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## COMMUNICATIONS

# FICKIAN AND RELAXATIONAL CONTRIBUTION QUANTIFICATION OF DRUG RELEASE IN A SWELLABLE HYDROPHILLIC POLYMER MATRIX

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## ABSTRACT

Hydroxypropylmethylcellulose (HPMC) is becoming very popular in the formulation of controlled release tablets, mainly because of its hydrophillic and swelling properties. In HPMC tablet matrix systems, the drug release occurs mainly by Fickian diffusion and by polymer relaxation. The amount of drug released by these two phenomena was quantified by applying a heuristic model recently proposed. Recent studies show that it is possible to modify the kinetics of drug release by restricting matrix swelling. The aim of this study is to present some new evidence that tends to confirm these findings and to quantify the Fickian and case II relaxational contribution of drug release by using a PCNONLIN computer software package. Results obtained show a direct relationship between releasing areas and the amount of drug dissolved. Tablets with matrix swelling restrictions exhibit a shift towards drug release by relaxational mechanism, which makes this technique a useful tool when a shift towards constant drug release is desired.

## INTRODUCTION

The use of swellable water soluble, or hydrophillic polymers, has become very important in the formulation of

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controlled release dosage forms. These polymers can be either synthetic or derived from a natural source like the cellulose ethers, such as methylcellulose (MC) hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) and sodium carboxymethylcellulose (NaCMC).

The operative principle that controls drug release in a HPMC-drug tablet matrix is that on exposure to aqueous fluids, the tablet surface becomes wet and the polymer starts to hydrate to form a viscous gel layer that controls drug release by diffusion through the gel and by its subsequent erosion. So, the mechanism of drug release from HPMC-drug matrices is controlled by matrix swelling and polymer dissolution (1). Swellable matrices as drug delivery systems exhibit anomalous non-Fickian release kinetics (2).

Mathematical models have been developed to describe the dissolution process of a polymer in a controlled release device (3) and also, to predict the controlled release of drugs from hydrophilic, swellable and soluble tablets (4).

Recent studies show that it is possible to modify the kinetics of drug release by imposing physical restrictions to matrix swelling (5). Calculation of the approximate contribution of the diffusional and relaxational mechanisms to the anomalous release process can be carried out by fitting the drug dissolution data to a heuristic model equation recently proposed (6).

The purpose of this work is to describe the release kinetics of theophylline from a HPMC matrix system and to quantify the percent of drug released by Fickian diffusion and by case II polymer relaxation from tablets with restricted and unrestricted matrix swelling by using computer software package.

## MATERIALS AND METHODS

### Materials

Theophylline anhydrous (Boehringer Ingelheim, Germany) was chosen as the model drug. Methocel™ K4M Premium (Dow Chemical Company, USA) was selected as the HPMC hydrophilic matrix. The apparent viscosity of 2% (w/v) aqueous solution of this polymer is 4176 cps. Lactose, N.F. Fast Flo™ (Foremost Ingredient Group, USA) was used as diluent and magnesium stearate as lubricant.

**Preparation of tablets**

All tablets were composed of 10% theophylline, 30% HPMC, 59% lactose and 1% magnesium stearate. The drug and HPMC were thoroughly blended in a turbula mixer (Willy A. Bachofen, Model T2C, Switzerland) for 10 minutes and subsequently mixed with lactose. The blend was wet granulated in a planetary mixer (Hobart MFG Co.,USA) using water as the granulating fluid. The wet granules were passed through sieve #8 and oven dried over 12 to 15 hours at 39-40°C (F.J Stokes, Model 38B, USA). The dry granules were milled and passed through sieve #12 using a granulator (F.J Stokes, Model 43B, USA) and mixed with 1% (w/w) magnesium stearate for 5 minutes in a twin shell dry blender (Patterson Kelley Co.,Model LB-1949,USA). A weighed amount of the mixture was fed manually into the die of a tablet rotary machine equipped with 0.953 cm. flat surface punch (Manesty Machines LTD, Model B3B, England) to produce tablets of 450 mg., 0.955 cm. in diameter and 0.510 cm. in thickness.

Three of the matrices produced were placed inside a plastic plug leaving free for dissolution only one face of the tablet. This was done in order to restrict matrix swelling and to reduce the available releasing area. Plain unrestricted matrices had a releasing area of 2.963 $cm^2$ and restricted matrices were of 0.716 $cm^2$.

**Dissolution studies**

The dissolution test was carried out in 900 ml distilled water at 37±0.5°C using the rotating basket apparatus (Hanson Research, Model SR2,USA) at speed of 50 rpm. Filtered samples were withdrawn manually at pre-determined time intervals and assayed using a UV spectrophotometer (Beckman Instruments, Model DU 65, USA) at 271 nm. Three replicates for restricted and unrestricted tablet matrices were tested and their mean percent release calculated.

## RESULTS AND DISCUSSION

Figure 1 shows the percent of theophylline released at different time intervals for restricted (case 1) and unrestricted (case 2) matrix tablets. The release behaviors of the two systems were significantly different. Tablets with unrestricted matrix, which have more surface area exposed to the releasing medium, show the higher percent of theophylline released.

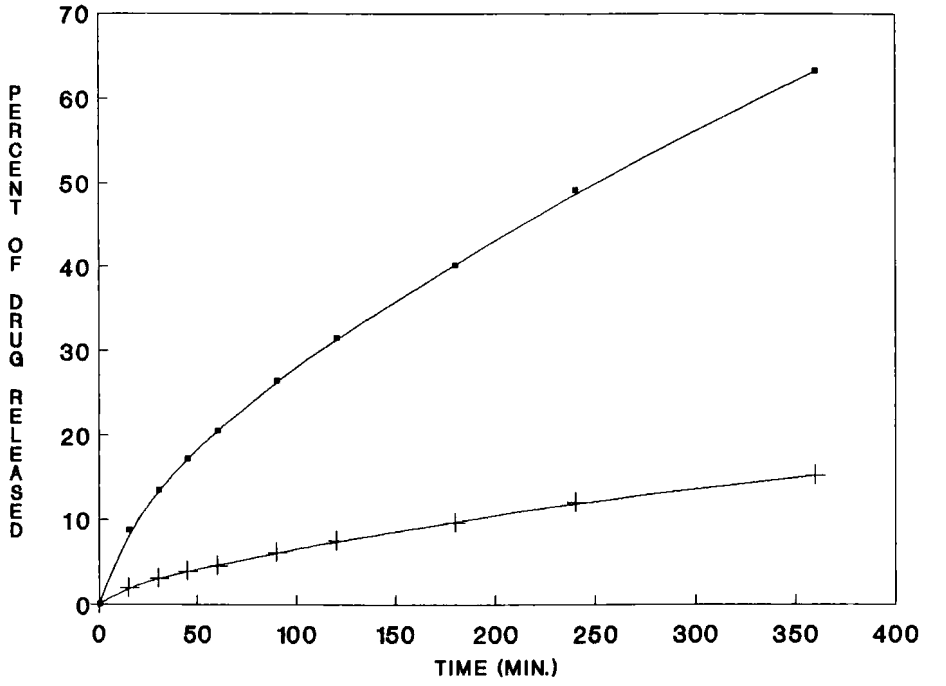


FIGURE 1

Percent of Theophylline Released for Case 1 (+) and Case 2 (□) Tablets (Non-Fickian)



The kinetics and mechanism of drug release for each system was investigated by fitting the release data into the simple relationship derived by Korsmeyer et al. (7), which is often used to describe drug release from polymeric systems:

$$M_t/M_\infty = kt^n \qquad \text{Equation 1}$$

where $M_t/M_\infty$ is the fractional release of drug, t is the release time, k is a constant that incorporates structural and geometric characteristics of the release device and n is the release exponent which indicates the kinetics of the release. For instance, n=0.5 for $\sqrt{t}$ kinetics (Fickian diffusion) and n=1 for constant zero-order release (case II transport). Intermediate values are indicative of anomalous (non-Fickian) diffusion. Polymer swelling and drug diffusion through a HPMC matrix generally do not follow a Fickian release behavior, due to the existence of a molecular relaxation process, which is believed to be responsible for this phenomenon.

TABLE 1

Fitting of Release Data to Equation 1

| Case | Kinetic Constant (k)($x10^3$)($min^{-1}$) | Kinetic Exponent (n)(±95% Confidence Limits) |
|---|---|---|
| 1 | 3.4 | 0.65 ± 0.008 |
| 2 | 16.2 | 0.61 ± 0.003 |

TABLE 2

Fitting of Release Data to Equation 2

| Case | Estimated $k_1$ ($x10^3$)($min^{-1}$) (± 95% Confidence Limit) | Estimated k2 ($x10^3$)($min^{-1}$) (± 95% Confidence Limit) |
|---|---|---|
| 1 | 4.47 ± 0.01 | 0.20 ± 0.01 |
| 2 | 20.56 ± 0.43 | 0.71 ± 0.04 |

Table 1 shows the n values obtained for both systems. As expected, results are indicative of anomalous non-Fickian drug release behavior. A modified release kinetics, which shows a shift towards constant release can be observed in tablets with matrix swelling restrictions.

Peppas and Sahlin (6) proposed a heuristic model and derived an equation which is very useful for quantifying the approximate amount of drug released by Fickian diffusion and by polymer relaxation:

$$M_t/M_\infty = k_1 t^{1/2} + k_2 t \qquad \text{Equation 2}$$

In here the first term on the right hand side represents the Fickian contribution and the second term, the case II relaxational contribution.

Drug release data was fitted to this equation by using computer software package called PCNONLIN Version

TABLE 3

Percent Drug released by Fickian Diffusion and Polymer Relaxation for Case 1 and Case 2 Theophylline Tablets

| Case | Time (min.) | Percent of Drug Released by Fickian Diffusion | Percent of Drug Released by Polymer Relaxation |
|---|---|---|---|
| 1 | 15 | 86.6 | 15.2 |
| | 30 | 79.0 | 19.5 |
| | 45 | 76.9 | 23.3 |
| | 60 | 75.3 | 26.3 |
| | 90 | 79.6 | 29.8 |
| | 120 | 65.3 | 22.3 |
| | 180 | 61.9 | 37.5 |
| | 240 | 57.3 | 40.1 |
| | 360 | 55.8 | 47.8 |
| 2 | | | |
| | 15 | 91.5 | 12.3 |
| | 30 | 83.4 | 15.8 |
| | 45 | 80.2 | 18.6 |
| | 60 | 77.7 | 20.8 |
| | 90 | 73.9 | 24.2 |
| | 120 | 71.5 | 27.1 |
| | 180 | 68.8 | 31.9 |
| | 240 | 64.9 | 34.8 |
| | 360 | 61.7 | 39.5 |

4.0 (SCI Software, Kentucky, USA). This program is designed to solve general nonlinear regression problems. Given a set of data and a nonlinear function, PCNONLIN will find estimates of the parameters of the nonlinear functions that provide the closest fit between the observations and nonlinear function based on the least squares significance.

Table 2 shows the estimated $k_1$ and $k_2$ values obtained when the drug release data was fitted to Equation 2.

It is then possible to estimate the percent of drug released by Fickian diffusion and the percent of drug released by polymer relaxation, as shown in Table 3. In both systems the percent of drug released by Fickian diffusion predominates, specially in the early stages of the dissolution experiment, but as time pass, more drug will be liberated by polymer relaxation. This is due to the fact that the thickness of the viscous gel layer that surrounds each tablet, will increase with time, creating a longer diffusional path length for the drug to diffuse into the external releasing medium. Soon thereafter, the long polymer chains will start to disentangle, until it dissolves (4).

Again, a shift towards constant drug release is clearly seen in tablets with restricted matrix swelling.

## CONCLUSIONS

In conclusion, this work presents some new evidence that tends to confirm recent findings in the sense that it is possible to modify the kinetics of drug release by imposing physical restrictions to matrix swelling, which makes this technique a useful tool when a shift towards constant drug release is desired. It also shows that it is possible to quantify the amount of drug released by Fickian diffusion and by polymer relaxation by fitting the release data into a useful polynomial expression proposed by Sahlin and Peppas, using a computer software package PCNONLIN Version 4.0.

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