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Quantitative structure-transportability relationship for the release of a series of substituted pyridines from a planar polydimethylsiloxane matrix

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Summary

The release of 10 substituted pyridines into water, loaded at their solubility limit in a silica-filled polydimethylsiloxane planar matrix, was studied using a quantitative structure-transportability relationship (QSTR) approach. Compounds contained seven different functional groups and a wide range of solubility in both water and the polymer matrix. Release was matrix diffusion controlled with initial release following the square root of time relationship. The release coefficients (slopes of the linear Q vs $\sqrt{t}$ plots) were found to be significantly related to structural characteristics of the pyridines. Hydrogen bonding between the pyridines and polymer matrix was found to be one of the factors governing the release rate. Using multiple linear regression, the release coefficients are described by a simple equation involving only the pyridine melting point and the hydrogen bonding parameter. Thus, the release rates of pyridines loaded at their solubility limit can be estimated using easily accessible physico-chemical properties by a QSTR approach without using the actual solubility and diffusion coefficient in the matrix.

Introduction

Drug release from polymer matrices has been a widely studied area in the field of the controlled release of pharmaceuticals. Polydimethylsiloxane (PDMS) has been one of the most commonly used materials for drug delivery (Folkman and Long, 1964; Dziuk and Cook, 1966; Roseman and Yalkowsky, 1976; Golomb et al., 1987, 1990).

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Mathematical expressions have been derived for diffusionally controlled release of drug from planar matrices with an initial concentration less than or equal to their matrix solubility. These include complicated exact solutions (Higuchi, 1960; Crank and Park, 1968) as well as a simplified short time approximation (Higuchi, 1962). Both forms involve the initial concentration distribution and diffusion coefficient, the determination of which is difficult. Thus, direct application of the exact solution expressions and the short time approximation for quick preformulation estimation of release rates is limited due to the

unknown concentration distribution and diffusion coefficient of a particular drug in a particular matrix.

Diffusion coefficient can be estimated by the Stokes-Einstein equation and other empirical approaches in a liquid phase (Cussler, 1984). There is no universally acceptable method for its estimation in a polymer. Different approaches for estimating diffusion coefficient have been summarized (Pitt et al., 1987), but their applicability remains to be tested. PDMS matrix, used in drug delivery, is crosslinked and often contains silica filler to increase mechanical strength, resulting in a more complicated situation for the estimation of diffusion coefficient.

In aqueous solutions, the solubility of a large number of compounds have been estimated using entropy of fusion, melting point and partition coefficient (Yalkowsky and Valvani, 1980), fragmental constants (Wakita, 1986), and other approaches (Yalkowsky and Banerjee, 1992). Solubility of *p*-aminobenzoates in water was correlated with alkyl chain length, but the relationship was not applicable to silicone oil (Yalkowsky et al., 1972). Estimation of solubility in a crosslinked polymer matrix is a more complicated situation. While a theoretical approach is yet to be developed, empirical methods using melting points were used to describe the solubility of steroids in polymers (Chien, 1976; Lee et al., 1985).

It has been shown that the maximum steady state flux of a series of substituted benzenes through PDMS membrane can be estimated using a quantitative structure-activity relationship approach without employing diffusion coefficient and concentration distribution in the membrane (Matheson et al., 1991; Moeckly and Matheson, 1991). The flux of alkyl *p*-aminobenzoate ester has been related to the alkyl chain length (Flynn and Yalkowsky, 1972). Permeabilities of steroids in different polymers were found linearly related to the steroid melting temperature (Michaels et al., 1975). Solubilities of steroids in poly(ether urethane) were also found related to steroid melting points as were their permeabilities (Lee et al., 1985). Based on these results, it appeared that some structural relationship existed for quantifying drug release from a polymeric matrix when the drug is loaded at its solubility limit, since release is also governed by a diffusional process.

The purpose of this study is to relate the in vitro release rates of a series of substituted pyridines from a planar PDMS matrix to their molecular structure by the establishment of a

TABLE 1

Physical parameters of substituted pyridines and their release coefficients

Compound	Mol.Wt	mp [a]	ΣHB (J/mol) [b]	Solubility in PDMS (μmol cm^{-3})	k [c] (μmol cm^{-2} min$^{-1/2}$)
2-Amino-4-methylpyridine	108.14	96	8400	108.79	0.290
3,5-Dichloropyridine	147.9	65	800	381.41	3.773
2-Pyridinecarboxylic acid	123.1	136	10000	17.81	0.046
3-Hydroxypyridine	95.10	126	20000	31.91	0.032
2-Hydroxy-5-nitropyridine	140.10	186	21500	3.70	0.004
2-Methoxy-5-nitropyridine	154.13	108	4500	37.22	0.400
2-Amino-5-nitropyridine	139.11	186	9900	6.34	0.013
2-Amino-4,6-dimethylpyridine	122.17	63	8400	127.32	0.506
2-Aminopyridine	94.12	59	8400	149.64	0.819
2-Hydroxypyridine	95.10	105	20000	67.11	0.052

[a] Obtained from manufacturer.
[b] Obtained from Barton (1983).
[c] Experimental results.

quantitative structure-transportability relationship. This model can be used to predict release rates using easily accessible physico-chemical properties, such as melting point and hydrogen bonding parameters. The structural relationship approach can also help to better understand the nature of mass transport in a matrix at the molecular level and to serve as a guide for formulation development.

Materials and Methods

Materials

The 10 substituted pyridines are listed in Table 1. 2-Amino-4-methylpyridine was obtained from Fluka Chemie AG, Buchs, Switzerland. The other compounds were obtained from Aldrich Chemical Co., Milwaukee, WI and all were used as received. The PDMS matrix at thicknesses of 0.102 and 0.152 cm was Silastic® sheeting, Medical Grade NRV, supported with silica filler. It was obtained from Dow Corning Corp., Midland, MI.

Equipment

The apparatus used for the in vitro release measurement was a modification of that used for the flux study (Moeckly and Matheson, 1991) described earlier. The diffusion cell was modified by placing two pieces of stainless-steel tubes (0.82 mm o.d. by 3.6 cm) in a cross-hair pattern on either side of the loaded matrix in order to hold it in place between two magnetic stirrers during the release experiment.

Experimental procedures

Solubility in PDMS matrix A 3 cm disc was punched out of the PDMS sheeting, using a stainless steel borer (Medical Instruments, University of Iowa, Iowa City, IA). The disc was soaked in isopropyl alcohol (IPA) at 30°C for at least 24 h to remove any leachable interfering materials. After drying at 50°C for 48 h in a oven (Thelco®, Model 19, Precision Scientific Co., Chicago, IL) to constant weight, the thickness of the disc was measured using a micrometer (Craftsman Commercial, Sears & Roebuck, Chicago, IL) in order to calculate the volume of the disc. The disc was then sealed in a 50 ml round bottom flask containing the saturated aqueous solution plus excess solid of a given pyridine. The flask was equilibrated in a 30°C water bath and rotated for one week using a sustained release apparatus (Vanderkamp, Model 103906, Vankel Industries, Inc., Edison, NJ). The disc was removed and quickly rinsed with water to remove surface drug. It was then soaked, first in 200 ml of IPA, and then in 50 ml of IPA for 24 h each time in a well-sealed Erlenmeyer flask at 30°C. After proper dilution, the concentration of the eluent was measured using a UV spectrophotometer (UV-160, Shimadzu Corp., Kyoto, Japan). It was determined that two elutions were sufficient for complete extraction. The solubility was calculated from the total amount eluted divided by the volume of disc.

In vitro release The PDMS disc was loaded to its solubility limit with pyridine derivative by the procedure described in the preceding section. After being equilibrated with drug for 1 week and washed with water, the disc was quickly mounted between the two halves of the diffusion cell. Distilled water from a common reservoir in a 30°C water bath was pumped on both sides (Lab Pump Jr., Model RHSY, Fluid Metering, Inc., NY) though the diffusion cell at a rate of 9 ml/min to initiate the release experiment. The volume of water was adjusted for each compound to maintain a 'sink' condition. A third pump was used to move solvent between the common reservoir and the spectrophotometer. Real time-absorbance was measured by the UV spectrophotometer and recorded by a personal computer (Epson, Model Q301A, Epson America, Inc., Torrance, CA) using a spectroscopy interface software (PC-160, version 3.0, Shimadzu Scientific Instruments, Inc., Columbia, MD). The release coefficient was then calculated from the slope of the linear portion of the Q vs $\sqrt{t}$ plot.

The release coefficients were related to physico-chemical parameters and structural properties by linear regression using the data analysis software previously employed (Moeckly and Matheson, 1991).

Results and Discussion

PDMS sheeting is a hydrophobic material and does not significantly swell in water. In this study, it was found that the weight of PDMS membrane increased only 0.16% after being soaked in water at 30°C for 4 days. The matrix is nonporous and release occurred by diffusion through the continuous polymer phase following Fick's law.

The short time approximation of the error function series (Crank and Park, 1968) can be simplified to

$$Q_t = 2C_0\sqrt{\frac{D_e t}{\pi}} \tag{1}$$

where Q_t is the accumulated amount released at time t from a unit area, C_0 denotes the loaded concentration and D_e is the effective diffusion coefficient in the matrix.

It can be seen from Eqn 1 that if the drug load, C_0, is equal to the solubility, C_s, it becomes a physical constant of the system. A release coefficient can be defined as a combination of the constant terms and Eqn 1 can be written as

$$Q_t = k\sqrt{t} \tag{2}$$

where the release coefficient is defined as

$$k = 2C_s\sqrt{\frac{D_e}{\pi}} \tag{3}$$

and the release rate can be given by Eqn 4.

$$\frac{dQ_t}{dt} = \frac{k}{2\sqrt{t}} \tag{4}$$

Eqn 2 shows, at least at early times, a Q vs $\sqrt{t}$ plot should be linear. All the compounds in this study were found to follow Eqn 2. The solubility, release coefficient and other physical parameters of the 10 compounds in this study are listed in Table 1.

It is apparent from Eqn 3 that if diffusion coefficient is inversely proportional to molecular weight as discussed by Lieb and Stein (1971), then the square root of the diffusion coefficient should remain almost constant, since the molecular weights of all the compounds in this study are similar. Thus, the release coefficient should be a linear function of solubility. Results show that this is the case. The relationship is given by the following linear regression equation:

$$\log k = -3.14 + 1.35 \log C_s \tag{5}$$

$$\text{S.D.} = 0.361; \quad r^2 = 0.864; \quad n = 10; \quad F = 50.64$$

where S.D. is the standard error of estimation, r^2 represents the coefficient of determination, n is the number of data point and F denotes the variance ratio. Eqn 5 shows that while experimental results generally agree with the theoretical expectation, solubility cannot be the only factor governing release. Another problem with this approach is that solubility is not easily determined in the PDMS sheeting.

It has been shown that solubility and permeability are related to melting point (Michaels et al., 1975; Chien, 1976; Lee et al., 1985). Results of our study produce a similar relationship, which is represented by Eqn 6:

$$\log C_s = 3.13 - 0.0131\text{mp} \tag{6}$$

$$\text{S.D.} = 0.1785; \quad r^2 = 0.929; \quad n = 10; \quad F = 105.2$$

where mp represents melting point in °C. It is clear from Eqn 6 that melting point can be used as a parameter to estimate solubility in the PDMS matrix. Eqn 7 also demonstrates that the replacement of log C_s in Eqn 5 by melting point is successful.

$$\log k = 1.13 - 0.0182\text{mp} \tag{7}$$

$$\text{S.D.} = 0.3902; \quad r^2 = 0.841; \quad n = 10; \quad F = 42.19$$

The goodness of fit of Eqn 7 is not significantly different from that of Eqn 5. However, the quality of fit of the two equations is not as good as desired. It would appear that assuming a constant diffusion coefficient for all the compounds is an oversimplification and other parameters are needed to improve the correlation with the release coefficient.

Eqn 1 was derived based on the assumption that there was no interaction between the polymer and drug molecule. Hydrogen bonding to the Si-O-Si polymer backbone has been found to be significant (West et al., 1961). Also the effects of the silica filler in the matrix were not taken into account. Filler in the polymer has also been found to be active and able to adsorb diffusant (Flynn and Roseman, 1971). Thus, the diffusant-polymer and diffusant-filler interactions need to be taken into consideration. One of the major interaction modes can be ascribed to hydrogen bonding. Assuming an additivity of the hydrogen bonding effects from different functionalities, group hydrogen bonding parameters (Barton, 1983a) were taken as an additional predictor for the release coefficient as shown in Table 1. Results were greatly improved as shown by Eqn 8:

$$\log k = 1.26 - 0.0136\text{mp} - 0.0000575\Sigma\text{HB} \quad (8)$$

S.D. = 0.1538; $r^2 = 0.972$; $n = 10$;

$F = 158.08$

where ΣHB is the summation of the hydrogen bonding parameter group contribution of all substituted groups on each pyridine. The negative signs for the two predictors indicate release rate will be inversely proportional to both melting point and hydrogen bonding strength, which is physically meaningful.

A systematic deviation was found to exist in the fitted results in a residual analysis of Eqn 8. This was determined to be related to the sum of the hydrogen bonding parameters by the existence of a parabolic shape of the plot of the residual versus the ΣHB. The systematic deviation resulted from Eqn 8 suggested that the relationship between diffusivity and hydrogen bonding parameter was not fully expressed and the form that the ΣHB term should assume needed to be reexamined. It has been shown that diffusion coefficient may be written in the following form (Flynn et al., 1974):

$$D = D_0 e^{(-E_a/RT)} \quad (9)$$

where D_0 is the hypothetical diffusivity at infinite temperature and E_a represents the activation energy, which includes the energy of all components of interaction between diffusant and diffusion medium. Logarithmic transformation of Eqn 9 results in Eqn 10.

$$\log D = \log D_0 - 2.303E_a/RT \quad (10)$$

At a given temperature, diffusion coefficient is a function of activation energy. If it is assumed that E_a is directly proportional to the hydrogen bonding energy, then it is clear that Eqn 8 is the proper equation.

Alternatively, E_a may be proportional to the

TABLE 2

Regression statistics for Eqn 11

Predictor	Coefficient	S.D.	*t*-ratio	*p*	VIF
Constant	1.7449	0.08437	20.68	0.000	
mp	−0.0133	0.00069	−19.19	0.000	1.4
$\sqrt{\Sigma HB}$	−0.0117	0.00088	−13.30	0.000	1.4

S.D. = 0.08136; r^2(adj) = 0.992.

Analysis of variance

Source	Degree of freedom	Sum of squares	Mean squares error	*F*	*p*
Regression	2	7.5947	3.7973	573.69	0.000
Error	7	0.0463	0.0066		
Total	9	7.6410			

solubility parameter, which is the square root of cohesive energy density (Barton, 1983b). Again, assuming that the hydrogen bonding energy is the dominant component of the cohesive energy and the strength of the solute-polymer interaction is proportional to that of the solute-solute interaction, the release coefficient should be proportional to the square root of the hydrogen bonding energy. Regression analysis showed that this was the case. The square root of hydrogen bonding parameter was added to Eqn 8 and the original ΣHB term was removed by the subsequent regression analysis because of an insignificant t-test value. This result suggests that the better theoretical basis is the relationship between E_a and the solubility parameter. The final fitted model is given by Eqn 11:

$$\log k = 1.745 - 0.0133\text{mp} - 0.0117\sqrt{\Sigma\text{HB}} \quad (11)$$

$$\text{S.D.} = 0.08136; \quad r^2 = 0.992; \quad n = 10;$$

$$F = 573.69$$

Results were significantly improved by using the square root of the sum of the hydrogen bonding parameters. The high r^2 and F values indicate the release coefficients are significantly related to the selected parameters. The probability of obtaining this relationship by chance is practically zero. Regression statistics for the final QSTR model, expressed by Eqn 11, are listed in Table 2 where t ratio is the t-test value, p denotes the level at which the t-test and F-test are significant and VIF is the variance inflation factor. The standard deviation of prediction is only $\pm 20.6\%$, which indicates the prediction of Eqn 11 is excellent over a 1000-fold range in the release rate. Calculated results of the release coefficients are listed in Table 3.

It can be seen that the release coefficient, and hence the release rates from PDMS for a series of substituted pyridines can be related to structural characteristics, which can be estimated with a simple QSTR model without using their solubility and diffusion coefficient in the polymer. The established model not only provides a good fit for the experimental results, but also reveals to some extent the nature of the mass transport process of drug release by its inverse correlation with the strength of the hydrogen bonding interaction. The applicability of the current model to the more complicated, but commonly encountered situation which occurs when the drug load is much higher than the solubility in the matrix, should be apparent. When drug load is high, the simplified form of Higuchi's equation (Higuchi, 1961) is written as

$$Q_t = \sqrt{2AD_eC_st} \quad (12)$$

where A is the concentration of drug in the matrix.

If a ratio is defined as:

$$R = \frac{A}{C_s} \quad (13)$$

TABLE 3

Calculated release coefficients using Eqn 11

Compound	Experimental log k	Calculated log k	Residual
2-Amino-4-methylpyridine	−0.5383	−0.5977	0.0594
3,5-Dichloropyridine	0.5767	0.5531	0.0236
2-Pyridinecarboxylic acid	−1.3354	−1.2254	−0.1100
3-Hydroxypyridine	−1.5000	−1.5765	0.0765
2-Hydroxy-5-nitropyridine	−2.4362	−2.4325	−0.0037
2-Methoxy-5-nitropyridine	−0.3985	−0.4699	0.0714
2-Amino-5-nitropyridine	−1.8989	−1.8822	−0.0167
2-Amino-4,6-dimethylpyridine	−0.2955	−0.1604	−0.1351
2-Aminopyridine	−0.0867	−0.1073	0.0207
2-Hydroxypyridine	−1.2842	−1.2982	0.0140

then using the same definition as in Eqn 3 and assuming the difference in diffusion coefficient caused by the differences in drug load is negligible, Eqn 12 can be rewritten in the following form:

$$Q_t = k\sqrt{\frac{R\pi t}{2}} \tag{14}$$

Comparing Eqn 14 with Eqn 2, it is clear that the slope for a matrix containing suspended drug differs by a factor determined by the drug loading. This suggests that this QSTR approach could be extended to the case of drug suspended in a matrix, but additional studies need to be conducted to confirm the applicability of the QSTR model for the release of suspended drugs.

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