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# Mechanisms of diphylline release from dual-solute loaded poly(vinyl alcohol) matrices

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ABSTRACT

The release kinetics of the model hydrophilic drug, diphylline (DPL), from physically crosslinked poly(vinyl alcohol) (PVA) matrices, is studied in relation to the drug load and the presence of a second solute incorporated in the matrix. The second solute, a gadolinium (III) complex (Gd-DTPA), is a commonly used MRI contrast agent. The water uptake kinetics by the glassy PVA matrix was found to deviate from $t^{1/2}$ law and to occur on time scales comparable to those of diphylline release. The corresponding rate of diphylline release was found to be substantially stabilized as compared to a purely diffusion-controlled release process, in line with theoretical predictions under conditions of relaxation-controlled water uptake kinetics. The release rate of DPL was found (i) to increase with increasing DPL load and (ii) for a particular DPL load, to increase in the presence of Gd-DTPA, incorporated in the matrix. The results were interpreted on the basis of the diphylline-induced plasticization of the polymer (evidenced by the depression of $T_g$) and of the excess hydration of the matrix at high solute loads. The latter effect was found to be additive in the case of dual-solute loaded matrices.



## 1. Introduction

Poly(vinyl alcohol) [PVA] is a low-toxicity biocompatible polymer, suitable for a wide range of biomedical applications including controlled release systems [1,2], arthroplasty [3] and tissue engineering [4]. As with other hydrophilic polymers, various methods are used for creating a three-dimensional polymer network in order to limit dissolution in water, to improve the mechanical properties and to modify the kinetics and equilibrium water uptake properties of the polymer as well as the drug release profiles. In comparison to chemically crosslinked networks [5,6], physically crosslinked ones, by heat treatment above the glass transition temperature or by repeated freezing–thawing cycles, have the advantage that their preparation is free from crosslinking agents [1,7,8].

Among the various biomedical applications of PVA are the matrix controlled release (MCR) systems [9–12]. In these systems the drug is incorporated in the polymer matrix and its release is activated by the ingress of water when the system is placed in an aqueous environment. The transport properties of water determine, to a great extent, the release profile of the drug and the uniformity of release rate, which is sought in most cases. Although other release patterns are desirable for specific applications (such as biphasic delivery of drugs with circadian rhythmic behavior; [13]) the achievement of a constant, or zero-order, release rate has been recently described by D.R. Paul as "the holy grail of controlled release technology" [14]. Conditions that favor an approach to uniform rate of release include the case of relaxation-controlled water uptake by a stiff polymer matrix (a more detailed discussion is given in the next section). PVA, being a glassy polymer in the dry state, falls in this category [15,8].

In recent years, there has been increasing interest in incorporating more than one bioactive substance in drug delivery systems of various forms, for simultaneous or sequential delivery [16–19]. In addition, doping polymeric drug delivery systems with MRI contrast agents has been proposed as a method for simultaneous imaging and therapy [20,21]. In the design of such practical dual-solute loaded systems, the possible effect of each one of the solutes on the release profile of the other should be taken into account.

The objective of the present work is to study a dual-solute loaded MCR system based on heat-treated PVA, focusing on the mechanisms that control the release kinetics of a model hydrophilic drug [diphylline (DPL)], in the presence of a second solute incorporated in the matrix. The second solute, a gadolinium complex, Gd-DTPA, is a commonly used MRI contrast agent [22,23]. The water uptake kinetics from PVA matrices subjected to the particular heat-treatment protocol applied here, has been previously shown to be partly relaxation-controlled [8], thus favoring, in principle, a relatively stable rate of drug release [15]. To gain insight on the release process, PVA matrices solely loaded with various amounts of diphylline were subjected to release kinetic experiments, during the course of which, the variation of the amount of water imbibed by the matrix, was also monitored. The release behavior of diphylline, in the absence and in the presence of the second solute,

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was supplemented by DSC studies on the effect of various loads of diphylline and/or Gd-DTPA on the thermal properties of the polymer.

Before proceeding to the experimental results, we considered it useful to present in the following section certain theoretical calculations on release kinetics from matrix systems relevant to those studied here, to serve as a basis for evaluating and interpreting the experimental data.

## 2. Solute release kinetics from model matrix systems

The calculated release kinetics presented in this section, demonstrating cases relevant to the experimental systems studied here, are based on a model simulating the performance of the MCR devices, under a broad range of experimental conditions [24,25]. Presentation of the mathematical formulation of the model is out of the scope of the present work. However, the interested reader can find details on model parameters used for calculating the curves of Fig. 1 in the cited references of the caption of this figure. In Fig. 1a and c, release kinetics are presented in the form of fractional amount of solute released at time $t$, $Q_{Nt}/Q_{N\infty}$, together with the concurrent fractional water uptake ($Q_{Wt}/Q_{W\infty}$) kinetics, from matrices in the form of a thin film of thickness $2L$. The time scale in these plots is the square root of a dimensionless time $\tau = tD_W/L^2$, where $D_W$ is the diffusion coefficient of water. In the present work, the data of Fig. 1a and c have been used to calculate the corresponding rates of release ($d(Q_{Nt}/Q_{N\infty})/d\tau$), which are plotted vs. $Q_{Nt}/Q_{N\infty}$, in Fig. 1b and d, respectively. Release rates are plotted here vs. $Q_{Nt}/Q_{N\infty}$ rather than vs. time, as this form of presentation permits the comparative assessment of different MCR devices, in terms of the fractional amount of solute, which can be released within the acceptable dose rate limits [26].

The simplest conditions of operation of an MCR device apply to a solute of effective diffusivity much lower than that of the solvent (water), so that solute transport to the external phase occurs by diffusion through the fully swollen matrix. The relevant kinetics of release is governed by Fick or by Higuchi equations depending on the state of solute in the matrix. Fick kinetics applies to a solute load, $C_{N0}$, lower or equal to the limit of solubility of the solute in the hydrated matrix, $C^o_{NS}$ (unsaturated or saturated matrix, solute in the "dissolved state" and fully mobile). Higuchi kinetics [27] applies to matrices loaded to $C_{N0} \gg C^o_{NS}$ (supersaturated matrix, where part of the solute load is immobilized). Early time release kinetics is given by Eqs. (1) and (2) for Fickian or Higuchi kinetics, respectively

$$\frac{Q_{Nt}}{Q_{N\infty}} = 2\left(\frac{D_N t}{\pi L^2}\right)^{1/2} \tag{1}$$

$$\frac{Q_{Nt}}{Q_{N\infty}} = \left(\frac{2D_N C^o_{NS}(1-C^o_{NS}/2C_{N0})t}{L^2 C_{N0}}\right)^{1/2} \approx \left(\frac{2D_N C^o_{NS} t}{L^2 C_{N0}}\right)^{1/2} \tag{2}$$

where $D_N$ is the diffusivity of the dissolved (mobile) solute in the fully swollen matrix.

Eqs. (1) and (2) with $D_N$ = const. hold for thermodynamically ideal systems, and fast water penetration. In addition, Eq. (2) is derived assuming that (a) the presence of dispersed solute has no material effect on the transport properties of the matrix, and (b) instantaneous

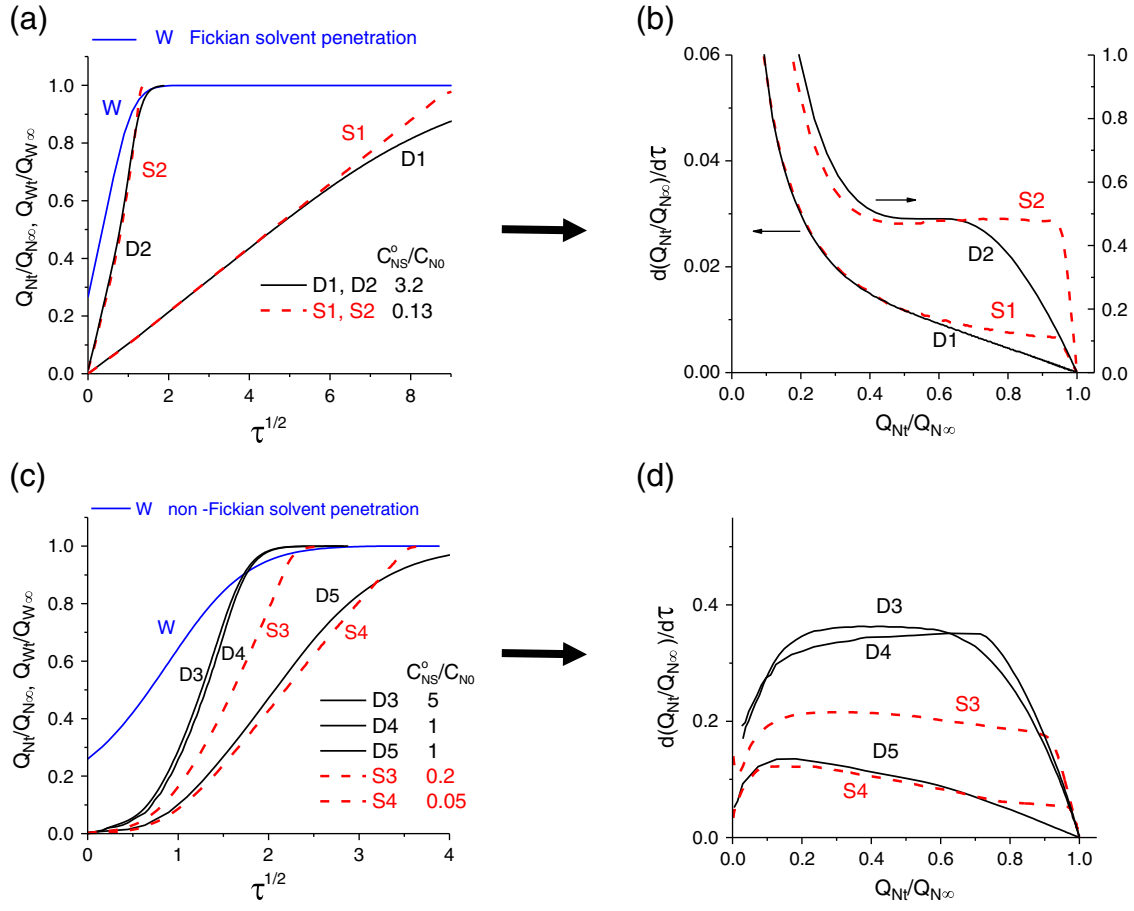


**Fig. 1.** Calculated results for solute release, and concurrent water uptake, kinetics (Fig. 1a, c) and the corresponding rates of release (Fig. 1b, d), under conditions of fast solvent penetration or comparable rates of solvent and solute transport. Water transport (curve W) follows Fickian kinetics in Fig. 1a and is partly relaxation-controlled in Fig. 1c (characterized by $\beta_W D_W/L^2 = 1$). Curves D1–D5 (solid lines) refer to solute load $C_{N0}$ lower or equal to the solubility limit $C^o_{NS}$ and curves S1–S4 (dashed lines) to supersaturated matrices with $C_{N0} \gg C^o_{NS}$. The data of Fig. 1a are taken from [26] (curves 1–4 of Fig. 2 therein). The data of Fig. 1c are taken from [25] (curves B1–B4 of Fig. 6 therein and curve B3 of Fig. 5 therein).