International Journal of Pharmaceutics, 30 (1986) 29–33
Elsevier

IJP 00994

The simultaneous degradation and sorption of diltiazem in aqueous solution

S.S. Davis [1], L. Illum [2], I.M. Triccas [1] and K.N. Winchcomb [1]

[1] *Pharmacy Department, University of Nottingham, Nottingham NG7 2RD (U.K.) and* [2] *Department of Pharmaceutics, Royal Danish School of Pharmacy, DK-2100 Copenhagen (Denmark)*

(Received November 22nd, 1985)
(Accepted December 5th, 1985)

Key words: diltiazem – degradation – sorption – plastic (PVC) container

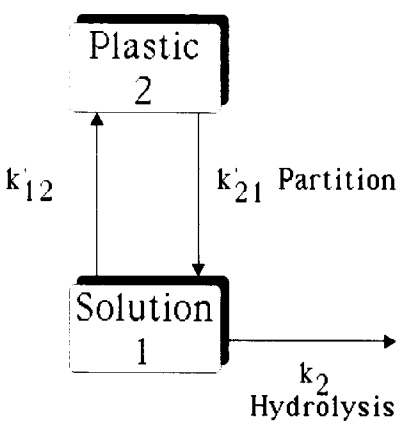
Summary

The disappearance of diltiazem from a solution stored in a plastic (PVC) container at a pH above 8 can be described by a simultaneous process of degradation (hydrolysis) and sorption. The appropriate rate and equilibrium constants can be derived from concentration versus time profiles using a two-compartment kinetic model. At pH 7 the disappearance of diltiazem from solution is dominated by the sorption process even at longer times while at higher pH values the degradation effect becomes more important. At pH 10 the process of degradation is rapid and the measured loss due to sorption is attributed largely to adsorption.

Introduction

In a previous publication, Illum et al. (1983) used a constant partition model for examining the sorption of drugs by plastic infusion bags. The sorption of two weak acids (warfarin and thiopentone) and two weak bases (chlorpromazine and diltiazem) into PVC containers was well described by a constant partition model. Sorption versus pH data were compared with partition data derived using liquid–liquid partition systems employing organic solvents such as octanol, dichloromethane and carbon tetrachloride. Octanol was found to be the preferred reference solvent and it was suggested that octanol–water partition data could be used to predict sorption behaviour.

Diltiazem is a calcium channel blocker that demonstrates significant instability at alkaline pH. The compound is hydrolyzed to the deacetyl form. Consequently in sorption experiments conducted at pH 8.0 and above, simultaneous degradation



Scheme 1. Model for simultaneous sorption (partition) and degradation.

Correspondence: S.S. Davis, Pharmacy Department, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

and partition will affect both the sorption kinetics and the amount taken up by the plastic container. Simultaneous degradation and partition can be described by a simple kinetic model (Scheme 1) (Byron et al., 1980; Tomlinson et al., 1980). This paper shows how such a model can be used to follow the sorption and degradation of diltiazem in aqueous solution.

Materials and Methods

Materials

Diltiazem (pK_a 7.7) was a gift from LERS/Synthelabo. Plastic infusion bags (Viaflex) were made from polyvinylchloride (PVC) and provided by Travenol Laboratories. Buffer substances and all other chemicals or solvents were of reagent grade.

Stability studies

The stability of diltiazem in aqueous solution was measured at different pH values using appropriate buffer solutions (Clark and Lubb's buffers) at 25.0 ± 0.5°C. Initial diltiazem concentrations of 100 $\mu g \cdot ml^{-1}$ were used and the degradation was followed over an appropriate time period (to give greater than 50% degradation) using a stability indicating HPLC method that separated diltiazem from the desacetyl degradation product. Chromatographic separation was performed on a Spherisorb ODS column using a Cecil HPLC system. The mobile phase was acetonitrile (55%), McIlvaines buffer pH 2.4 (40%) and methanol (5%) and detection was by UV spectroscopy at a wavelength of 246 nm.

Stability and sorption studies

The stability studies described above were repeated in the presence of plastic (PVC) strips (10 g plastic/250 ml of buffer solution). Control experiments were also conducted using 10 ml of 1-octanol per 250 ml of buffer solution.

Data analysis

Disappearance kinetics data were analyzed by non-linear regression analysis methods (Yamaoka et al., 1981).

Results and Discussion

Diltiazem stability

Diltiazem was hydrolyzed to the desacetyl derivative by a pseudo-first-order process. Plots of amount remaining versus time on semi-logarithmic scale were linear (Fig. 1). The rate constants for degradation (k_2) derived from linear regression analysis of such plots are given in Table 1 and are plotted against pH in Fig. 2. Above pH 7 the gradient of the log k_2 versus pH plot is approximately unity indicating general base catalysis. Included in Fig. 2 are data obtained elsewhere (Lewis, 1983) for the stability of diltiazem. The plotted values have been predicted from data obtained at elevated temperatures (40–60°C) assuming that the activation energy (71.0 $kJ \cdot mol^{-1}$) was constant with change in pH. The agreement is quite reasonable.

Stability and sorption

In the presence of strips of PVC (or octanol) the disappearance kinetics for diltiazem are altered. The plot on a semi-logarithmic scale is no longer linear (Fig. 1) and reflects the simultaneous processes of degradation and sorption as depicted in Scheme 1.

The data for octanol shown in Fig. 1 can be analyzed to provide an estimate for the octanol–water partition coefficient of diltiazem.

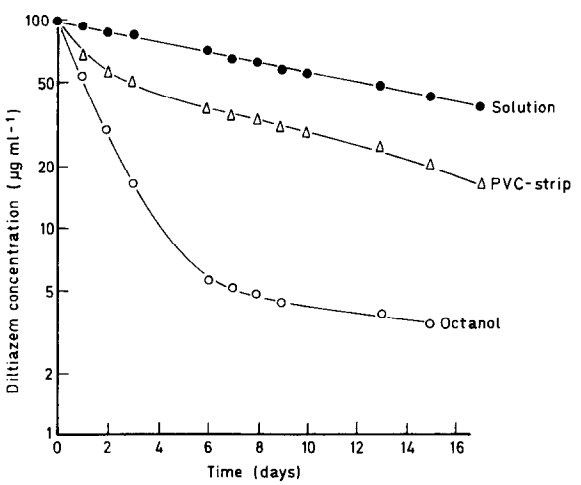


Fig. 1. Disappearance–time profile for diltiazem at 25°C. ●, solution; △, added PVC strips; ○, added octanol.

TABLE 1

RATE AND EQUILIBRIUM CONSTANTS FOR THE DEGRADATION AND PARTITIONING OF DILTIAZEM AT 25.0°C

pH	k_2 measured (min^{-1})	Rate constants from Eqn 2 (min^{-1})			$K_d = k'_{12}/k'_{21}$	log K_d unionized
		k_2	k'_{12}	k'_{21}		
7.05	9.6×10^{-6}	1.5×10^{-5}	1.6×10^{-5}	7.5×10^{-5}	0.21	1.35
8.04	3.9×10^{-5}	3.7×10^{-5}	1.6×10^{-4}	1.3×10^{-4}	1.23	1.66
9.12	4.2×10^{-4}	2.2×10^{-4}	2.2×10^{-3}	1.6×10^{-3}	1.40	1.56
10.17	2.4×10^{-3}	2.1×10^{-3}	8.8×10^{-3}	2.8×10^{-2}	0.31	(0.31)
						Mean 1.54

At 10 days we can assume a pseudo-equilibrium situation such that the partition coefficient (K_d) can be written as:

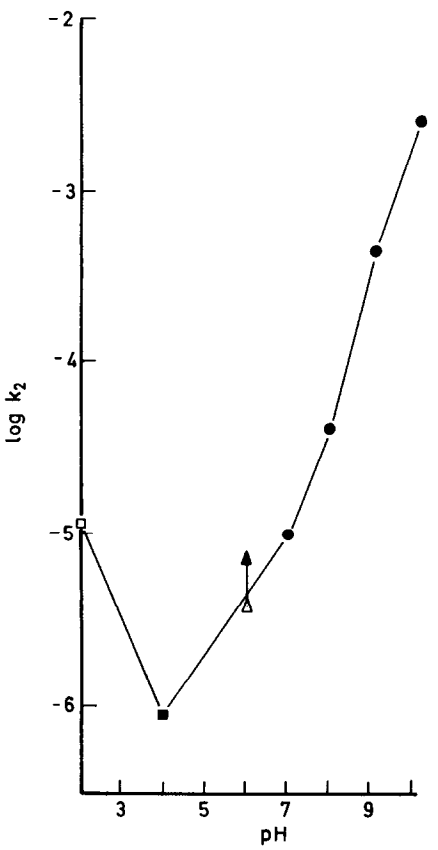


Fig. 2. pH–stability profile for diltiazem at 25°C. ●, Present work [predicted from elevated temperature studies (Lewis, 1983)]; ■, 40–60°C Arrhenius plot (McIlvaines buffer); □, 60°C (HCl/KCl); △, 50°C McIlvaines buffer; ▲, 60°C McIlvaines buffer; (E_a = 71.0 kJ·mol^{-1}).

$$K_d = \frac{(C^0_{aq} - C_{aq} + C_{deg})V_{aq}}{C_{aq} \cdot V_d} \quad (1)$$

where C^0_{aq} is the original diltiazem concentration, C_{aq} is the aqueous phase concentration at 10 days, C_{deg} is the amount of diltiazem lost by degradation at 10 days, V_{aq} the volume of the aqueous phase and V_d the volume of the octanol phase.

K_d at 10 days at pH = 8.04 was found to be 283 which, when corrected for ionization (diltiazem pK_a = 7.7) gives a K_d value for the unionized base of 442 and log K_d = 2.65. Illum et al. (1983) have reported log K_d (diltiazem base) = 2.70 and a value of 2.67 can be calculated from the value obtained at pH 7.4 by Ochs and Knuchel (1984).

Partitioning kinetics with simultaneous irreversible loss of solute can be described by a bioexponential equation of the form (Byron et al., 1980)

$$C_{aq} = X' e^{-\alpha t} + Y' e^{-\beta t} \quad (2)$$

where

$$X' = C^0_{aq}(\alpha - k'_{21})/(\alpha - \beta)$$

$$Y' = C^0_{aq}(k'_{21} - \beta)/(\alpha - \beta)$$

$$\alpha = 0.5\left(k_3 + \sqrt{k_3^2 - 4k'_{21}k_2}\right)$$

$$\beta = 0.5\left(k_3 - \sqrt{k_3^2 - 4k'_{21}k_2}\right)$$

and

$$k_3 = k'_{12} + k'_{21} + k_2$$

where C_{aq}^{0} is the initial aqueous phase concentration.

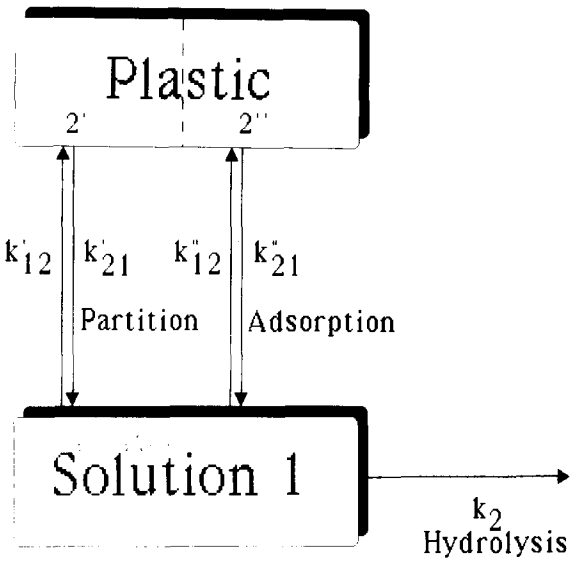
The partition coefficient (K_d) can be written in terms of the forward and reverse rate constants

$$K_d = \frac{k'_{12}}{k'_{21}} \quad (3)$$

The rate constants k'_{12}, k'_{21} and k_2 can be derived by graphical or iterative procedures (Notari, 1980). The values given in Table 1 were obtained by non-linear regression analysis. The derived values of k_2 agree quite well with those obtained by experiments on the stability of diltiazem solutions. The values of k'_{12} and k'_{21} are highly dependent on pH. The ratio k'_{12}/k'_{21} is the apparent partition coefficient which can be corrected for volume of the plastic and aqueous phases and degree of ionization to give a value of log K_d for the unionized diltiazem base. The values of log K_d obtained at pH's 7.05, 8.0 and 9.12 are in reasonable agreement and they give a mean of 1.54 which is very close to that reported previously by Illum et al. (1983) for the partition of diltiazem into plastic strips at pH values where degradation would be negligible (log K_d = 1.5).

The value of K_d obtained at pH 10.17 is much lower than for the values obtained at lower pH values and this suggests that the simple model described in Scheme 1 may not be valid at high pH as will be discussed below.

The change in the forward and reverse rate constants with pH can be discussed in terms of the known relationship between kinetics of partitioning and partition coefficient and the role of unstirred layers. de Haan and others (1983) have shown, using simple two-phase systems that log k'_{12} will increase linearly with log K_d when the process of partition is controlled by the non-aqueous phase. However, when K_d becomes larger (for octanol–water systems log K_d greater than about 1.5), k'_{12} becomes independent of K_d when the controlling process is one of diffusion through the unstirred aqueous layer between aqueous and organic phases. Clearly in the present work for the partition of diltiazem into PVC strips the partitioning process is controlled by the plastic phase and k'_{12} increases with increase in K_d.



Scheme 2. Modified model for simultaneous partition, adsorption and degradation.

The data derived at pH 10 suggest that the simple model for simultaneous degradation and partitioning may not be correct when the drug is degrading rapidly (half life = 400 min). Indeed one would have expected that the disappearance due to partitioning would have been small compared to loss due to degradation. We believe that the measured loss due to sorption at pH 10 is largely due to adsorption to the surface of the plastic. The kinetic model is therefore better described by three compartments rather than two where the plastic compartment of the model comprises adsorption and absorption (partition) (Scheme 2).

The adsorption process will be rapid but of limited capacity, while the partition process will be much slower but of much greater capacity. Thus the derived rate constants in Table 1 are a composite of adsorption and partition. The data derived at pH values 7–9 over extended time scales (days) reflect largely the partition process whereas the data obtained at pH 10, obtained over 7 h, reflect largely adsorption. The model in Scheme 2 can be represented by a tri-exponential equation of the form

$$C_{aq} = X' e^{-\alpha t} + Y' e^{-\beta t} + Z' e^{-\gamma t} \quad (4)$$

TABLE 2

RELATIVE CONTRIBUTIONS TO SORPTION AND DEGRADATION OF DILTIAZEM AT 25°C

pH	Percentage loss											
	Time 5 h				24 h				8 days			
	Total	Degn.	Sorp.	s/d	Total	Degn.	Sorp.	s/d	Total	Degn.	Sorp.	s/d
7.05					8	2	6	3.0	29	11	18	1.6
8.04					26	7	19	2.7	65	37	28	0.75
9.12	32	10	22	2.2	60	38	22	0.56				
10.17	66	49	17	0.35								

s/d = ratio of degradation to sorption.

where X′, Y′, Z′ and α, β and γ can be expressed in terms of the various microconstants.

Such tri-exponential equations for three-compartment models have been described in pharmacokinetic studies but are tedious to use and require collection of many data points.

The contribution that degradation will make to the loss of diltiazem contained in a plastic infusion container can now be better defined. As an illustration, Table 2 provides values for total loss and the relative contributions from the two competitive processes. At pH 7 sorption dominates even at longer times. However, as the pH rises the degradation effect becomes more important.

Illum et al. (1983) presented data for the sorption of diltiazem into plastic bags (Viaflex 100 ml nominal capacity) for a range of pH values. Above pH 8 the reported values were uncertain because of the degradation of diltiazem. We can now present the corrected sorption profile for diltiazem using a value of 14.0 ml for the volume of plastic (Fig. 3).

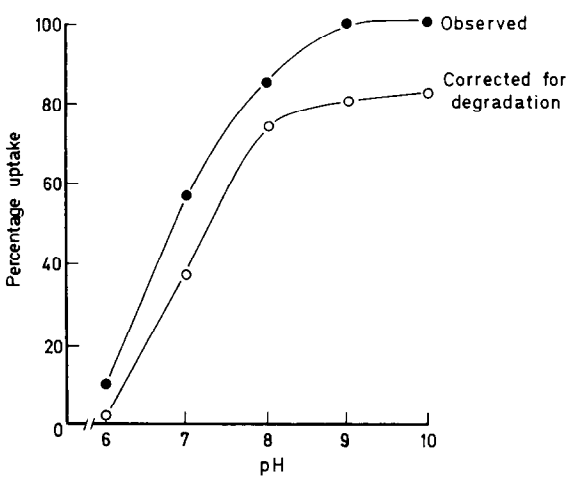


Fig. 3. pH–sorption profile for diltiazem (8 days storage at 25°C). ■, observed values (Illum et al., 1983); ●, corrected for degradation.

Acknowledgements

The authors wish to thank Dr. N. Farraj and Dr. E.S. Johansen for assistance with the non-linear regression analysis, and Dr. G.A. Lewis for providing data on the stability of diltiazem.

References

Byron, P.R., Notari, R.E. and Tomlinson, E., Calculation of partition coefficient of an unstable compound using kinetic methods. J. Pharm. Sci., 69 (1980) 527–531.

de Haan, F.H.N., de Vringer, T., Van de Waterbeemd, J.T.M. and Jansen, A.C.A., Transport rate constants and transport rate parameters in various organic solvent–water systems. Int. J. Pharm., 13 (1983) 75–87.

Illum, L., Bundgaard, H. and Davis, S.S., A constant partition model for examining the sorption of drugs by plastic infusion bags. Int. J. Pharm., 17 (1983) 183–192.

Lewis, C.A., personal communication (1983).

Notari, R.E., Biopharmaceutics and Clinical Pharmacokinetics, 3rd edn., Dekker, New York, 1980, pp. 20–25.

Ochs, H.R. and Knuchel, M., Pharmacokinetics and absolute bioavailability of diltiazem in humans. Klin. Wochenschr., 62 (1984) 303–306.

Tomlinson, E., Notari, R.E. and Byron, P.R., Simultaneous partitioning and hydrolysis kinetics of amoxicillin and ampicillin. J. Pharm. Sci., 69 (1980) 655–658.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn., 4 (1981) 879–885.