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Mechanisms of solute release from porous hydrophilic polymers

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Summary

Porous hydrophilic discs were prepared from two grades of poly(vinyl alcohol) of varying degree of hydrolysis. The influence of the molecular size of the tracer used (potassium chloride, phenylpropanolamine hydrochloride and bovine serum albumin), that of the addition of a second water-soluble polymer poly(N-vinyl-2-pyrrolidone) and poly(ethylene glycol)) and the effect of the tracer/excipient ratio on the release profile were examined. Finally the role of the dynamic swelling and the dissolution of the polymer matrix on the release mechanism are discussed.

Introduction

Porous hydrophilic polymeric systems have attracted considerable attention in recent years as sustained and controlled release devices for the delivery of water-soluble bioactive agents (Langer and Peppas, 1981). Of particular interest is the potential use of these systems as inexpensive devices for release of drugs at controlled, and perhaps time-independent, rates.

Several aspects of the mechanisms of solute release from non-porous, initially glassy, water-swellable polymer slabs have been discussed in recent work by Korsmeyer and Peppas (1981, 1982). Mathematical criteria have been established to aid in the evaluation of the mechanisms of solute release under various physical conditions. Controlled-release devices which function by release mechanisms which

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are dependent on the penetration of the solvent (e.g. water) have been termed 'swelling-controlled release systems' (Langer, 1980; Hopfenberg, 1981; Langer and Peppas, 1981).

Similar devices prepared by incorporation of model drugs or tracers in polymers to form porous, swellable release systems have been studied in recent years, although physical mechanisms of solute release and mathematical analysis of the release profiles are not as well understood as for the non-porous systems. Recent work has concentrated on analyzing the release profiles in terms of simple mathematical models (Salomon et al., 1979; Bamba et al., 1979a and b; Buri and Doelker, 1980; Peppas et al., 1980; Brossard et al., 1981, Carstensen et al., 1981). These studies have shown that release of water-soluble drugs from porous, swellable systems can be expressed by a variety of mathematical models which predict a square-root-of-time dependence of the fractional solute release over a wide range of release times, excluding the initial portion of the release profile (usually $M_t/M_\infty < 0.15$) and the late stage of solute release.

Of the several physical and mathematical models mentioned in this recent work, two models discuss the importance of the water penetration front and the associated swelling process of the porous polymer on the observed diffusional release (Bamba et al., 1979b; Peppas et al., 1980). However, improvements in modelling of solute release cannot be expected without careful characterization of the physical phenomena occurring during release.

When a drug-containing, porous polymer system, produced by compression of two solids in powder form is brought in contact with water, a series of mass transport phenomena occur. First, the pores near the surface of the matrix are filled by water and initial drug diffusion is controlled by the dissolution of the solute in the water-filled pores and by its continuous diffusion in water (Gurny et al., 1982). This type of unsteady diffusion for slabs that do not exhibit polymer swelling may be expressed by Eqn. 1, as discussed by Gurny et al. (1982) and Swan and Peppas (1981).

$$\frac{\partial c}{\partial t} = D_{eff}\frac{\partial^2 c}{\partial x^2} + k(c_s - c) \tag{1}$$

Here c_s is the solubility of the drug in the water-filled pores, k is the dissolution constant, and D_{eff} is the effective diffusivity in the pores, expressed according to Eqn. 2, where ϵ is the porosity (void fraction) of the system, τ is the tortuosity of the diffusional path, and D_{iw} is the diffusivity of the drug in water.

$$D_{eff} = D_{iw}\frac{\epsilon}{\tau} \tag{2}$$

However, when the slab is hydrophilic, progressive swelling of the polymer particles is observed, leading to considerable structural changes. These include change of the mobility of the macromolecular chains, macromolecular relaxations, and changes of the porous structure including alteration of the shape and size

distribution of the pores. These will change the porosity and tortuosity of the slab during swelling and diffusional release.

Finally, as swelling progresses, diffusion of the drug occurs both through the water-filled pores with diffusivity D_{iw}, and through the swollen polymer with diffusivity D_{ip}. The last parameter depends on the physical structure of the polymer and is affected by such properties as the cross-linking density and degree of crystallinity (Korsmeyer and Peppas, 1981) as well as the thermodynamic interactions between polymer and solute.

In the present investigation, poly(vinyl alcohol) (PVA) was chosen as the model polymer. PVA is glassy at room temperature, but readily undergoes glass-to-rubber transition at room temperature in the presence of water. The release behavior of different PVA-based formulations containing several different tracers and varying amounts of a third soluble polymeric component was investigated.

Materials and Methods

Materials

Two grades of PVA were employed: Elvanol 85-82 (DuPont de Nemours, Wilmington, DE, U.S.A.) with number average molecular weight $\overline{M}_n = 55{,}800$, polydispersity index $\overline{M}_w/\overline{M}_n = 2.14$, predominantly atactic, with degree of hydrolysis of 99.8%; and Polyviol W40/140 (Wacker-Chemie, F.R.G.) with $\overline{M}_n = 100{,}000$ polydispersity index $\overline{M}_w/\overline{M}_n = 1.60$ and degree of hydrolysis of 86–89%.

Other water-soluble polymers utilized as additives were poly(N-vinyl-2-pyrrolidone) (PNVP; Merck, Darmstadt, F.R.G.) with $\overline{M}_n = 25{,}000$–$30{,}000$ and poly(ethylene glycol) (PEG 4000, Fluka, Buchs, Switzerland) with $\overline{M}_n = 3500$–4000. Both polymers were much more readily soluble in water than either grade of PVA.

Water-soluble tracers used in these studies were potassium chloride (KCl, USP), phenylpropanolamine hydrochloride (PPA · HCl, USP), and bovine serum albumin (BSA; Cohn Fract. V, Serva Feinbiochimica, Heidelberg, F.R.G.; mol. wt. 69,000).

Diffusion / dissolution studies

Samples were prepared in the form of disks by direct compression of 500 mg of the powdered components of particle size 63–125 μm in a 15 mm acrylic die using a hydraulic press (Specac, Sidcup, U.K.) at a compression force of 50 kN corresponding to a pressure of 280 MPa. All disks were initially approximately 2 mm thick.

Single-face release experiments were performed at 37°C using the previously reported experimental procedure (Korsmeyer et al., 1982). The sample holder was immersed in 500 cm^3 of distilled water for experiments using KCl or 800 cm^3 artificial gastric juice (Ph. Helv. VI) for all other experiments. Agitation was provided and the concentration of drug in the dissolution medium was measured as a function of time. The concentration of KCl was determined by continuous conductivity measurements, as described before (Korsmeyer et al., in press), while the concentrations of PPA · HCl and BSA were determined by monitoring the UV absorbance of the dissolution medium at 256 nm and 276 nm, respectively.

Results and Discussion

Results of release experiments with 3 solutes of widely varying molecular size and solubility are presented here. The solute release data may be analyzed using Eqn. 3 and 4 where M_t/M_∞ is the fractional solute release, t is the release time, k is a kinetic constant characteristic of the drug/polymer system, A is the area of the sample, c_d is the tracer loading concentration and n is an exponent which characterizes the mechanism of release of the tracers.

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

$$\frac{dM_t}{Adt} = nc_d kt^{n-1} \tag{4}$$

Clearly, a desirable mechanism for many applications is that which leads to n = 1, which characterizes zero-order release behavior. Table 1 summarizes the general dependence of n on the diffusional mechanism (Langer and Peppas, 1981).

Here we present evidence of the influence of: (i) the molecular weight or molecular size of the tracer; (ii) the dynamic swelling and dissolution of the polymer matrix; and (iii) the combined characteristics of two hydrophilic polymers, on the overall diffusional release of a bioactive agent.

Influence of the size and water-solubility of the tracer

The effect of the molecular size and water-solubility of the diffusing species on the magnitude of the release rates and the type of diffusional release was studied using 3 agents, KCl, PPA · HCl and BSA released from the Elvanol and Polyviol systems. All studies are for initial composition of 50 wt.% PVA/50 wt.% tracer. The error bars represent standard error for 3 experiments.

The data from these experiments were fitted to Eqn. 3 and the results of this fitting are given in Table 2. As expected, the values of k correlate inversely with molecular weight. The values of the exponent of time, n, indicate that release of the smaller (high diffusivity) species (KCl) is at least partially controlled by viscoelastic

TABLE 1

ANALYSIS OF DIFFUSIONAL RELEASE MECHANISMS

Diffusional release exponent (n)	Overall solute diffusion mechanism	Time-dependence of solute release rate (dM_t/dt)
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous (non-Fickian) diffusion	t^{n-1}
1.0	Case II transport	zero-order (time-independent) release
$n > 1.0$	Super Case II transport	t^{n-1}

TABLE 2

FITTING OF SOLUTE RELEASE DATA OF PVA-BASED TABLETS TO EQN. 3

System	Kinetic constant, k (h^{-n})	Exponent (n)	r
KCl/Polyviol	0.229	0.600	0.9919
PPA/Polyviol	0.158	0.600	0.9995
PPA/Elvanol	0.136	0.558	0.9987
BSA/Elvanol	0.070	0.467	0.9880

relaxation of the matrix during solvent penetration. Release of BSA appears to be purely controlled by its low diffusivity in the gel layer formed as the tablet swells.

Effect of the water solubility of the polymer

PPA · HCl release profiles from two grades of PVA are compared in Fig. 1. The increasing scatter observed at long times for the Polyviol formulations is the result of a very slight erosion. This problem was not observed with tablets compounded from Elvanol 85-82. This effect may be attributed to the fact that Polyviol, due to its lower degree of hydrolysis (86–89% versus 99.8% for Elvanol) is more readily water-soluble than Elvanol (Finch, 1972). In general, the release from Polyviol systems was faster and nearly constant between 1 and 13 h, corresponding to $M_t/M_\infty = 0.6$.

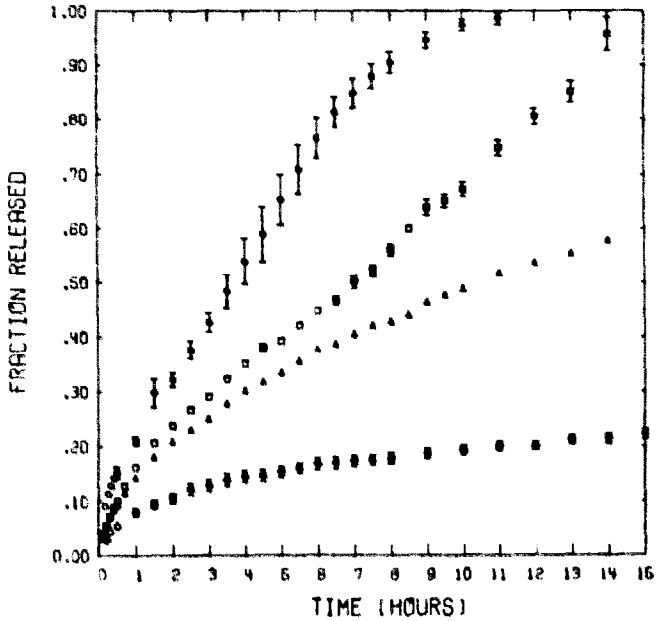


Fig. 1. Release of different agents from compressed PVA tablets: ○, KCl/Polyviol; □, PPA/Polyviol; △, PPA/Elvanol; ◇, BSA/Elvanol.

Influence of additional water-soluble polymer

Another method of influencing the solute release from hydrophilic swellable polymers is by replacing part of the original matrix by a second polymer which is freely soluble in water. The additives used were PNVP and PEG 4000.

The effect of adding varying amounts of PNVP to the formulation is shown in Fig. 2 for release of PPA · HCl from Elvanol-based formulations and in Fig. 3 for release of PPA · HCl from Polyviol-based tablets containing a more finely dispersed drug. The addition of PNVP was an effective method of increasing the release rate at longer times, but was limited by the unpredictable disintegration of tablets containing more than 15% PNVP (e.g. 25 wt.%). The effect of the disintegration is shown by the increasing size of the error bars after 2.5–3.0 h. The effect of PEG added to Elvanol tablets is shown in Fig. 4. The disintegration observed with PNVP was even more severe when the PNVP was replaced with PEG.

The release data from experiments in which no erosion was noticed could be fitted to Eqn. 3 for $M_t/M_\infty \leq 0.6$. The results of this fitting are presented in Table 3. It was observed that the kinetic constant for release, k, which incorporated the overall solute diffusion coefficient and geometric characteristics of the system increased with increasing total solubility of the matrix. However, the exponent, n, characteristic of the overall mechanism of solute release increased as the amount of water-soluble additive, PNVP, increased. This may be attributed to the fact that as the matrix swelled, the soluble additive was also removed by dissolution, thus decreasing the resistance of the gel layer to diffusion of drug. This resulted in a

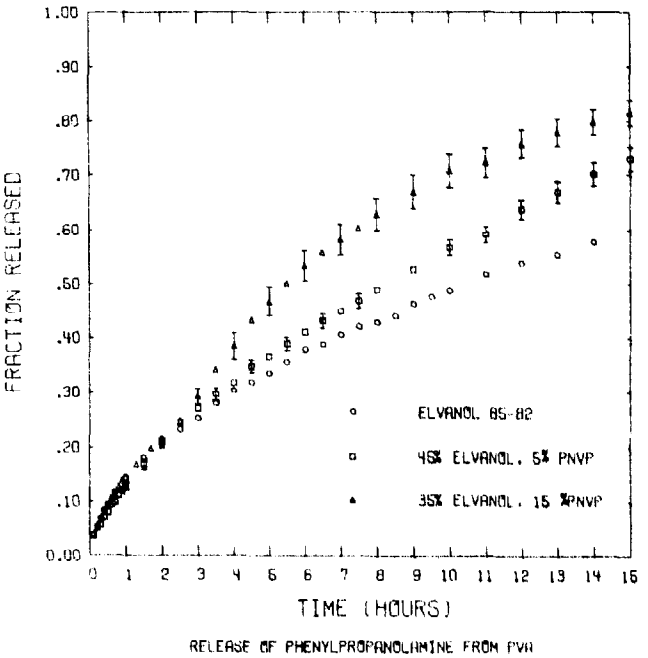


Fig. 2. Release of phenylpropanolamine from Elvanol/PNVP tablets: ○, 50% Elvanol; □, 45% Elvanol/5% PNVP; △, 35% Elvanol/15% PNVP.

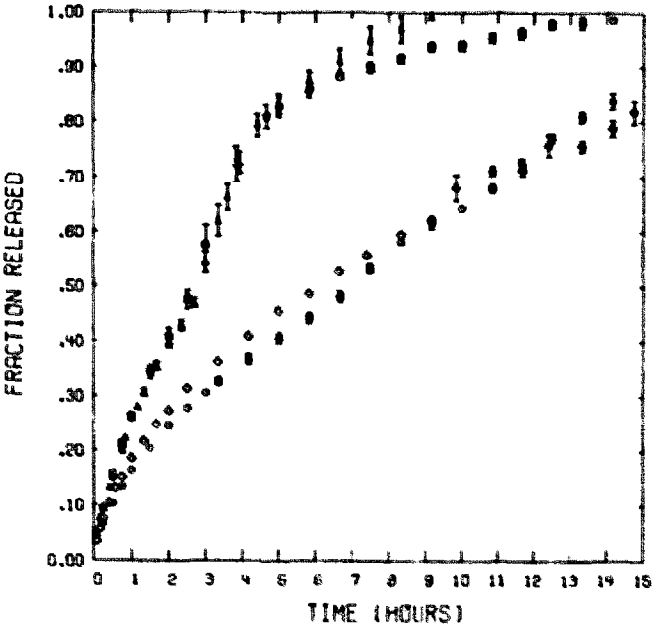


Fig. 3. Release of phenylpropanolamine from Polyviol/PNVP tablets: ○, 50% Polyviol; ◇, 35% Polyviol/15% PNVP; □ and △, 25% Polyviol/25% PNVP.

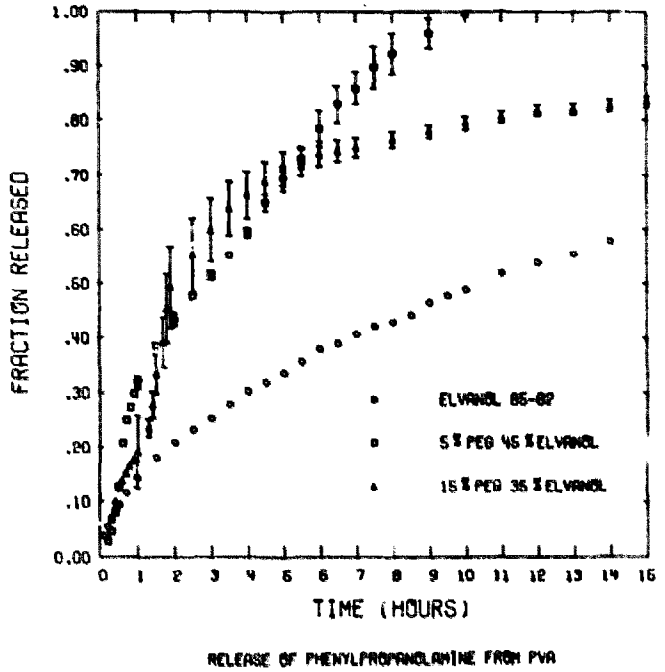
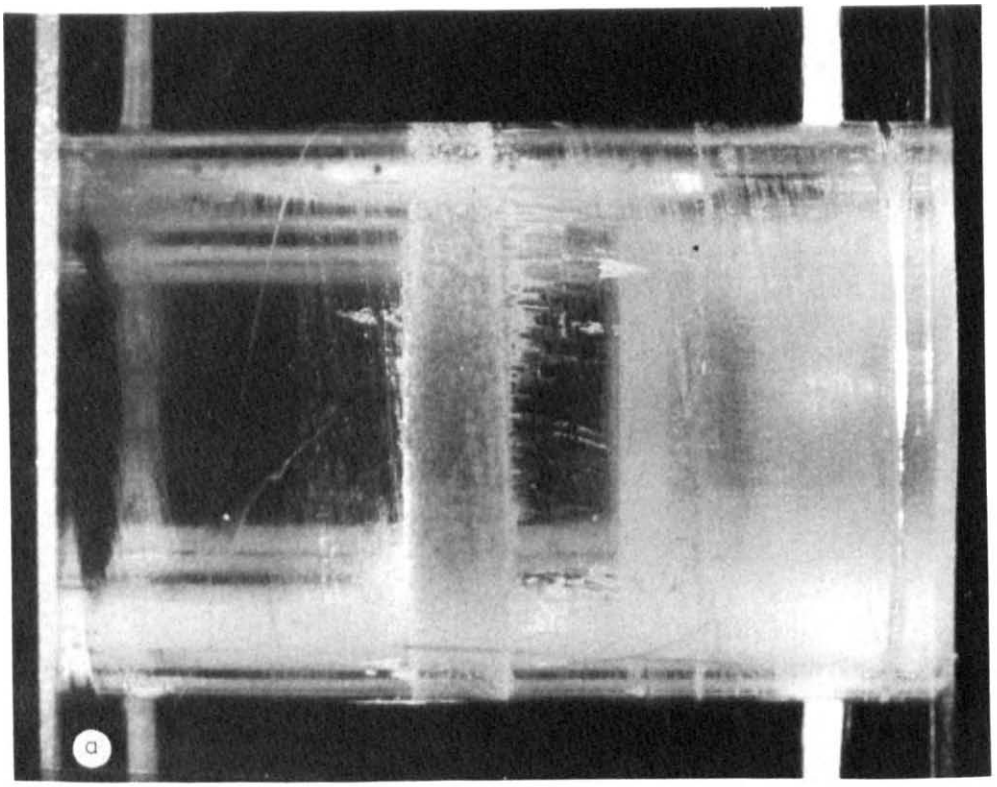


Fig. 4. Release of phenylpropanolamine from Elvanol/PEG tablets: ○, 50% Elvanol; □, 45% Elvanol/5% PEG; △, 35% Elvanol/15% PEG.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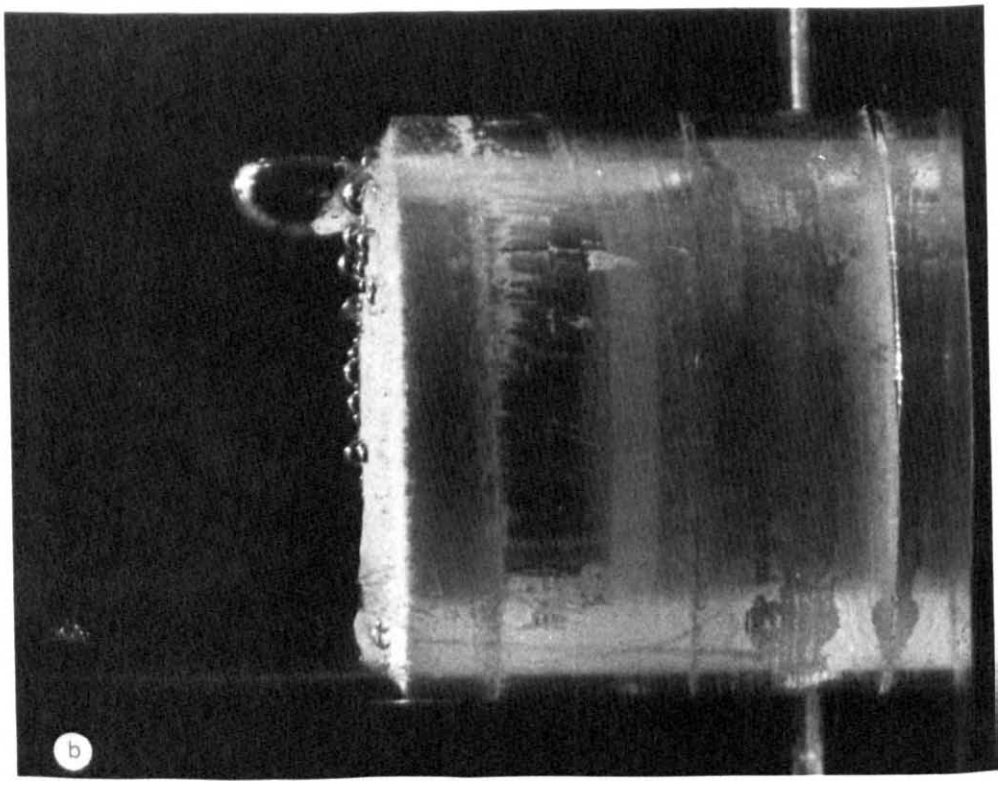
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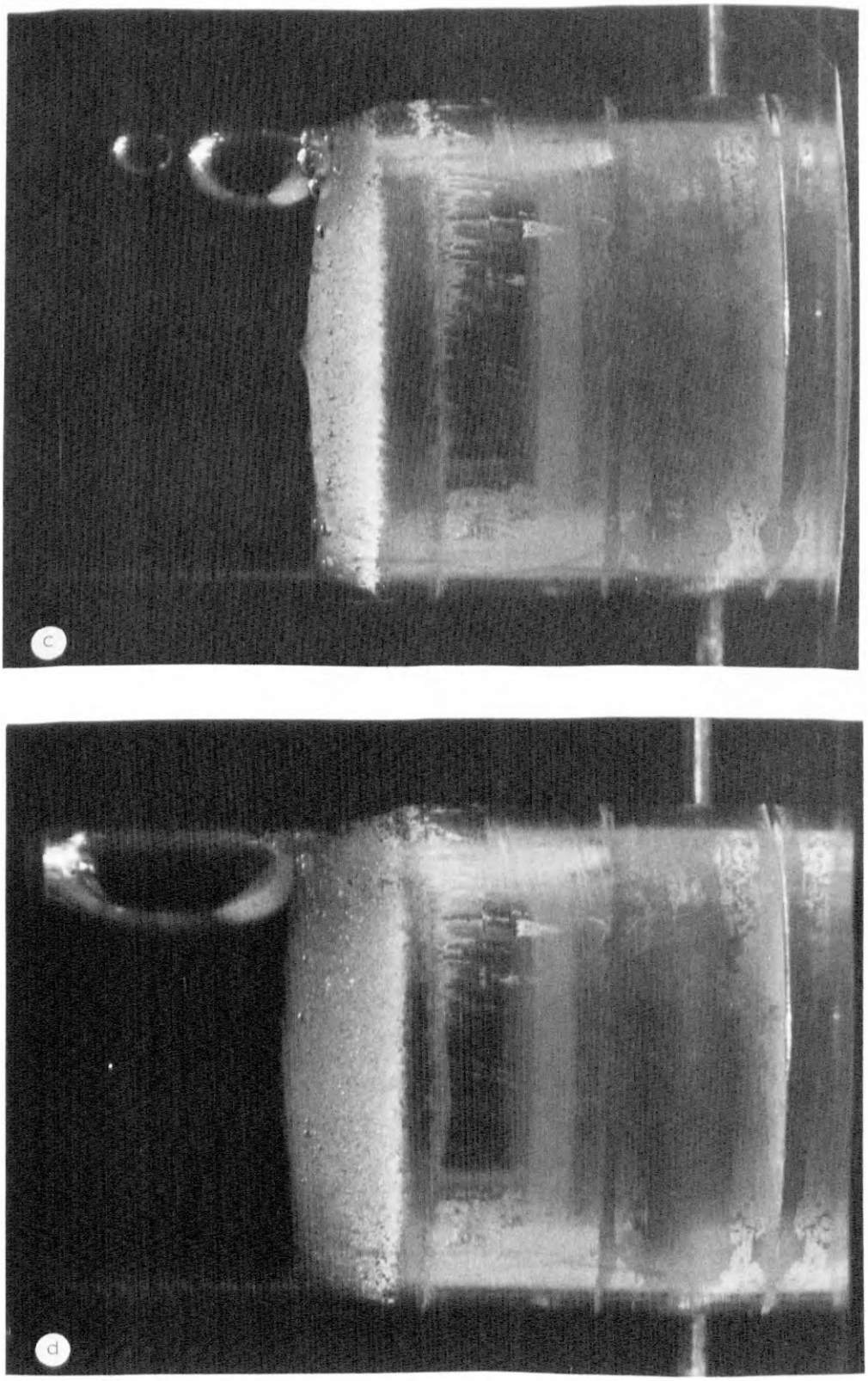

Fig. 5. Swelling of a typical tablet (50% Polyviol/50% PPA): (a) Before release; (b) 4 min; (c) 60 min; (d) 3.5 h. The tablet holder is sealed by a stopper on the right and the gel layer is forming on the left side of the tablet.

TABLE 3

FITTING OF SOLUTE RELEASE DATA OF ADDITIVE-CONTAINING SYSTEMS TO EQN. 3

System (wt.%)	Kinetic constant, k (h^{-n})	Exponent (n)	r
50% PPA·HCl/50% Elvanol	0.136	0.558	0.9987
50% PPA·HCl/5% PNVP/45% Elvanol	0.133	0.624	0.9981
50% PPA·HCl/15% PNVP/35% Elvanol	0.151	0.662	0.9957
50% PPA·HCl/50% Polyviol	0.158	0.600	0.9995
50% PPA·HCl/15% PNVP/35% Polyviol	0.174	0.604	0.9986
50% PPA·HCl*/25% PNVP/25% Polyviol	0.252	0.696	0.9993

* Average of 6 experiments. All other values are the average of 3 experiments.

release rate that decreased with time more slowly than for systems without added polymer. Swelling behavior of a typical formulation is illustrated in Fig. 5.

It might be expected that increasing the relative amount of drug in the formulations would have an effect similar to adding a very soluble polymer. This was not found to be the case with PPA · HCl release as shown in Fig. 6. Tablets prepared with 55 wt.% PPA · HCl and 45 wt.% PVA (Elvanol-grade) exhibited release profiles almost identical to the 50 wt.%/50 wt.% formulations. Tablets with 65 wt.% PPA · HCl disintegrated almost immediately, giving irreproducible release.

These findings suggest that the nature of the soluble fraction of the tablet is as

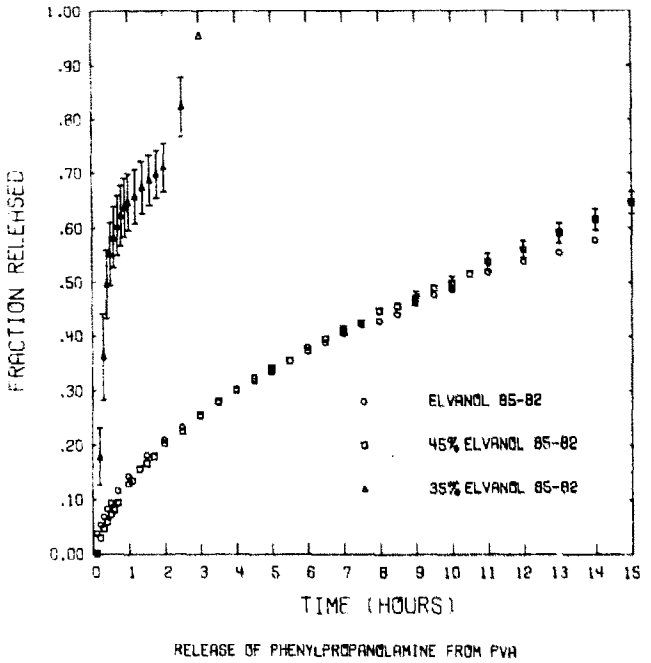

Fig. 6. Release of phenylpropanolamine from Elvanol tablets: ○, 50% Elvanol/50% PPA; □, 45% Elvanol/55% PPA; △, 35% Elvanol/65% PPA.

important a factor as the amount. When a macromolecular additive is used, the voids formed by dissolution initially contain a rather viscous solution, characteristic of dissolved polymers. The high viscosity in the pores serves to retard the diffusion of the drug at the early stages of release. At the later stages of release, the polymer solution becomes dissipated and resistance to diffusion is decreased. The net effect of this process is that the decrease in release rate, which is normally observed as the drug concentration in the tablet decreases, is reduced. If materials for the matrix and additive(s) are chosen carefully, it should be possible to balance the decrease in resistance with the decrease drug concentration, leading to drug/polymer systems which exhibit constant release at a desired rate.

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