Pharmaceutical Research, Vol. 5, No. 8, 1988

Research Article

Drug/Polymer Matrix Swelling and Dissolution

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Received November 12, 1987; accepted March 2, 1988

The swelling and dissolution behavior of pharmaceutical systems containing a drug and a polymer can be analyzed by a mathematical model which predicts the drug released and the gel layer thickness as a function of time. It is possible to approximate the values of several of the physicochemical parameters of this model in order to obtain an order-of-magnitude analysis of the tablet dissolution process. Selected experimental results of tablet dissolution and drug release are analyzed and conclusions are made about the importance of the drug and polymer content and solubility in the release behavior.

KEY WORDS: swelling; dissolution; matrix; tablet; cimetidine · HCl; sodium diclofenac; diprophylline.

INTRODUCTION

The problem of tablet dissolution is one of great importance in pharmaceutical science, as dissolution is the limiting step of drug bioavailability. In addition, in the development of controlled-release systems, especially in oral applications, it is necessary that the *in vitro* release be maintained during the *in vivo* delivery. Therefore, a mathematical and physical analysis of matrix dissolution becomes an important pharmaceutical research subject.

Commercial hydrophilic matrices consist of a significant amount of drug dispersed in and compressed with a hydrophilic polymer, sometimes prepared with the addition of a soluble or insoluble filler. When these systems are placed in water or in a fluid simulating biological fluids, they start dissolving by a process which is the composite of two phenomena. For example, in the early 1980's Lee (1) and Peppas *et al.* (2) had proposed two distinct mechanisms, one of swelling and another of dissolution, for the overall phenomenon. In addition, Colombo *et al.* (3–5) presented the first data on substance dissolution in the pharmaceutical field containing unequivocal evidence of this dual phenomenon (swelling and dissolution).

Effectively, in the early stage of "dissolution," the polymer starts swelling, and the tablet thickness increases. Soon thereafter, the polymer (and drug) dissolution starts occurring. The polymer dissolves because of chain disentanglement (6). Thus, there is a slow diminution of the thickness until, finally, the tablet disappears. Figure 1 presents the position of the fronts observed during this process. The first front (R) separates the originally glassy from the rubbery state. The second front (S) indicates the interface between the swollen polymer and the dissolution medium.

Lee and Peppas (7–9) recently presented mathematical models to describe the overall dissolution process in the absence or in the presence of drug. In the absence of drug (7,8) it was shown that the thickness of the continuously changing gel layer (i.e., the rubbery-state thickness) was a function of the square root of time in the early portion of the overall phenomenon. It was also noted that this initial behavior was followed by a synchronization of the polymer (S) and swelling (R) fronts and, therefore, that the gel layer thickness became independent of time (see Fig. 2). The mathematical expressions developed and the agreement with some of the available data can be found in another publication (8).

More recently, Lee and Peppas (9) have also developed a model to describe the dissolution process and drug release from tablets. Figure 3 indicates the relevant fronts and concentrations involved in this analysis. The pertinent parameters are defined as follows:

c_s is the drug solubility (expressed as the volume fraction) at the drug core interface (R),

c_b is the drug volume fraction at the gel/solution interface (S),

c^* is the polymer volume fraction at R,

c_d is the polymer volume fraction at S,

c_{cd} is the drug volume fraction in the glassy core,

c_{cp} is the polymer volume fraction in the glassy core,

D_s is the solvent diffusion coefficient in the drug/polymer matrix,

D_d is the drug diffusion coefficient in the swollen polymer system, and

k is the mass transfer coefficient of the dissolved drug at S.

For a cylindrical tablet of original thickness a and orig-

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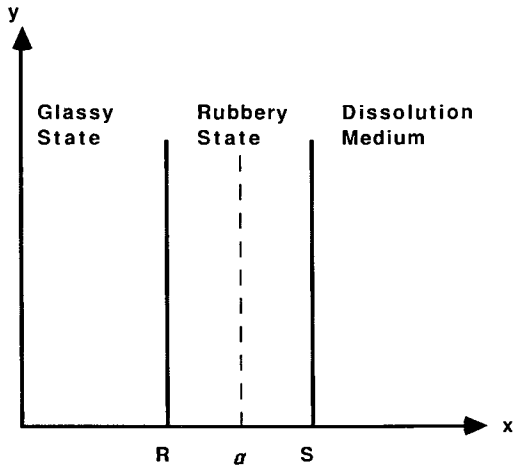

Fig. 1. Tablet dissolution in contact with a dissolution medium indicating the original position of the tablet surface, a, the dissolution medium/swollen polymer front, S, and the rubbery/glassy front, R. The coordinate (0,0) is the center of the tablet.

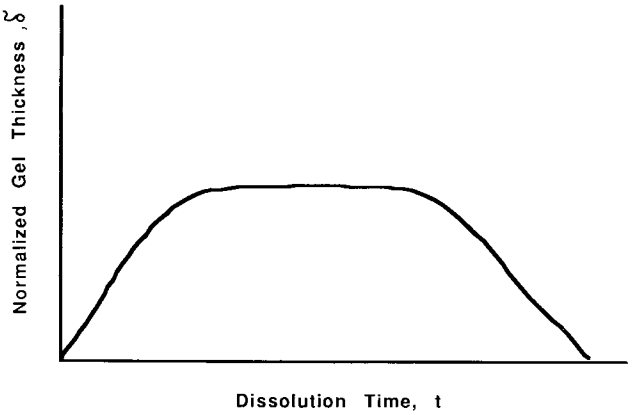

Fig. 2. Dependence of normalized gel (rubbery state) layer thickness, $\delta = (S - R)/a$, on dissolution time, t, for polymer tablets in the absence or presence of drugs.

inal base surface area A, which is placed in water from which the drug is released only from one face in a one-dimensional diffusion, the normalized gel layer thickness, $\delta = (S - R)/a$, is described (9) by Eq. (1):

$$\frac{a\delta}{kc_d} + \frac{[D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c_s - c_b)(c^* + c_s)]}{(1 - c^* - c_s)k^2c_d^2} \times \ln\left[1 - \frac{(1 - c^* - c_s)kc_d a\delta}{D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c_s - c_b)(c^* + c_s)}\right] + t = 0 \quad (1)$$

It must be noted that

(i) this and all subsequent equations were obtained from the solution of the diffusional release problem with a constant diffusion coefficient and
(ii) all parameters with the symbol c appearing in the equations are dimensionless volume fractions, not concentrations.

Depending on the relative importance of the diffusion and true dissolution terms, Eq. (1) predicts that the normalized gel layer thickness, δ, in the presence of drug will vary with time in a manner similar to that presented in Fig. 2 for tablets without drug. Indeed, a rise in the gel thickness will be observed which is indicative of considerable swelling of the drug/polymer mixture with slower dissolution of the same mixture. Later, the two fronts may be synchronized and a constant gel thickness will be observed.

As mentioned before (9), the amount of drug released, M_t/M_∞, is given by:

where ρ_d is the drug density. Obviously, the term δ changes with time in the early (swelling) region and becomes independent of time when synchronization of the two fronts occurs.

For analysis of the results obtained from dissolution of pharmaceutical tablets, we may, therefore, distinguish the following cases.

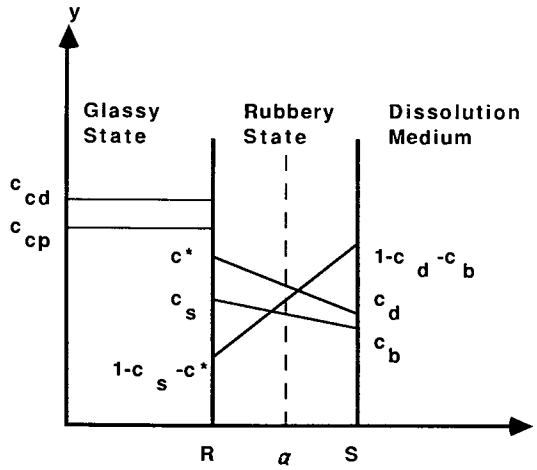

Fig. 3. Parameter definition for drug/polymer tablet dissolution system.

$$\frac{M_t}{M_\infty} = \frac{1}{c_{cd}\rho_d a}\int_0^t c_b\rho_d \left\{\left[\frac{-D_s(c_s + c^* - c_d - c_b) + D_b(c_s - c_b) + (D_d/c_b)(c_s - c_b)}{a\delta}\right] + kc_d\right\} dt \quad (2)$$

Early Swelling Region. In this region, the amount of drug release can be calculated by combining Eqs. (1) and (2). Since Eq. (1) is difficult to solve explicitly for δ, which changes with time, a computer algorithm is recommended, whereby the data of $\delta(t)$ versus t are placed in Eq. (2) and the integration is carried out.

A very special approximate solution is obtained when the term inside the logarithm of Eq. (1) is close to one. Then, the logarithm may be expanded in Taylor series, the first two terms kept, and the resulting equation can be placed in Eq. (2) to yield Eq. (3).

$$\frac{M_t}{M_\infty} = \frac{c_b}{c_{cd}a}\left(\left\{\frac{2[-D_s(c_s + c^* - c_d - c_b) + D_d(c_s - c_b) + (D_d/c_b)(c_s - c_b)]^2(1 - c^* - c_s)t}{[D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c^* + c_s)(c_s - c_b)]}\right\}^{1/2} + kc_d t\right) \quad (3)$$

This last equation should be used only when

$$\frac{(1 - c^* - c_s)kc_d a\delta}{D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c_s - c_b)(c^* + c_s)} \ll 1 \quad (4)$$

It must be noted that Eq. (3) predicts that the amount of drug released is expressed as:

$$\frac{M_t}{M_\infty} = \alpha t^{1/2} + \gamma t \quad (5)$$

Synchronization Region. In the synchronization region, the value of δ is constant and can be expressed by Eq. (1), which is substituted in Eq. (2). The final form of this equation will be:

$$\frac{M_t}{M_\infty} = \zeta + \epsilon t \quad (6)$$

In this contribution, it was our intention to analyze recent experimental data obtained for dissolution of and drug release from pharmaceutical releasing systems and to calculate important structural parameters involved in the swelling/dissolution process.

EXPERIMENTAL

Preparation of Systems

Experimental studies were conducted with a series of hydrophilic matrices prepared by compression of three components: a model drug, a hydrophilic polymer, and a soluble filler. The model drugs used were sodium diclofenac (Pharmatec, Milan, Italy; m.w., 282.68; m.p., 283–285°C), diprophylline (Rhône-Poulenc, Milan, Italy; m.w., 254.25; m.p., 158°C), and cimetidine · HCl (Farma-Co, Milan, Italy; m.w., 288.79); they all had a purity higher than 99%. They were selected because of their wide range of solubility in water. The hydrophilic polymer was polyvinyl alcohol [PVA; Mowiol 40-88, Hoechst, Frankfurt, FRG; MW 130,000; degree of hydrolysis, 87.7%; viscosity of the 4% (w/v) aqueous solution at 20°C, 0.04 Pa · sec]. The soluble filler was mannitol (Gianni, Milan, Italy; m.w., 182.17; m.p., 166–168°C). Each mixture was prepared and compressed as described by Colombo *et al.* (5). The final diameter of the tablets was 9.50 mm and the thickness was from 2.22 to 2.51 mm.

Finally, the tablets were coated on three sides with a 15% (w/w) acetone solution of cellulose acetate prepionate (CAP; Eastman Kodak, Kingsport, Tenn.). This coating CAP is insoluble in and impermeable to water so that any further drug release could be followed only from one face.

Swelling

Swelling experiments were performed in a USP XXI dissolution apparatus 2 at 37°C. For sodium diclofenac the dissolution medium was intestinal simulating fluid, whereas for the other drugs distilled water was used. The positions of the eroding and swelling fronts were measured with a penetrometer as described by Colombo *et al.* (5).

Release Experiments

Release experiments were also performed in a USP XXI apparatus at 37°C using perfect sink conditions. The dissolution medium was water for diprophylline and cimetidine · HCl and a simulated intestinal fluid solution for sodium diclofenac. The agitation rates used were 25, 50, 100, and 200 rpm.

The analysis of the drug concentration was done in a UV spectrophotometer at 275 nm for sodium diclofenac, 273 nm for diprophylline, and 218 nm for cimetidine · HCl.

RESULTS AND DISCUSSION

Dissolution Phenomena

The dissolution process of drug/polymer matrices is described by a combination of two phenomena: a swelling phenomenon, which leads to transition of the glassy polymer state to a rubbery state; and a "true dissolution" phenomenon, according to which the rubbery polymer is disentangled and eroded.

In the previous publications describing this model, Lee and Peppas (9) commented on the relative importance of the swelling and dissolution processes. Indeed, the form of Eq. (1) is such that both diffusion and dissolution contributions are included. Additional comments and details of this analysis are presented in a paper by Lustig *et al.* (10), where an analysis of the simulation prediction of this model is included.

The normalized gel layer is an increasing function of time for the period when the swelling process is much faster

than the true dissolution process. At some later point, the two processes may be occurring at the same rate, thus leading to a normalized gel layer thickness which is independent of time, as shown in Fig. 2. No doubt, if the polymer does not exhibit hydrogen bonds or other barriers prohibiting dissolution, in the final stage the gel layer will decrease with time, the swelling process having been effectively complete. It is the middle-section behavior that has been called by Colombo and his collaborators (4,5) *the front synchronization process* and has been proposed and actually used for the successful release of drugs at constant rates from devices of a constant release area. These conclusions will be correct for analysis of systems where the active component (drug) is incorporated in small amounts, so that deviations from thermodynamic ideality can be neglected. Such deviations could include nonconstant diffusion coefficients, drug/water and drug/polymer interactions, etc.

However, very often the controlled-release technologist is asked to analyze the release behavior of pharmaceutical systems where at least two components are present at high concentrations. In such situations, it is not clear from our previous publications (7–10) how the theory described by Eqs. (1) through (5) can be used to analyze dissolution of tablets containing high amounts of drugs.

The recent work of Colombo *et al.* (5) describes the swelling, dissolution, and release behavior of tablets containing three such components (a drug, a polymer, and a filler) in significant quantities. It was thus the intention of this contribution to indicate how such calculations can lead to prediction of the dissolution behavior.

Analysis of Dissolution Results for the Front Synchronization Region

Experimental results of gel layer formation and drug release were obtained and analyzed here. In all cases, the drug was loaded at 50 wt%, the polymer was PVA at 30 wt%, and the filler was mannitol at 20 wt%. A typical set of graphs is shown in Fig. 4. All situations of drug release from PVA systems belong to the class of front synchronization systems, despite the fact that the drugs used were of widely varying solubilities.

To analyze these data, first the drug released, M_t/M_∞, was plotted as a function of time. All the data could be analyzed by an equation of the form of Eq. (6). From these graphs the slope, ϵ, was calculated. Here

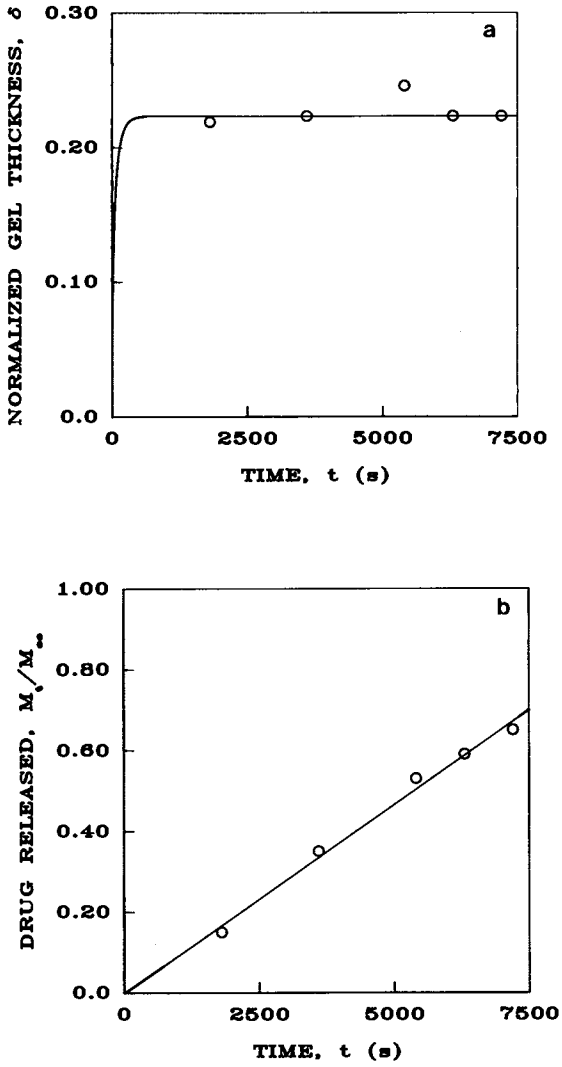

Fig. 4. Variation of the normalized gel layer thickness (a) and the sodium diclofenac released (b) with the dissolution time. This tablet was prepared with 30 wt% PVA, 20 wt% mannitol, and 50 wt% sodium diclofenac and was tested at 37°C in intestinal simulating fluid at 100 rpm. The lines indicate the prediction of the new dissolution model.

$$\epsilon = \frac{c_b}{c_{cd}a}\left[\frac{-D_s(c_s + c^* - c_d - c_b) + D_d(c_s - c_b) + (D_d/c_b)(c_s - c_b)}{\delta a} + kc_d\right] \tag{7}$$

Then the data for the normalized gel layer thickness, $\delta = (S - R)/a$, were plotted as a function of time and the *plateau region* (time-independent gel thickness region) was identified.

According to the original model (10), the equation describing the change of this gel layer thickness is

Thus, by setting $d(S - R)/dt = 0$ in the plateau region, the value of the gel layer thickness, $S - R$, could be determined, and the normalized gel layer thickness of the plateau region, δ_{plat}, could be related to the other system parameters by Eq. (9):

$$(1 - c_s - c^*)\frac{d(S - R)}{dt} = \frac{D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c_s - c_b)(c^* + c_s)}{(S - R)} - (1 - c^* - c_s)kc_d \tag{8}$$

Table I. Analysis of Tablet Dissolution at 37°C

Drug	Agitation used (rpm)	Drug dissolution constant, $k \times 10^3$ (cm/sec)	Drug volume fraction at S, c_b
Sodium diclofenac	25	2.4	0.051
	50	3.1	0.052
	100	6.3	0.036
	200	5.0	0.083
Diprophylline	25	5.3	0.009
	50	7.4	0.010
	100	7.3	0.017
	200	11.5	0.028
Cimetidine · HCl	100	32.3	0.002

temperature (=37°C), α_f is the linear expansion coefficient of the polymer [$=\alpha_l - \alpha_g$ and approximately equal to 3.7×10^{-4} K for most polymers according to Ferry (11)], and β is the contribution of the dissolution medium (water) to the expansion coefficient of the polymer [=0.20 for many polymer–liquid systems according to Fujita and Kishimoto (12)]. Thus, first the term c_0^* (as grams of water per gram of polymer) can be calculated (=0.042 g water/g PVA in our case). In addition, Eq. (11) calls for knowledge of the densities of polymer (ρ_p = 1.269 g/cm³ for PVA), dissolution medium (ρ_{dm} = 1 g/cm³ for the present dissolution media), filler (ρ_f = 1.49 g/cm³ for mannitol), and drugs used (see Table II) and the weight concentrations of filler (w_f = 0.666 g mannitol/g PVA) and drug (w_d = 1.666 g drug/g PVA).

$$\delta_{plat} = \frac{D_s(2 - c^* - c_s)(c^* + c_s - c_d - c_b) + D_d(c_s - c_b)(c^* + c_s)}{a(1 - c^* - c_s)kc_d} \tag{9}$$

Finally, the numerical values of ϵ and δ_{plat} were used in Eqs. (7) and (9) to determine the drug volume fraction at S, c_b, and the mass transfer coefficient, k.

Table I shows the values of these parameters as calculated for three different systems prepared with sodium diclofenac, diprophylline, and cimetidine · HCl and tested at various agitation rates. Evidently, calculations of these parameters have been made with knowledge or estimation of all other volume fractions and diffusion coefficients of the systems.

The initial drug and polymer volume fractions in the glassy core, c_{cd} and c_{cp}, respectively, are known or can be calculated from the initial tablet loading and the true densities of these components. For the purpose of this preliminary analysis, mannitol and the drug were considered as one component.

At the glassy/rubbery interface, R, two volume fractions, c^* and c_s, must be determined. The polymer volume fraction, c^*, can be calculated from the equation of polymer glass transition temperature depression due to the existence of the dissolution medium [as given by Eq. (10)], by taking into account the densities and quantities of all other components, as shown in Eq. (11).

$$c_0^* = \frac{T_g - T}{\beta/\alpha_f} \tag{10}$$

$$c^* = \frac{1/\rho_p}{(1/\rho_p) + (c_0^*/\rho_{dm}) + (w_f/\rho_f) + (w_d/\rho_d)} \tag{11}$$

In these equations, T_g is the glass transition temperature of the polymer (=60°C for PVA as determined by us using differential scanning calorimetry), T is the experimentation

The drug volume fraction at the drug core interface R, c_s, represents the drug solubility in the polymer phase. If the drug solubility in water, c_{s0} (as grams per milliliter of solution), is known, the value of c_s can be approximated by

$$c_s = \frac{c_{s0}(1 - c^*)}{\rho_d} \tag{12}$$

For the three drugs used here, the values of c_{s0} are presented in Table II.

The values of component volume fractions at the front S, c_b and c_d, are usually more difficult to estimate. Thus, it is recommended that the drug volume fraction, c_b, be calculated from the results (as done here and shown in Table I), whereas the value of the polymer volume fraction, c_d, can be estimated from knowledge of the molecular characteristics of the dissolution process. Indeed, as discussed by Brochard and deGennes (6) and Parsonage *et al.* (7), the polymer dissolution process at the front S is a chain disentanglement process characterized by a threshold concentration, c_d. In the case of PVA we have used c_d = 0.075. Other values of c_d and their influence on the final calculations are discussed by Lustig *et al.* (10). For example, realistic values of c_d for pharmaceutical tablets can be obtained using the analysis presented by Peppas *et al.* (13).

The diffusion coefficients, D_s and D_d, either are available from the literature or can be experimentally determined. For our case, the drug diffusion coefficients have been measured experimentally and are indicated in Table II. The water diffusion coefficient, $D_s = 2.12 \times 10^{-5}$ cm²/sec, was calculated using the Davis equation (13), with 2.14×10^{-5} cm²/sec being the water self-diffusion coefficient.

Table II. Physicochemical Characteristics of the Drugs Used

Drug	Density (g/cm³)	Solubility in water, c_{s0} (g/cm³ solution)	Diffusion coefficient in swollen PVA, $D_d \times 10^6$ (cm²/sec)
Sodium diclofenac	1.50	0.031	1.10
Diprophylline	1.40	0.342	1.48
Cimetidine · HCl	1.50	1.000	1.30

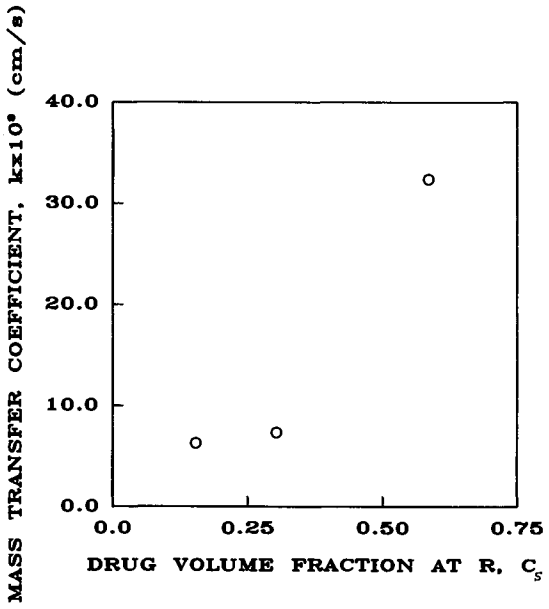

Fig. 5. Effect of drug solubility, expressed as the volume fraction of drug at the drug core interface R, c_s, on the mass transfer coefficient of drug dissolution at 37°C and 100 rpm.

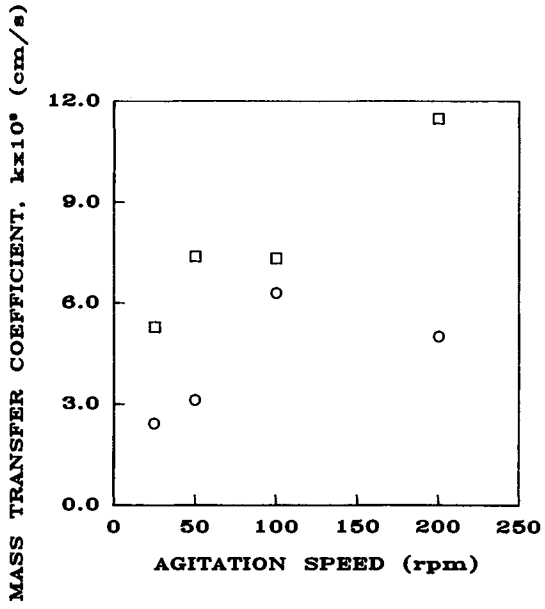

Fig. 7. Effect of agitation rate on drug mass transfer/dissolution coefficient for PVA-containing tablets of sodium diclofenac (○) and diprophylline (□) at 37°C.

Using the aforementioned values and the calculation scheme described earlier, the values of k and c_b were calculated as reported in Table I. It is evident that the method of analysis is able to give interesting values of important system parameters. To indicate the good fit of the model with the data, the reader's attention is directed to Figs. 4a and b, where dissolution data are presented for a sample containing sodium diclofenac. Obviously, this analysis has the ability to predict the data for these pharmaceutical products.

It can be seen that in sodium diclofenac-containing systems the constant gel layer thickness region is attained after the relatively short time of about 400 sec. This is the situation of front synchronization, and as Fig. 4b indicates, the amount of drug released is effectively described by a curve [presented by Eq. (3)] which, for all practical purposes, approaches the limiting case of the straight line of Eq. (6). The correlation coefficient for this line was calculated as $r = 0.995$.

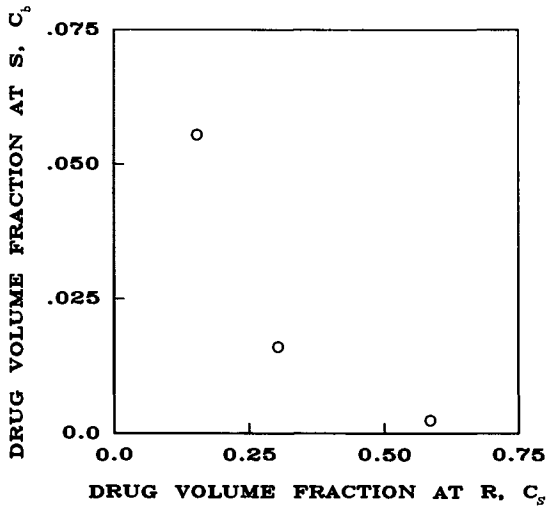

Fig. 6. Effect of drug solubility, expressed as the volume fraction of drug at the drug core interface, R, c_s, on the drug volume fraction at the interface S, c_b, for drug dissolution at 37°C and 100 rpm.

The results of this analysis indicate that the mass transfer coefficient of the drug, k, is a function of the drug solubility as shown in Fig. 5. Indeed, as the solubility increased, the mass transfer coefficient increased. It must be noted that in the present analysis this mass transfer coefficient is descriptive of the dissolution of not only the drug but also mannitol. Thus, the model developed by Lee and Peppas can be applied to realistic situations of pharmaceutical tablet dissolution.

An additional advantage of the new model is that, even without knowledge of specific values of the volume fractions and diffusion coefficients, the release behavior of certain soluble pharmaceutical systems can be plotted according to the function given by Eq. (5) or (6), and certain parameters can be approximated.

The optimization process using the solution of the model presented here led to the calculation of values of both k and c_b for the three pharmaceutical systems studied. There seem to be a direct relationship between the drug volume fractions at the two fronts R and S, as shown in Fig. 6. At the front S, a drug of low solubility (low c_{s0}) would transfer from the polymer to the dissolution medium at a rate slower than that of the polymer. Thus, the term c_b would be higher, since it is a measure of the relative concentration of drug to polymer.

Probably the most interesting conclusions of this work are related to the ability of this model to predict the dependence of the drug mass transfer and dissolution coefficient

on the agitation speed, as shown in Fig. 7 for two pharmaceutical formulations. A more complete analysis of the importance of agitation to drug/polymer tablet dissolution in terms of Sherwood number analysis will be discussed in a future contribution.

CONCLUSIONS

The controlled release of drugs from hydrophilic, swellable, and soluble tablets can be predicted with a new mathematical model of drug/polymer matrix dissolution. We have shown that this process is characterized by two distinct fronts, one which separates the dissolution medium from the rubbery (gel-like) polymer and another which separates the rubbery from the glassy state.

In the overall dissolution mechanism, both swelling and pure dissolution phenomena occur. Thus, the drug released is related to a diffusional term (with $t^{1/2}$ dependence) and a dissolution term (with t dependence). However, when the two front movements are synchronized, the diffusional term becomes negligible and the drug release rate is independent of time and of the drug solubility, c_{s0}.

The new model seems to retain one interesting characteristic of the earlier Lee model (1), albeit with a major modification. In the previous model, constant release was obtained upon synchronization of diffusional and erosion fronts. Here, the same is achieved when swelling and erosion fronts are synchronized.

ACKNOWLEDGMENTS

We wish to thank Professor Ubaldo Conte of the University of Pavia and Mr. Steven Lustig of Purdue University for helpful discussions.

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