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RESEARCH PAPER

Relationship Between the Swelling Process and the Release of a Water-Soluble Drug from a Compressed Swellable-Soluble Matrix of Poly(Vinyl Alcohol)

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ABSTRACT

An attempt was made in this study to relate the release of a highly water-soluble model drug from tablet matrices of poly(vinyl alcohol) (PVAL) with the factors that may affect the release behavior. Swelling was evaluated using a simple projection method. The swollen layer was photographed to monitor its thickness. The polymer and drug dissolution were determined simultaneously by spectrophotometric methods. The resulting change of tablet area showed that the process of swelling occurred in three different stages that were intimately related to polymer dissolution: (a) *a rapid initial swelling, resulting in an increased area;* (b) *a period with an approximately constant area; and* (c) *a decrease of the tablet area. In spite of the significant dissolution of PVAL during the release process, the thickness of the gel layer gradually increased. Thus, the delivery was governed by the drug concentration gradient along the diffusional path length. The drug release appeared to be controlled by a diffusion process according to Higuchi-type kinetics. The data analysis of drug and polymer profiles confirmed the diffusional mechanism.*

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INTRODUCTION

The term *swellable systems* is used to describe formulations with a release mechanism dependent on the penetration of the solvent and, consequently, on the swelling phenomenon that includes the simultaneous or subsequent dissolution of the polymer (1–3). The drug release mechanism for these swellable matrix tablets is complex due to the interfaces involved, which consist of two fronts: a glassy-rubber swelling front and a dissolution (eroding) front, both in movement during the release process. The glassy-rubber swelling front is defined as the interface between the nonrelaxed polymer and the gel; the dissolution front is defined as the interface between the gel and the dissolution medium. At the glassy-rubber swelling front, hydration, swelling, and coalescence of polymer particles occur, whereas at the dissolution front, polymer chain disentanglement and dissolution of the hydrated polymer take place (4,5). A high load of drug and/or a limited solubility in the swollen polymer implies the presence of a third front: the drug diffusion front, which consists of nondissolved drug in the gel layer (6).

Several recent studies have provoked a debate about the relative importance of the interfaces for predicting release and constructing new models. Möckel and Lippold (7) found that, for hydrocolloids with low viscosities, only polymer dissolution (erosion front movement) controls the drug release rate. An interesting model was proposed by Ju et al. (8,9) that describes the swelling/dissolution mechanism and the drug release from hydrophilic matrices; the model is based on a polymer disentanglement concentration that is equal to the polymer concentration below which polymer chains detach themselves from the gelled matrix. Wan, Heng, and Wong (10) correlated swelling measurements with the drug release profiles, which provided a useful method for predicting drug release. On the other hand, Colombo et al. (6) identified the presence of undissolved drug in the rubbery state (diffusion front movement). They concluded that this front is the main parameter that affects drug release, and that, in this case, phase erosion does not play a major role in drug delivery. It is clear from these studies that the release process is complex, and that it cannot be explained by isolating the factors involved or simply by describing the fronts. In the present work, the phenomena involved in the release of a highly water-soluble drug from a poly(vinyl alcohol) (PVAL; for the purpose of this work, the abbreviation PVAL designates the partially hydrolyzed form, although the correct abbreviation, according to International Organization for Standardization norms, is VA/VAL) (11) swelling-soluble matrix obtained by direct compression were studied to gain insight into the mechanism of drug release and to determine the importance of polymer dissolution. The factors affecting drug release, such as matrix swelling (surface expansion), polymer dissolution, and thickness of the gel layer, were evaluated in the same experiment using a nonstressing system. Solvent uptake was also measured by a unidirectional method.

MATERIALS AND METHODS

Materials

PVAL (Elvanol® 5222) with a degree of hydrolysis of the corresponding polyvinyl acetate (USP XXIII) of 88.93% was a generous gift from Dupont S.A. de C.V. (Mexico). The *d*-pseudoephedrine hydrochloride, dihydrogen potassium phosphate, sodium hydroxide, boric acid, resublimated iodine, and potassium iodide were purchased from Sigma (St. Louis, MO). Distilled water was purified using a Milli-Q system (Millipore, USA, Bedford, MD). All the other reagents were of analytical grade and were used without further purification.

Methods

Matrix Preparation

To achieve a nondisintegrating matrix, different particle sizes of the polymer were tested. The best compression characteristics were obtained with the PVAL passing through a mesh 80 (177-μm sieve). The drug and the PVAL were mixed in a 20:80 proportion using a cube blender (Erweka type AR 400, Germany) for 30 min. The homogeneity of the mixture was determined by scooping out samples of the bulk mixture. Then, 500 mg of the mixture was fed into the die of a laboratory hydraulic press (Carver Press, Mod. C, USA) and compressed using flat punches (diameter 11 mm) at a pressure of 490 MPa for 50 sec. The average crushing force ($n = 10$) was 44 $\pm$ 3 N (Erweka type TB24, Germany), with a thickness of 4.96 $\pm$ 0.10 mm and a diameter of 11.36 $\pm$ 0.10 mm (vernier caliper, Mitutoyo, Japan).

Swelling Studies

Release and swelling experiments ($n = 6$) were performed at 37°C $\pm$ 0.5°C using the system shown in Fig. 1. The tablet was immersed in a crystallizer with 500 ml of 0.1 M phosphate buffer, pH 7.0. The crystallizer was previously installed on a projector that was at a constant distance from a screen with a millimetric scale. Stirring

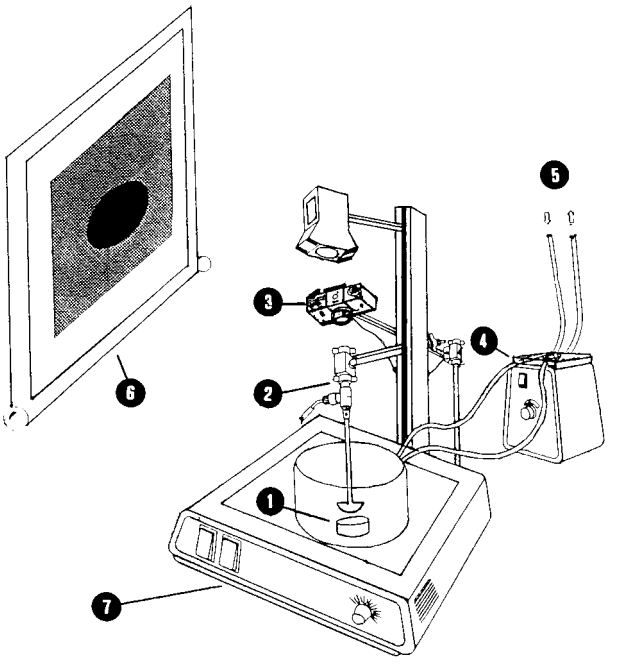

Figure 1. Dissolution system: (1) tablet; (2) paddle stirrer; (3) camera; (4) peristaltic pump; (5) heating (at 37°C); (6) screen; (7) projector.

was provided by a paddle (USP XXIII) at 100 rpm. Temperature was stabilized using a peristaltic pump (Jubile JU/86, Switzerland). Tablet dimensions were determined at fixed intervals by measuring the image on the screen and taking photographs.

Drug Release Studies

Samples of 5 ml of the dissolution medium were taken at different intervals of time. The concentrations of *d*-pseudoephedrine hydrochloride were determined by monitoring the ultraviolet (UV) absorbance at 258 nm (Hitachi spectrophotometer 100-60, Japan).

Poly(Vinyl Alcohol) Dissolution

Spectrophotometric assays were performed on 1-ml samples at 640 nm after forming a blue PVAL–boric acid–iodine complex, which was prepared by the addition of 2 ml of 0.65 M aqueous boric acid solution and 1 ml of I_2/KI solution (0.05 M I_2:0.15 M KI) (12,13). This highly sensitive method has been previously validated (14), and the absence of interactions or interference with pseudoephedrine has also been confirmed.

Unidimensional Solvent Uptake Determination

The unidimensional solvent uptake determination was carried out using the modified apparatus of Nogami et al. (15); the apparatus consists of a graduated capillary tube connected to a microporous filter, which contains the matrix tablet by means of a ''U'' glass tube. The temperature of the reservoir was maintained at 37°C by water recirculation in a jacketed system. The liquid uptake was measured as the volume lost in the capillary tube.

RESULTS AND DISCUSSION

The area values obtained from the projected image during the dissolution experiment were normalized according to the following expression (19):

$$\delta = \frac{A_t - A_o}{A_t} \times 100$$

where A_o is the initial surface area of the dry tablet, A_t is the surface area of the swollen matrix at time t, and δ is the normalized change of the matrix area in the radial direction during the swelling process expressed as a percentage and called the *swelling index*. Figure 2 shows the change of δ as a function of time; this change can be visualized as having three stages. The first is A, from 0 to 20 min, and has the establishment of the first gel layer and is characterized by a rapid solvent uptake and initial swelling. In the stage shown in B, from 20 to 180 min, δ is almost constant. The gel layer formed in stage A behaved like a waterlogged gel. The solvated polymer molecules, at the system surface, gradually become disentangled from each other; then, they dissolve and diffuse

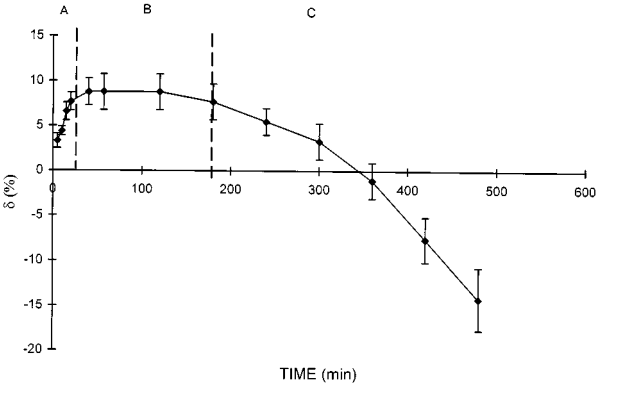

Figure 2. Change of swelling index δ versus time (error bars = 1 SD; $n = 6$).

into the solvent. A new gel layer is simultaneously exposed due to the solvent penetration into the vitreous matrix. The constant area of the tablet can be explained by the compensation between swelling and dissolution of the polymer. Finally, in stage C, from 180 to 480 min, an evident decrease in δ was observed. Considering that a dry core exists in this final stage (the matrix was completely hydrated after 420 min), it is supposed that polymer dissolution is more significant than the swelling. It is important to mention that stage C extends over 60% of the release process. The dissolution of PVAL began as soon as the tablet came into contact with the solvent. Up to 180 min, a moderate nonlinear dissolution was observed; at this time, the dissolved quantity of PVAL is about 30% of the total amount dissolved at the end of the experiment. After that, an increasing linear dissolution was obtained, which explains the decrease of δ during the last stage of the process.

It was difficult to determine quantitatively the thickness of the gel layer throughout the release experiment by the photographic method. The system showed a swollen, viscous, translucent outer layer that covered an evidently glassy core after the first 20 min. Despite the significant PVAL dissolution (more than 75% at the end), the gel layer was never constant, but increased during dissolution, whereas the glassy center gradually decreased. These results are in marked contrast to those obtained elsewhere (16,17), which indicated a rapid synchronization state between the swelling and the dissolution front for similar PVAL matrices. However, it is important to point out that these authors included excipients in the formulation. Thus, the presence of a third component could change the overall hydrophilicity of the system due to a modification of polymer plastification (18). Furthermore, in that study, a single face of the tablet was exposed to the dissolution medium, resulting in a limited radial increase.

Figure 3 shows the kinetics of solvent uptake. A rapid initial solvent absorption was observed during the first 40 min due to solvent penetration into the pores near the surface of the matrix. This led to macromolecular relaxation and changes in the porous structure, including an alteration of the distribution of the pore size and shape (3). Subsequently, solvent absorption became very slow and was almost linear. This suggests that the volume of solvent absorbed in the first few minutes was responsible, to a large extent, for the development of the gel layer throughout the process. However, it is important to stress that this experiment was carried out by exposing only one face of the tablet; thus, it was not directly connected to the phenomena involved in the release experiment performed. In addition, the porous filter that held the tablet

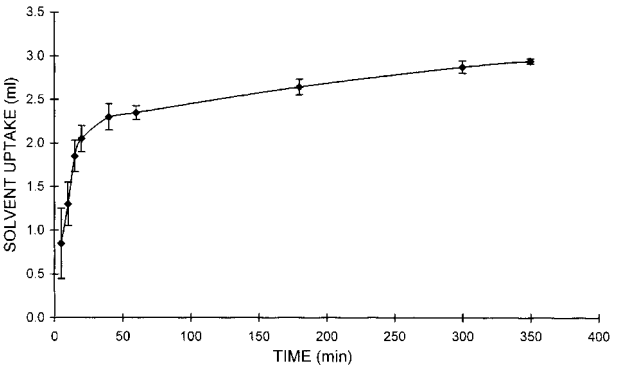

Figure 3. Solvent uptake kinetics (error bars = 1 SD; $n = 3$).

may limit polymer dissolution and hence subsequent water uptake. For the matrices evaluated in the crystallizer, it is well established that the thickness of the gel layer depends on solvent uptake and on polymer dissolution rate. Therefore, an increase of the gel layer suggests that solvent uptake occurs faster than polymer dissolution.

The release profile of *d*-pseudoephedrine hydrochloride is shown in Fig. 4. A slight burst effect was observed, which was attributed to the rapid dissolution of the drug placed in the surface and pores before gel layer formation. The drug release rate profile was not linear, but concave. This behavior seems to be logical considering, first, that a highly water-soluble drug was used, which implies that a drug diffusion front ideally did not exist; second, the increase of the gel layer thickness provoked the decrease of the drug concentration gradient along the diffu-

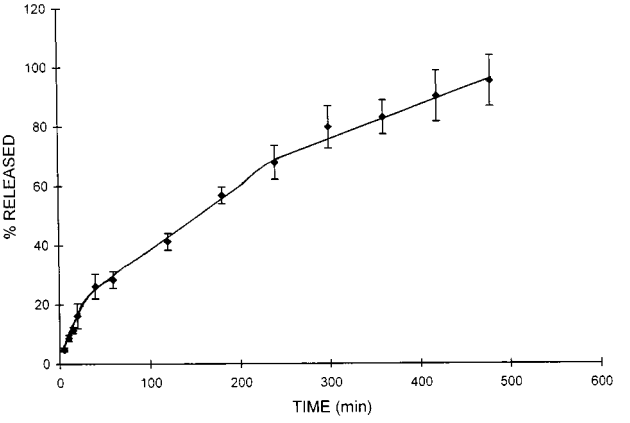

Figure 4. Release profile for *d*-pseudoephedrine hydrochloride from the PVA matrix (error bars = 1 SD; $n = 6$).

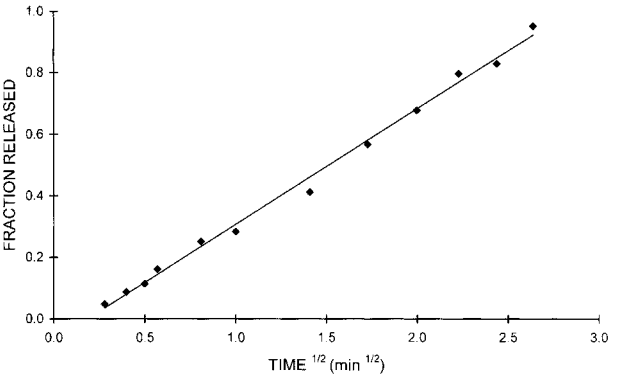

Figure 5. Fraction of *d*-pseudoephedrine hydrochloride released versus the square root of time.

sional path length, therefore decreasing the drug release rate during the experiment.

The Higuchi expression describing Fickian drug release was used to analyze the data. Figure 5 shows the fraction of drug released versus the square root of time. The r^2 value for the linear regression was 0.995, and the residuals were randomly distributed, indicating that the data fit the Higuchi model very well. According to this result, drug release was presumably based on a diffusional mechanism. Möckel and Lippold (7) observed a similar $t^{1/2}$ behavior with highly soluble drugs and similar PVAL matrices. However, these authors considered the tablet as a strict matrix without including the swelling parameters. Wan et al. (10) have demonstrated that hydroxypropylmethylcellulose (HPMC) matrices with ibuprofen (>10% w/w) follow a Higuchi-type release. These authors found that the constants obtained from the Higuchi drug release rate were inversely related to the swelling rate. Consequently, the swelling was expressed by these authors as an increase of the tablet thickness without considering the influence of polymer dissolution. Skoug et al. (19) and Sung et al. (20) have recently pointed out that the mechanistic information obtained using the Higuchi equation should be confirmed by the polymer release data because matrix dissolution is not taken into consideration in this model. When drug and polymer release (on a percentage basis) are superimposable, one may conclude that drug is released through a matrix dissolution mechanism. In contrast, when polymer release is slower than drug release, it can be concluded that diffusion contributes at least partially to drug release. In our case, this analysis supports the conclusion that *d*-pseudoephedrine hydrochloride is released primarily by diffusion of the drug throughout the gel layer.

CONCLUSIONS

The results indicate that diffusion through the gel layer was the controlling parameter for the release of the highly water-soluble model drug from PVAL matrices. This conclusion is based on the good correlation observed for the Higuchi model and by the data analysis using drug and polymer release profiles. Despite the significant polymer dissolution observed, in this case this parameter was not the key to explaining the drug release, but it is evident that it played a fundamental role in the swelling process, influencing the movement of the other fronts. Furthermore, the polymer dissolution data may be a useful tool to determine the release mechanism. Although the mechanism was apparently a simple diffusion-controlled release, the release process from swellable systems is related to the dynamics of complex swelling–polymer dissolution phenomena for which none of the parameters involved can be used alone for predicting drug release rates. In summary, the system proposed in this work is an interesting alternative for the simultaneous study (without tablet manipulation) of the parameters involved in the drug release of swellable matrices.

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