PHARMACEUTICAL SCIENCES

Mechanisms of Chlorpheniramine Maleate Release from Hydrophilic Swellable Polymer Systems

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ABSTRACT . The main objective of this work is to attempt to understand better the mechanism of release of highly water soluble drugs from a swellable polymer and to quantify the amount of drug released. Tablets containing 10% w/w drug, hydroxypropylmethyl-cellulose E4M (10%w/w, 20% w/w and 30% w/w), 1 % w/w magnesium stearate and quantity sufficient to 100% w/w with Lactose Fast Flo as diluent were prepared using the direct compression method. The amount of drug released due to Fickian diffusion and non-Fickian diffusion (polymer relaxation) was quantified at different time intervals. In order to determine if the drug release was Fickian diffusion or non-Fickian diffusion, the exponent n obtained from the equation: $M_t / M_{\infty} = Kt^n$ was calculated. It was found to be above 0.5 for restricted and unrestricted systems indicating non-Fickian diffusion. Also, the approximate contribution of Fickian diffusion and polymer relaxation to the non-Fickian anomalous release process was calculated. The data obtained from one tablet surface and all surfaces exposed to the dissolution medium demonstrated that Fickian diffusion predominated for the first hour. After one hour of testing dissolution, the relaxational mechanism predominated. The percent drug release from restricted matrices at 6 hours of dissolution testing was 77.9% by polymer relaxation and 27.9% by Fickian diffusion.

The importance and pharmaceutical applications of hydrophilic polymers are established in providing controlled release from a desired dosage form. There have been several studies (1-11) reported which have evaluated controlled drug release from hydrophilic polymeric matrix tablets.

Mathematical models have been developed to describe the release pattern from a hydrophilic swellable matrix. Lee and Peppas (12) developed a model to describe the dissolution process of a swellable polymer and Colombo et al. (13) showed that it is possible to modulate drug release kinetics by imposing physical restrictions on matrix swelling in tablets. Also Colombo et al. (14) studied drug release mechanisms for four different types of matrices prepared by hydroxypropylmethylcellulose.

Wan et al. (15) investigated the relationship between swelling and drug release in a hydrophilic matrix.

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Korsmeyer et al. (16) derived an equation linking swelling and drug release from polymer systems and Ford et al. (17) studied the dissolution of soluble drugs from hydroxypropylmethylcellulose matrices in order to determine the time exponent (t^n) required to produce linear dissoltion profiles.

Pappas and Sahlin (18) proposed a heuristic model equation which is very useful for calculation of the approximate contribution of the diffusional and relaxational mechanisms which are believed to be responsible for the drug release in hydroxypropylmethyl-cellulose.

In our lab (19) the mechanism of theophylline release from swellable system prepared by wet granulation was investigated. The data obtained presented some new evidence that tends to confirm other finding and it was possible to modify the kinetics of drug release by imposing physical restrictions on matrix swelling. Few studies were published on the problem of penetrant transport into an initially glassy polymer which undergoes swelling.

This work was focused on describing the kinetics model for the release of water soluble drug from swellable

systems prepared by direct compression. This work was also an attempt to have control over drug release from these systems and to achieve constant drug release when it is desired

Theoretical Considerations

Drug release models from systems containing polymer can be summarized as follows:

$$M_t / M_\infty = Kt^n \qquad \text{(equation 1)}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released over a very long time, which corresponds in principle to the initial loading, K is a kinetic constant characteristic of the drug polymer system, t is the release time, and n is the diffusion exponent. The values of the exponent n give an indication of the release mechanism. For cylindrical geometry tablets, a value of n close to 0.5 corresponds to Fickian diffusion release (model a); intermediate values ($0.5 < n < 1.0$) are indicative of anomalous non-Fickian diffusion or coupled diffusion/relaxation (model b), and $n = 1$ for a constant zero order release rate (model C).

Peppas and Sahlin developed a more simple equation for estimation of approximate contribution of Fickian diffusion and polymer relaxation. The drug kinetics can be estimated using the following empirical equation:

$$M_t / M_\infty = K_1 t^{1/2} + K_2 t \qquad \text{(equation 2)}$$

where the first term on the right hand side represents the Fickian contribution and the second term represents the polymer relaxation or surface erosion.

Materials

Except when noted, all chemicals were analytical grade and used as received. Chlorpheniramine maleate was selected as the model drug and was generously supplied by SmithKline Beecham (Cidra, P.R.); Hydroxypropylmehylcellulose, E4M premium CR grade (HPMC) was selected as the swellable polymer and was kindly supplied by Dow Chemical Company, U.S.A.; Lactose Fast Flo (Foremost Ingredient Group, U.S.A.); and magnesium stearate were used as lubricant (Ammend Drug and Chemical Co., U.S.A.).

Methods

Preparation of Blends. All blend formulations composed of 10% w/w chlorpheniramine maleate, hydroxypropylmethylcellulose E4M(10% w/w, 20% w/w and 30% w/w), magnesium stearate (1% w/w) was added as lubricant and Lactose Fast Flo quantity sufficient to 100%. The batch size for all formulations was 2 Kg. All materials were passed manually through screen #12 except the lubricant which was passed through screen #30.

The powder mixing was performed by geometrical dilution in Turbula mixer (Willy A. Bachafen, Model T2C, Switzerland) at a speed of 90 rpm for 5 minutes. The drug and polymer mixture was transferred to a V-Blender (PK Processor, Patterson Kelly, Model LB-5322), Lactose Fast Flo added, and the powder mixture was mixed for 10 minutes. Finally, the lubricant was added and the blend mixed for an additional 5 minutes.

Matrices Preparation. The matrices were made by direct compression of the mixture in Manesty B3B rotating machine equipped with 12/32 inches flat faced punches. Target tablet weight was 450 mg ± 5% and target hardness was 7-9 Kp. Three of the matrices produced from each batch 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 available releasing area. Plain unrestricted matrix had a releasing area of 2.963 cm^2 and restricted matrices had an area of 0.716 cm^2.

Drug Content. Five tablets were pulverized and three samples each of 450 mg were transferred to a 1000 mL volumetric flask and completed to volume with distilled water. Samples were stirred for 4 hours with a magnetic stirrer. An aliquot was filtered and analyzed for drug content by measuring absorbance in a UV spectrophotometer at a wave length of 261 nm.

Dissolution Testing . The dissolution of chlorpheniramine maleate from matrices was measured in 900 mL distilled water at 37°C ± 0.5°C using a rotating basket apparatus (Hanson Research), Model SR2, U.S.A.) at a speed of 50 rpm.

Filtered samples were withdrawn and assayed using a UV spectrophotometer (Bechman Instruments, Model DU 65, U.S.A) at 271 nm.

Three replicates for restricted and unrestricted tablet matrices were tested and their mean percent release was calculated.

Statistical Analysis. The one way analysis of variance test (ANOVA) was used to determine if there were significant differences between compared samples (three samples or more). A 95% least significance test was performed. Probability value (p values) less than 0.05 indicated that significant differences exists between the samples while a p value greater than 0.05 showed no significant difference exists.

A pair multiple comparison (T-Test) was performed to analyze the data at different time intervals of dissolution test. If the probability level is less than 0.05 in more than 50% of the intervals, a significant difference exists between

a pair of experimental samples.

The drug release data from matrices containing 10% w/w chlorpheniramine maleate, 30% w/w hydroxypropylmethylcellulose E 4M, 59% Lactose Fast Flo, and 1% w/w magnesium stearate was fitted to the equations described by Pappas and Sahlin and described under release models using a computer software package called PCNONLIN version 4.0 (SCI software, Kentucky, U.S.A.). This program is designed to solve general non-linear functions, PCNONLIN finds estimates of the parameters of the non-linear functions that provide the best fit between observations and a non-linear function based on the least squares significance.

The drug release data from all matrices containing 10% w/w chlorpheniramine maleate , Lactose Fast Flo and different concentrations of the polymer was fitted to the equation described by Shah et al, and described under drug release models.

Results and Discussions

The percent chlorpheniramine maleate released from matrices containing 10% w/w chlorpheniramine maleate, 30% w/w hydroxypropylmethylcellulose E4M, and Lactose Fast Flo at different time intervals for restricted and unrestricted matrix tablets is shown in Figure 1. There was a significant difference in drug release between the two systems. Tablets without physical restriction which had a high surface area gave higher dissolution rate than tablets with a physical restriction (only one surface of the tablet was exposed to the dissolution medium).

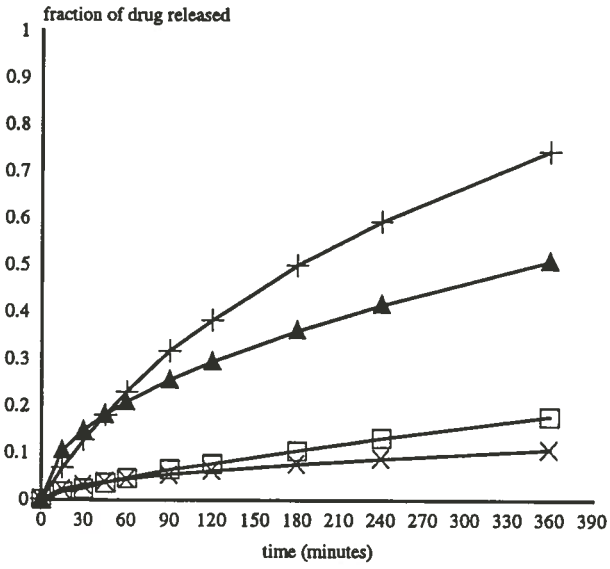

Figure 1. Model (a) for 10% w/w chlorpheniramine maleate, 30% w/w E4M HPMC and 59% w/w Lactose Fast Flo. Key: (+) observed, all surface; (△) estimated, all surface; (□) observed, one surface; (x) estimated, one surface.

The kinetics and mechanism of drug release for each system was investigated by plotting the fraction of drug release observed and estimated by PCNONLIN versus time. As shown in Figures 1-3, the best fitting model was the one in which the estimated values are close to the observed values.

Table I shows that model b was the best model that fit for restricted and unrestricted matrix, according to PCNONLIN, since it showed the smallest weighted squared residual values.

Table II shows the n values obtained for both systems and as expected the n values were 0.780539 and 0.756833 for restricted and unrestricted matrix respectively, indicating anomalous non-Fickian drug release.

Table 1. Kinetic Drug Release from Tablets Containing 10% w/w Chlorpheniramine Maleate, 30% E4M HPMC and Lactose Fast Flo Using PCNONLIN

Tablet Surface	Sum of Weighted Squared Residuals		
Exposed	Model (a)	Model (b)	Model (c)
One	0.000777	0.000027*	0.000034
All	0.017349	0.001085*	0.002200

Models: (a) $M_t/M_\infty = Kt^{1/2}$; (b) $Mt//M_\infty = Kt^n$; (c) $M_t/M_\infty = K_1 t^{1/2} + K_2 t$
*Best fit

In order to quantify the approximate amount of drug released by Fickian diffusion and by polymer relaxation, the drug release data was fitted to equation 2 by using PCNONLIN.

The values obtained for both restricted and unrestricted systems are shown in Table II. Also, K_1 and K_2 obtained when the drug release was fitted to equation 2 are shown in Table II and as expected the results indicate anomalous non-Fickian drug release.

Table 2. Kinetic Constants for the Different Models Evaluated by Using PCNONLIN

Tablet Surface Exposed	Model (a)	Kinetic Constants Model (b)		Model (c)	
	K	K	n	K_1	K_2
One	0.00563	0.00181	0.78054	0.00260	0.00038
All	0.02680	0.00959	0.75683	0.01355	0.00167

Models: (a) $M_t/M_\infty = Kt^{1/2}$; (b) $M_t/M_\infty = Kt^n$; (c) $M_t/M_\infty = K_1 t^{1/2} + K_2 t$

As is shown in Figures 4 and 5, the percent of drug release by Fickian diffusion predominated in the early stages of the dissolution experiment but as time passed more drug was released by polymer relaxation.

At 15 minutes of dissolution testing, the percent drug release from restricted matrices and unrestricted matrices released by Fickian diffusion were 62.9% and 78.3%

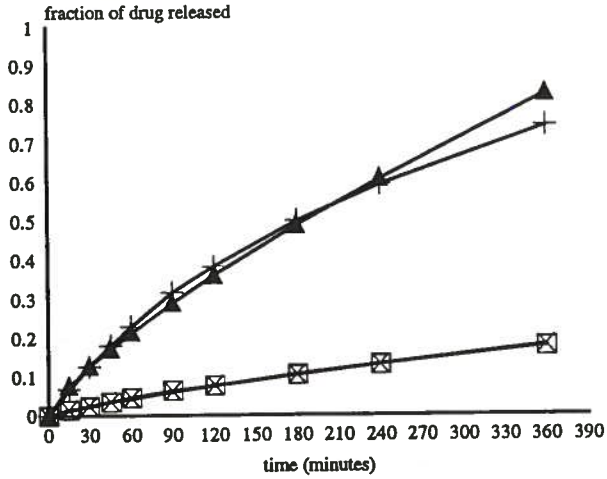

Figure 2. Model (b) for 10% w/w chlorpheniramine maleate, 30% w/w E4M HPMC and 59% w/w Lactose Fast Flo. Key: (+) observed, all surface; (Δ) estimated, all surface; (□) observed, one surface; (X) estimated, one surface

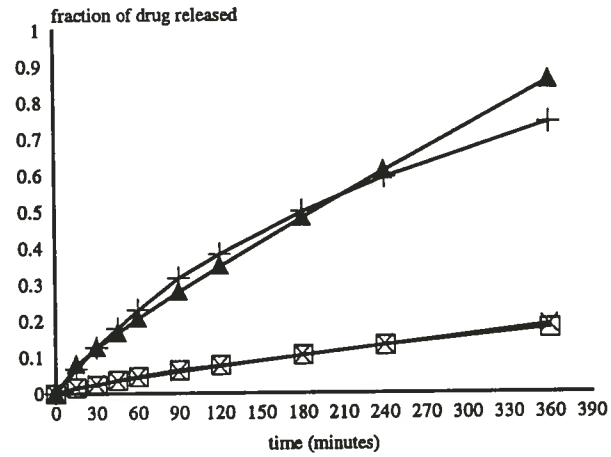

Figure 3. Model (c) for 10% chlorpheniramine maleate, 30% w/w E4M HPMC and 59% w/w Lactose Fast Flo. Key: (+) observed, all surface; (Δ) estimated, all surface; (□) observed, one surface; (X) estimated, one surface

respectively, while percent of drug released by polymer relaxation were 35.9% and 37.7% respectively.

At 240 minutes, the percent released by Fickian diffusion from the same tablets were 30.7% and 35.4%, while the percent released by polymer relaxation were 70.2% and 67.6% respectively. This result is due to the increase in the thickness of the viscous gel layer that surrounds each tablet with time, creating a longer diffusional path length for the drug to diffuse into the external releasing medium. Soon after, the long polymer chains started to disentangle until they dissolved.

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

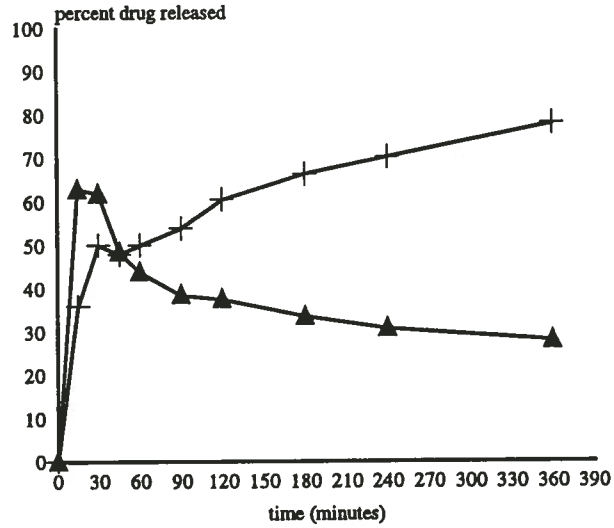

Figure 4. Estimation of the relaxation (+) and Fickian contribution (Δ) to the total percent of drug released from tablets with only one surface exposed to the dissolution medium.

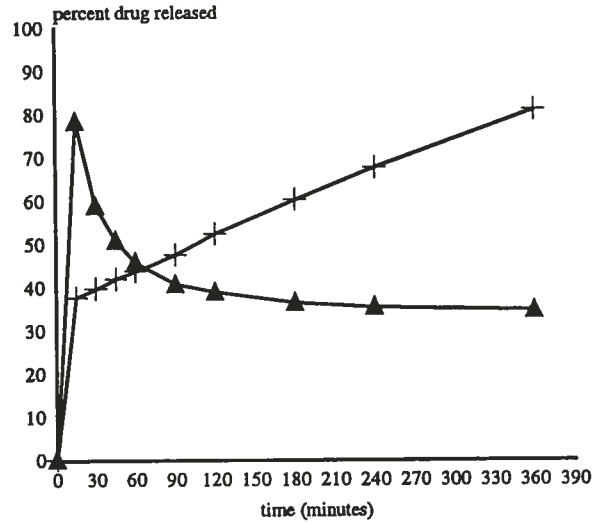

Figure 5. Estimation of the relaxation (+) and Fickian contribution (Δ) to the total percent of drug released from tablets with **all surface** exposed to the dissolution medium.

Conclusion

The release kinetics of highly water soluble drug from hydrophilic swellable matrix follows two mechanisms: drug diffusion and polymer relaxation or erosion. The kinetic exponents (n values) obtained from the equation of drug release from polymer system such as tablet matrices containing 10% w/w chlorpheniramine maleate,30% w/w E4M hydroxypropylmethylcellulose, and Lactose Fast Flo as diluent with one and or all surfaces exposed to dissolution medium, were indicative of anomalous non-Fickian diffusion.

The study shows that it is possible to quantify the amount of drug released due to Fickian diffusion and polymer relaxation by fitting the release data in a polynomial expression proposed by Sahlin and Peppas using PCNONLIN software.

Additionally, the amount of drug released from hydrophilic swellable matrices can be modified and controlled by imposing physical restriction to tablet matrices.

Resumen

El objectivo principal de este trabajo es comprender mejor el mecanismo por el cual drogas altamemente solubles en agua se liberan de un polimero que se expande y cuantizar la cantidad de droga liberada. Las tabletas contienen 10% de la droga, hidroxipropilmetilcelulosa E4M al 10% , 20% y 30% por peso y 1% de estearato de magnesio completado hasta el 100% por peso con lactosa fast flo como diluente, utilizando el metodo de compresion directa. La cantidad de droga liberada debido a la difusion Fickian y no-Fickian (relajacion de polimero) fue cuantizada a diferentes intervalos de tiempo. Para determinar si la droga liberada fue por difusion Fickian o no-Fickian, el exponente "n" obtenido fue calculado de la ecuacion $M_t / M¥ = Kt^n$. Se encontro que este fue sobre 0.5 para sistemas restringindos y no-restringidos indicando difusion no-Fickian. Ademas se calculo la contribucion aproximada de la difusion Fickian y de la relajacion no-Fickian del polimero en un proceso de liberacion anomalo.

Los datos obtenidos de la superficie de todas las tabletas expuestas a un medio de disolusion demonstraban que la difusion Fickian predomino por la primera hora. Despues de una hora de prueba de disolusion el mecanismo de relajacion predomino. El porciento de droga liberada de matrices restringindas en una prueba de disolusion de 6 horas fue 77.9% por relajacion del polimero y 27.9% por difusion Fickian.

Acknowlegment

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