-examination of the Contributions of Diffusion and Polymer Erosion to Overall Drug Release from Hydrophilic Matrix Tablets

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# ***A Re-examination of the Contributions of Diffusion and Polymer Erosion to Overall Drug Release from Hydrophilic Matrix Tablets***

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## **Introduction**

Hydrophilic matrix tablets continue to be an extremely important type of dosage form for oral delivery of drugs over a prolonged period. Knowledge of the factors that contribute to drug release is important not only in the selection of formulation parameters (polymer level, polymer composition and molecular weight, tablet geometry) during the formulation development phase, but also has relevance to the *in vivo* performance of the tablet. The purpose of this work was to examine not only the *in vitro* release of a drug substance but also the release of the rate-controlling polymer and filler, and from the knowledge of these release profiles to determine if the relative contributions of Fickian diffusion and polymer erosion/relaxation to overall drug release can be discerned from the application of commonly employed models to the drug release data. Tablets containing model drugs with differing aqueous solubilities were employed.

## **Materials and Methods**

Matrix tablets contained hypromellose substitution type 2208 (METHOCEL™ K4M Premium CR, lot PE23012N31, The Dow Chemical Company), lactose (FAST-FLO Grade 316, lot 850030162, Foremost Farms), and a drug (hydrochlorothiazide (HCTZ, Abbott Laboratories, lot 0617AK00); theophylline (BASF, lot 10190); or pentoxifylline (Spectrum Chemicals, lot SI0095)). Powders were mixed in prescribed proportions (Table 1), and tablets were prepared by direct compression. Pre-weighed portions (400 mg) of the formulations were hand-fed into a Carver Press (Model C) equipped with 0.375-inch (9.5-mm) round flat-face tooling. The compression force was 3000 lb (13.45 kN) with a 6 second dwell time. Magnesium stearate was not added to the formulations but was applied to the die and punches from an acetone solution to prevent tablet sticking.

Dissolutions were performed in a Type II dissolution apparatus, standard vessels, 900 mL deionized (DI) water (not degassed) at 37°C ± 0.5°C. Stirring rate was 50 rpm. Tablets were placed in

stationary baskets [1] suspended above the paddles. Six tablets were tested for each formulation; the average value was used in subsequent analyses. Samples collected at 10 time intervals were analyzed for all three components by liquid chromatography. The chromatographic system consisted of a Waters Alliance 2690 LC system with a Waters 2410 differential refractometer and an Applied Biosystems 757 UV detector. The column was a YMC Diol 120-NP, 5 µm, 4.6 x 250 mm. Mobile phase was water, pumped at 0.8 mL/min.

**Table 1. Tablet formulations.**

Formulation Component	Formulation Number				
	2	3	4	5	6
Spray-dried lactose (% w/w)	20	20	30	50	—
METHOCEL K4M Pr CR (% w/w)	50	30	50	20	50
Drug (% w/w)	30	50	20	30	50

## **Results and Discussion**

In the vast majority of the literature dealing with *in vitro* release from hydrophilic matrix tablets, the only data available is that for the drug itself. Invariably, drug release mechanisms are assigned solely on the basis of correlation coefficients to various equations in time purported to describe these mechanisms. The two most common equations applied are the Higuchi equation [2] and a power law equation succinctly presented by Ritger and Peppas [3].

This current work is part of a larger study to re-examine drug release in light of complementary release data for the rate-controlling polymer hypromellose and fillers. Although data were collected for five formulations of three different drugs (Table 1), the analysis here will be restricted to Formulation 3. The aqueous solubilities of pentoxifylline, theophylline, and HCTZ are approximately 190, 8.3, and 1 mg/mL, respectively. These drugs were chosen to represent a broad range of solubilities since drug solubility continues to be strongly linked to the release rate from hydrophilic matrix tablets. Most researchers have restricted their analysis to the data where the percentage of drug

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released Q is less than 60%. This convention is followed here (9 and 13 h data points excluded for pentoxifylline and theophylline), although it should be noted that this restriction is a tacit admission of the inadequacy of a model to explain the entire dissolution profile.

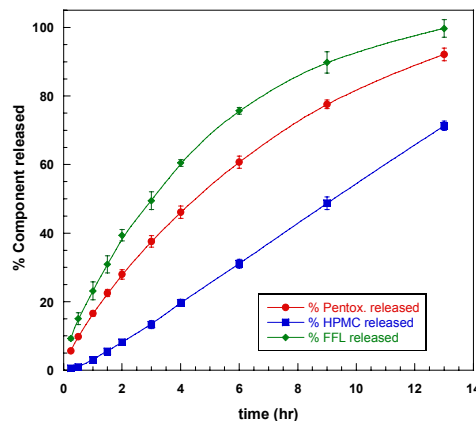
Figures 1 through 3 clearly show differences in drug release, both in absolute terms (% drug released) and in relative terms, *i.e.*, compared with the release of hypromellose and lactose. Note that the release profile for hypromellose is remarkably similar for all three formulations (the only significant difference is a very slightly lower percentage at  $t = 13$  h for the HCTZ formulation). The same statements can be made for lactose release. We observe at  $t = 9$  h that % pentoxifylline released is  $\approx 30\%$  greater than % hypromellose released, % theophylline is  $\approx 13\%$  greater than % hypromellose released, but % HCTZ released is  $\approx 6\%$  less than hypromellose release. From these simple observations we conclude that HCTZ release is largely controlled by the rate of hypromellose release, that theophylline release has a contribution from diffusion through the gel layer, but that overall pentoxifylline release has a much greater contribution from diffusion than is the case with theophylline.

In light of the data presented in Figures 1 through 3, we more closely examined fits to the Higuchi and Ritger-Peppas equations in the hope that this exercise might suggest ways in which pharmaceutical scientists could use these equations to draw valid conclusions about the performance of the dosage form. The study was expanded to include analysis of the drug release data using the "zero order" equation ( $\text{release} \propto t$ ) and the equation of Peppas and Sahlin [4], which is reported to give information on the relative contributions of drug diffusion and polymer relaxation to overall drug release.

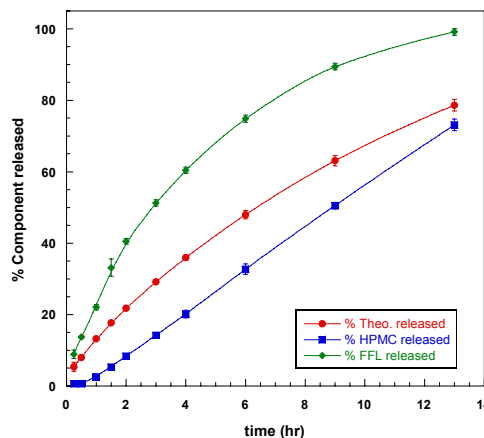
Simple inspection of Figures 1 through 3 would suggest that zero order drug release is not relevant to pentoxifylline or theophylline, but a significant portion of HCTZ release does appear to be somewhat linear with time. Data presented in Table 2 confirms these impressions, although one should note that  $R^2$  for pentoxifylline and theophylline are  $> 0.98$ . For the insoluble drug HCTZ,  $R^2 = 0.9979$ ; at this point many analysts would declare that HCTZ drug release follows zero order kinetics. However, this is not strictly true for  $t < 1.5$  h due to the nonlinear release of hypromellose from the matrix at early time points.

Turning to the simple Higuchi model, Table 2 shows that the  $R^2$  is only marginally higher than that for the zero order equation for pentoxifylline, and the  $R^2$  are virtually identical for theophylline.

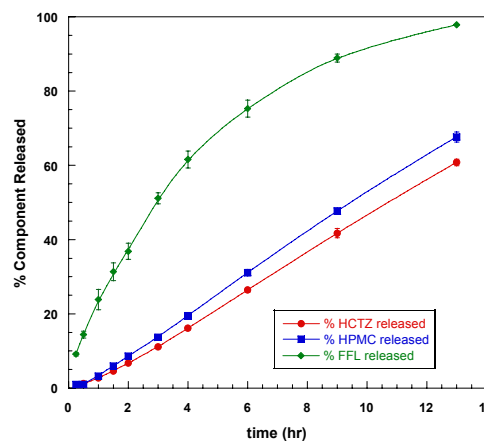
**Figure 1. Rate of release of components of Formulation 3 containing pentoxifylline.**



**Figure 2. Rate of release of components of Formulation 3 containing theophylline.**



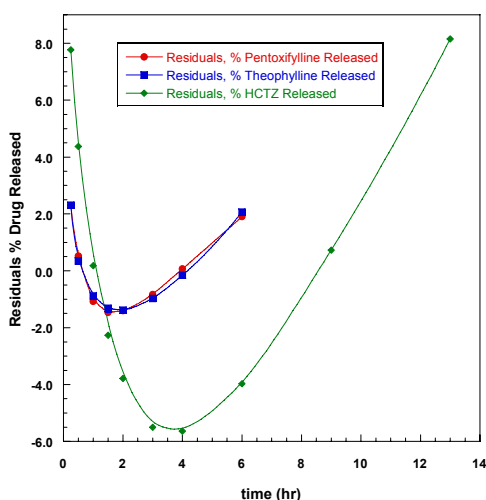
**Figure 3. Rate of release of components of Formulation 3 containing HCTZ.**



The  $R^2$  for  $Q$  vs.  $t^{1/2}$  for HCTZ release is considerably lower (0.9246). At this point, many researchers would hastily conclude that release of both pentoxifylline and theophylline from the matrix tablets is "diffusion controlled." However, further insight into the goodness of fit can be gained by a simple examination of the residuals (Figure 4). (Residuals are plotted vs. time instead of against the more normal "predicted response" in order to facilitate the comparison between drugs.)

The residuals are clearly not randomly distributed about zero for any of the drugs, indicating that the model does not fully describe the data. Given

**Figure 4. Plot of residuals of drug release vs time, Higuchi equation.**



that the standard deviation of the drug release data was typically on the order of a few tenths of one percent, with the maximum standard deviations ranging from 1.2% (HCTZ) to 1.8% (pentoxifylline), the residuals plotted in Figure 4 are for the most part greater than the experimental error of the dissolution equipment. The very large positive and negative residuals for HCTZ data further highlight the inadequacy of the simple Higuchi model to describe the data. It is interesting to note that the residuals for pentoxifylline and theophylline fits are nearly identical in magnitude and periodicity, so neither the small differences in  $R^2$  nor the residuals are able to clearly establish the difference in the extent to which drug diffusion contributes to overall drug release so easily seen in Figures 1 and 2.

Fitting the Ritger-Peppas and Peppas-Sahlin equations may be approached in two ways: performing a nonlinear fit, or transforming the data into a form where linear fits can be applied. To our knowledge, the advantages and disadvantages of these two approaches have not been widely discussed. In general, nonlinear models are more difficult to fit than linear models, there is no well-defined  $R^2$  statistic, and the standard errors of the estimates are approximations [5].

Nonlinear and transformed linear fits of the Ritger-Peppas and Peppas-Sahlin equations are given in Table 3. It is clear that the  $R^2$  obtained for these models are generally greater than those presented in Table 2. For both equations, two parameters are fit, and it is observed that the values of the parameters are not the same for the two approaches.

**Table 2. Parameters and correlation coefficients for zero order and Higuchi equations.**

Drug	Zero Order: $Q = k_0t + c$			Huguchi: $Q = k_H t^{0.5} + c$		
	$k_0$	Intercept	$R^2$	$k_H$	Intercept	$R^2$
Pentoxifylline	9.52	6.63	0.9844	28.44	-10.85	0.9939
Theophylline	7.39	5.53	0.9897	21.97	-7.89	0.9898
HCTZ	4.81	-2.61	0.9979	19.24	-16.71	0.9329

**Table 3. Parameters and correlation coefficients for Ritger-Peppas and Peppas-Sahlin equations.**

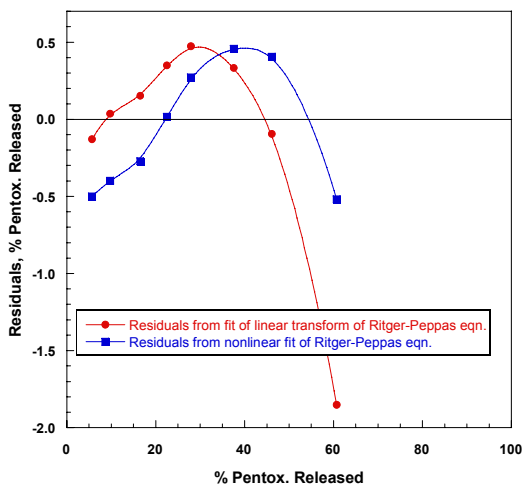
Drug	Ritger-Peppas: $Q = kt^n$			Peppas-Sahlin: $Q = k_1 t^{0.45} + k_2 t^{0.90}$		
	$k$	$n$	$R^2$	$k_1$	$k_2$	$R^2$
Pentoxifylline (nonlinear fit)	16.8	0.722	0.9996 (approx.)	8.17	8.66	0.9981 (approx.)
Pentoxifylline (transformed linear fit)	16.4	0.748	0.9995	15.3	6.25	0.9997
Theophylline (nonlinear fit)	13.3	0.716	0.9998 (approx.)	6.73	6.63	0.9996 (approx.)
Theophylline (transformed linear fit)	13.5	0.698	0.9986	8.68	5.98	0.9998
HCTZ (nonlinear fit)	3.34	1.13	0.9989 (approx.)	-5.40	7.73	0.9988 (approx.)
HCTZ (transformed linear fit)	3.02	1.18	0.9978	-8.89	8.59	0.9998

In all cases, if a given parameter obtained from the linear fit is smaller than the corresponding parameter from the nonlinear fit, then the second parameter obtained from the linear fit will be greater than that obtained by the nonlinear fit.

A simple comparison of the goodness of fit using  $R^2$  is difficult for the reason given above. Another approach is to compare the standard errors for the estimates of the exponent "n" in the Ritger-Peppas equation. These errors are on the order of 1.0 to 1.7% of n for the three drugs, so they are quite small. The standard errors are very similar for both the nonlinear and linear approaches for pentoxifylline and HCTZ. In the case of theophylline, the standard error for the linear transformed fit is about twice as large as that for the nonlinear fit.

Consistent with the somewhat higher values of  $R^2$ , the residuals for the fits to the Ritger-Peppas and Peppas-Sahlin models are somewhat smaller. Residuals for the nonlinear fits are in terms of % drug released, whereas residuals for the transformed linear fits must be transformed back to % drug released. The residuals vs. % pentoxifylline released using the Ritger-Peppas model are plotted in Figure 5. Once again, a nonrandom distribution is obtained, but here the magnitudes are smaller than the random error in the dissolution data. The only significant difference in the two approaches is the large negative residual at 60% drug released using the transformed data.

**Figure 5. Plot of residuals vs % pentoxifylline released, Ritger-Peppas equation.**



However, despite the impressive statistics ( $R^2$ , standard errors and residuals), the values for the parameters obtained for the Ritger-Peppas and Peppas-Sahlin models are of little value in helping the pharmaceutical scientist to evaluate the relative contributions of diffusion and polymer relaxation or erosion for these formulations. For example, we

have previously pointed to the greater contribution of diffusion to the release of pentoxifylline relative to theophylline (Figures 1 and 2). According to Ritger and Peppas, the value for n for the pentoxifylline data should be closer to 0.5 (or 0.45) than that of n for theophylline, yet this is not the case. Values of n obtained from the HCTZ release data are greater than 1.1, which greatly exceeds that of "Case-II transport." Turning to the Peppas-Sahlin equation, the authors state that the fraction F of drug release due to Fickian diffusion can be calculated from the formula

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^{0.45}}$$

At  $t = 3$  h, this formula gives 0.36 for pentoxifylline and 0.38 for theophylline, results which are not consistent with the difference between % drug and % polymer released illustrated in Figures 1 and 2. Furthermore, the negative values for  $k_1$  obtained when the Peppas-Sahlin equation is fit to the HCTZ release data generates a meaningless value for F, so the validity of this approach for insoluble drugs is questionable.

## Conclusions

Simply measuring the coincident release of the drug, hypromellose and filler provides valuable insight into the mechanism of drug release from hydrophilic matrix tablets. Regression of drug release data alone can lead to misleading conclusions based on simple judgments on the magnitude of correlation coefficients. In addition, the models most frequently applied to drug release data do not appear to be able to distinguish between drugs for which the contributions of diffusion to total drug release are different.

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