Linear Relationships between Plasma Binding and Lipophilicity of Disopyramide Derivatives

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Abstract ☐ The extent of plasma binding and the partition coefficient of disopyramide and 20 disopyramide derivatives were determined. Structural variations on the four functional groups around the tetrahedral carbon in the disopyramide molecule were found to influence both parameters to varying degrees. Three linear equations were developed to correlate the observed effects, depending on the type of chemical modification. The linear correlation between drug-plasma interaction and lipophilic character was analyzed theoretically. A simple model was derived to relate quantitatively the variation in the extent of plasma binding to the change in lipophilicity of disopyramide derivatives.

Keyphrases ☐ Disopyramide and 20 derivatives—linear relationship between plasma binding and lipophilicity determined ☐ Lipophilicity and structure of disopyramide and 20 derivatives—relationship to protein binding ☐ Plasma binding, disopyramide and 20 derivatives—determination, relationship to lipophilicity and structure ☐ Partition coefficients, disopyramide and 20 derivatives—determination

Much effort recently has been spent on separating the various physicochemical properties of drugs to correlate the partial contributions of hydrophobic, electronic, and steric parameters to their overall biological properties (1–3). Although the details of how drug action is related to physicochemical properties of drugs remain unclear, it is profitable to use the phenomenological approach to differentiate and classify such molecular properties (4).

It has long been recognized that most administered drugs interact to some degree with serum proteins (5). Recently, several successful attempts were made to correlate these protein binding data quantitatively with the hydrophobicity of drugs (6–10).

The reported antiarrhythmic activities of a series of disopyramide derivatives were investigated and appeared to be quantitatively dependent on the combined effect of the lipophilicity and carbonyl vibrational energy of the drug (3, 11). Disopyramide and its derivatives (Table I) contain an asymmetric carbon center with four varying substituent groups. The availability of this series of compounds permitted the study of which groups were the predominant sites for protein binding and how structural variations affected the extent and strength of interaction.

This paper reports on the correlation of lipophilicity and structure with the protein binding of disopyramide and 20 derivatives.

EXPERIMENTAL

Materials—Human plasma was collected by centrifuging whole blood at 2500 rpm and 4° for 20 min[1]. Approximately 50 ml of plasma was obtained from the centrifugation of 100 ml of whole blood.

The 20 derivatives of disopyramide[2] were synthesized[3] by previously described methods (12, 13).

Binding Studies—Drug solutions (16×10^{-5} *M*) were prepared in isotonic 0.1 *M* phosphate buffer (pH 7.4) immediately prior to binding measurements. From 2 to 5 ml of this solution was added to 5 ml of human plasma, and buffer was added to 10 ml. The resultant mixtures, after equilibrating at 37° for 1 hr, were poured into membrane ultrafilters[4] and centrifuged at 1250 rpm and 4° for 30 min. The filtrates were assayed spectrophotometrically from 240 to 360 nm[5]. The absorbance of the peaks in the range of 250–~280 nm was recorded for calculating the free drug concentration. Drug solution, in the absence of proteins, was also centrifuged at the same time to correct for drug loss by membrane absorption. The absorption sometimes accounted for up to 60% of drug, depending on the nature of drug species examined.

Plasma binding results are expressed as fraction of drug, β (%),

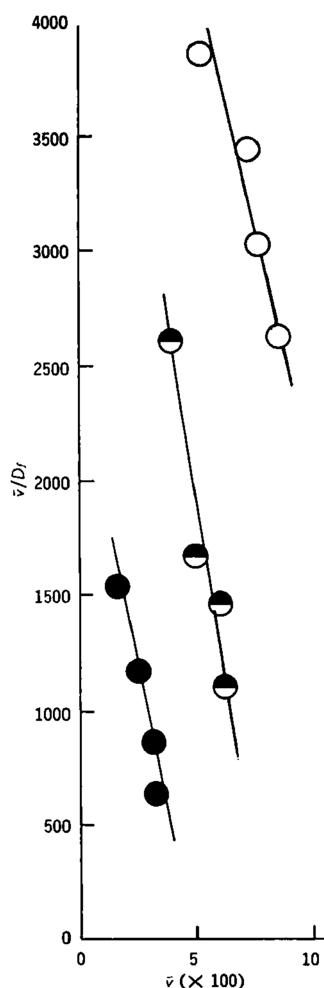


Figure 1—*Scatchard analysis for V (○), XVI (◓), and disopyramide (●). The linearity of the $\bar{\nu}/D_f$ versus $\bar{\nu}$ plots indicates that only one group of binding sites is involved in the interaction of disopyramide derivatives with plasma proteins in the concentration range (3.2- ~ 8.0 × 10^{-5}* M*) examined.*

[1] Sorvall RC-3 automatic refrigerated centrifuge.

[2] SC-7031. The brand name for disopyramide phosphate (SC-13957) is Norpace (Searle Laboratories, Division of G. D. Searle & Co., Chicago, IL 60680).
[3] Dr. J. W. Cusic, Dr. H. W. Sause, Mr. J. H. Yen, and Mr. P. K. Yonan, Chemical Research Department, Searle Laboratories.
[4] Centriflo, model CF 50A, Amicon Corp., Lexington, Mass.
[5] Coleman model 124 D spectrophotometer.

Table I—Relationship between Structural Variations around the Asymmetric Carbon Center of Disopyramide and the Extent of Drug–Plasma Interaction

$R_2-\overset{R_1}{\underset{R_3}{C}}-R_4$

Compound[a]	R_1	R_2	R_3	R_4	β, %	p.c.[b]
Disopyramide	$-\overset{O}{\overset{\parallel}{C}}-NH_2$	C_6H_5	C_5H_4N	$-CH_2CH_2N(iso\text{-}C_3H_7)_2$	27.3	0.66
I	H	C_6H_5	C_5H_4N	$-CH_2CH_2N(iso\text{-}C_3H_7)_2$	58.5	11.97
II	$-\overset{O}{\overset{\parallel}{C}}-NH_2$	H	C_5H_4N	$-CH_2CH_2N(iso\text{-}C_3H_7)_2$	4.6	0.0488
III	$-\overset{O}{\overset{\parallel}{C}}-NH_2$	C_6H_5	H	$-CH_2CH_2N(iso\text{-}C_3H_7)_2$	53.6	5.4
IV	$-\overset{O}{\overset{\parallel}{C}}-NH_2$	C_6H_5	C_5H_4N	H	27.3	6.87

[a] SC-7031, SC-26000, SC-21799, SC-5260, and SC-16571, respectively. [b] Partition coefficient.

bound to plasma:

$$\beta(\%) = \frac{(\text{drug concentration without plasma} - \text{drug concentration with plasma}) \times 100}{\text{drug concentration without plasma}} \quad \text{(Eq. 1)}$$

Partition Studies—Drug solutions, with a concentration of 8×10^{-5} M, were freshly prepared in 1-octanol-saturated phosphate buffer (0.1 M, pH 7.4, isotonic). Ten milliliters was agitated and equilibrated with 10 ml of phosphate buffer-saturated 1-octanol. The drug concentration in the phosphate buffer phase before and after partitioning was measured spectrophotometrically and utilized to calculate the magnitude of the partition coefficient.

RESULTS AND DISCUSSION

For plasma binding studies, four drug concentrations, ranging from 3.2×10^{-5} to 8.0×10^{-5} M, were examined. In this concentra-

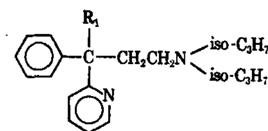


Table II—Structural Variation of the Amide Moiety of Disopyramide Derivatives

Compound[a]	R_1	log (p.c.)	log (D_b/D_f) Observed	Estimated Eq. 10	Estimated Eq. 13
I	H	1.078	0.149	0.206	0.234
V	OH	0.918	0.171	0.131	0.142
Disopyramide	$-\overset{O}{\overset{\parallel}{C}}-NH_2$	−0.182	−0.425	−0.389	−0.493
VI	$-\overset{S}{\overset{\parallel}{C}}-NH_2$	0.208	−0.091	−0.205	−0.268
VII	$-\overset{O}{\overset{\parallel}{C}}-NHC_2H_5$	0.028	−0.299	−0.290	−0.372
VIII	$-\overset{O}{\overset{\parallel}{C}}-NHNHCOCH_3$	−0.752	−0.656	−0.659	−0.822
IX	$-\overset{O}{\overset{\parallel}{C}}-NHN=C(CH_3)_2$	0.058	−0.321	−0.276	−0.355
X	$-\overset{O}{\overset{\parallel}{C}}-NH-C_6H_5$	1.468	0.316	0.391	0.459
XI	$-\overset{O}{\overset{\parallel}{C}}-NH-C_6H_{11}$	1.082	0.191	0.208	0.267
XII	$-\overset{O}{\overset{\parallel}{C}}-NH-C_5H_4N$	1.568	0.520	0.438	0.517

[a] SC-26000, SC-26658, SC-7031, SC-25888, SC-26481, SC-26553, SC-26529, SC-27063, SC-29359, and SC-27071, respectively.

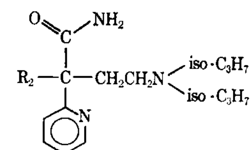


Table III—Structural Variation on the Phenyl Ring of Disopyramide Derivatives

Compound[a]	R_2	log (p.c.)	log (D_b/D_f) Observed	log (D_b/D_f) Estimated Eq. 11	log (D_b/D_f) Estimated Eq. 13
II	H	−1.310	−1.317	−1.209	−1.145
Disopyramide		−0.182	−0.425	−0.485	−0.493
XIII	CH_3	0.174	−0.343	−0.257	−0.288
XIV	CH_3	0.232	−0.203	−0.220	−0.254
XV	OCH_3, OCH_3	−0.788	−0.745	−0.874	−0.843
XVI	F	0.083	−0.294	−0.315	−0.340
XVII	Cl	0.603	−0.015	−0.018	−0.040

[a] SC-21799, SC-7031, SC-12875, SC-24874, SC-12857, SC-13234, and SC-13068, respectively.

tion region, the results of a Scatchard analysis (Fig. 1) demonstrated that only a primary binding site was involved in the interaction with disopyramide derivatives; a linear plot was observed. By following the Scatchard relationship (Eq. 2), the equilibrium binding constant, K_n, may be estimated from the slope of the linear $\bar{v}/D_f$ *versus* $\bar{v}$ plots:

$$\bar{v}/D_f = nK_n - \bar{v}K_n \qquad \text{(Eq. 2)}$$

Which of the four functional groups around the tetrahedral carbon center in this molecule was the predominant site for plasma binding? The results demonstrated that the omission of the amide or pyridyl groups (Table I) resulted in an approximately twofold increase in the extent of plasma binding (β values were increased from 27.3 to 58.5 or 53.6%, respectively). But the absence of the phenyl ring yielded a sixfold decrease in β (from 27.3 to 4.6%). The replacement of the diisopropylaminoethyl group produced neither gain nor loss in the extent of drug–plasma interaction. The results observed here indicate that the planar phenyl ring of the disopyramide intercalated into the plasma protein helix (14). An NMR study also provided evidence that the phenyl ring is the site binding to serum protein (15).

In addition, the observed partition coefficients demonstrated that the amide, pyridyl, and diisopropylaminoethyl groups increased the hydrophilicity of disopyramide derivatives. (Their absence resulted in increases in the partition coefficient from 0.66 to 11.97, 5.4, and 6.87, respectively.) On the other hand, the phenyl substitution added lipophilic character to the molecule. The replacement of this group substantially decreased the magnitude of the partition coefficient (from 0.66 to 0.049). The omission of the diisopropylaminoethyl group produced no change in the extent of plasma binding while the lipophilicity, as represented by the partition coefficient, was enhanced more than 10-fold (from 0.66 to 6.87). This observation may be explained by the fact that 90% of the diisopropylaminoethyl group (pKb = 8.36) is protonated at the physiological pH of 7.4, which may allow this group to project into the aqueous phase surrounding the protein molecule and not interact with the protein (8).

For a fuller understanding of the mechanisms by which disopyramide derivatives interact with plasma protein, the studies were expanded to additional derivatives in which the amide, phenyl, or pyridyl group was modified chemically while the other three functional groups were held constant. The results of these experiments are found in Tables II–IV along with estimated values for log (D_b/D_f) obtained with the following analysis.

At equilibrium (16), the partition coefficient (p.c.) for the partitioning of drug molecules from an aqueous phase to an organic phase may be related to the standard chemical potentials ($\mu_0°$ and $\mu_a°$) in organic and aqueous phases:

$$\mu_0° - \mu_a° = -2.303RT \log (\text{p.c.}) \qquad \text{(Eq. 3)}$$

The standard free energy change ($\Delta F°$) for the interaction of drug with plasma protein (16) may be related to the equilibrium binding constant, K_n, as follows:

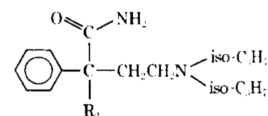
$$\Delta F° = \mu_p° - \mu_a° \qquad \text{(Eq. 4a)}$$

$$\Delta F° = -2.303RT \log K_n \qquad \text{(Eq. 4b)}$$

where $\mu_p°$, $\mu_a°$, and $\mu_0°$ are the standard chemical potentials for a drug species bound to a protein molecule and in the aqueous and organic phases, respectively. Substituting Eq. 3 for the $\mu_a°$ term in Eq. 4*a* and rearranging give Eq. 5:

$$\log K_n = \frac{\mu_0° - \mu_p°}{2.303RT} + \log (\text{p.c.}) \qquad \text{(Eq. 5)}$$

Table IV—Structural Variation on the Pyridyl Group of Disopyramide Derivatives



Compound[a]	R_3	log (p.c.)	log (D_b/D_f) Observed	Estimated Eq. 12	Estimated Eq. 13
III	H	0.732	0.063	0.061	−0.034
Disopyramide	2-pyridyl	−0.182	−0.425	−0.609	−0.493
XVIII	3-pyridyl	0.316	−0.141	−0.244	−0.206
XIX	4-pyridyl	0.055	−0.315	−0.436	−0.356
XX	naphthyl	1.393	0.482	0.546	0.416

[a] SC-5260, SC-7031, SC-12748, SC-12773, and SC-24115, respectively.

The Scatchard relationship (Eq. 2) may be expressed alternatively by Eq. 6

$$K_n = \frac{\bar{\upsilon}}{(\bar{n} - \bar{\upsilon})D_f} = \frac{D_b}{D_f} \times \frac{1}{(\bar{n} - \bar{\upsilon})P} \quad \text{(Eq. 6)}$$

where $\bar{\upsilon}$ is the average number of drug molecules bound per molecule of plasma protein (D_b/P); $\bar{n}$ is the total number of binding sites in a protein molecule; D_b and D_f are the concentrations of drug bound to plasma protein and freely existing in the solution phase, respectively; and P is the overall concentration of plasma protein in the bloodstream. Equation 5 may be equivalently expressed as:

$$\log \frac{D_b}{D_f} = \frac{\mu_0{}^\circ - \mu_p{}^\circ}{2.303RT} + \log (\bar{n} - \bar{\upsilon})P + \log (\text{p.c.}) \quad \text{(Eq. 7)}$$

Experimentally, it was observed that $\bar{n} = 3.51$ and $\bar{\upsilon} \leq 0.12$ for disopyramide in the drug concentration range investigated. So, Eq. 7 may be simplified to:

$$\log \frac{D_b}{D_f} = \text{intercept} + \log (\text{p.c.}) \quad \text{(Eq. 8)}$$

where:

$$\text{intercept} = \frac{\mu_0{}^\circ - \mu_p{}^\circ}{2.303RT} + \log \bar{n}p \quad \text{(Eq. 9}a\text{)}$$

$$\text{intercept} = \log (D_b/D_f)_0 = \text{constant} \quad \text{(Eq. 9}b\text{)}$$

Equations 7 and 8 define a linear relationship between the degree of plasma binding (as represented by D_b/D_f) and the lipophilic character of the molecule (expressed as the partition coefficient). Under the condition of $\bar{n} \gg \bar{\upsilon}$, the magnitude of D_b/D_f is directly proportional to the equilibrium binding constant (K_n) with a proportionality of $(\bar{n} - \bar{\upsilon})P$ (Eq. 6). Therefore, the degree of plasma binding (D_b/D_f) may be directly estimated from a binding measurement without requiring a Scatchard analysis to calculate the magnitude of K_n.

A literature survey indicated that correlations between protein binding and the lipophilicity of drugs have usually employed a Hammett-type linear free energy relationship (6). In this treatment, log $(1/c)$ values are plotted against π, the lipophilicity of the drug. To do this, a series of drug–protein interaction measurements must be conducted at several drug concentrations to collect data points for estimating the molar concentration of drug necessary to produce a 1:1 drug–protein complex. Thus, a substantial workload is created when dealing with a large number of drugs. In such a situation, the development of a simple methodology with equivalent theoretical validity becomes necessary. In the present analysis, the protein binding (D_b/D_f) of all drugs investigated was done at a single, optimal, initial drug concentration (D_T). This practice allows biopharmaceutical screening of a large number of newly synthesized drugs.

The linear correlation of log (D_b/D_f) with π was successfully used in investigating (8) the binding of penicillins to serum protein. The linear log (D_b/D_f) *versus* π relationship was utilized empirically without the inclusion of a mathematical derivation from fundamental principles. The derivation of Eq. 8 from simple physicochemical laws (Eqs. 3 and 4) demonstrates how the degree of plasma binding [log (D_b/D_f)] is related theoretically to the lipophilicity (log p.c.) of the drugs examined.

On the basis of Eq. 8, the data on D_b/D_f (obtained from the β values) and the partition coefficients (Tables II–IV) were submitted to multiple-regression analysis. Three equations were obtained.

For the effect of structural variation of the amide moiety:

$$\log \left(\frac{D_b}{D_f}\right) = -0.303 + 0.473 \log (\text{p.c.}) \quad \text{(Eq. 10)}$$

n	γ	s^2
10	0.986	0.0034

For the effect of structural variation of the phenyl ring:

$$\log \left(\frac{D_b}{D_f}\right) = -0.369 + 0.641 \log (\text{p.c.}) \quad \text{(Eq. 11)}$$

n	γ	s^2
7	0.982	0.0059

For the effect of structural variation of the pyridyl group:

$$\log \left(\frac{D_b}{D_f}\right) = -0.476 + 0.734 \log (\text{p.c.}) \quad \text{(Eq. 12)}$$

n	γ	s^2
6	0.923	0.0303

In Eqs. 10–12, n is the number of derivatives used in the analysis, γ is the correlation coefficient, and s^2 is the residual variance. Both the correlation coefficient (γ) and the residual variance (s^2) demonstrate that the degree of plasma binding of disopyramide derivatives is highly correlated to their lipophilicity. By using Eqs. 10–12, estimated D_b/D_f values for the disopyramide derivatives

Table V—Estimation of the Relative Lipophilicity (π) for Disopyramide Derivatives with Structural Variation on the Phenyl Ring

Compound	Estimated π Values[a]		
	Benzene System	Benzoic Acid System	Phenoxyacetic Acid System
II	0	0	0
Disopyramide	1.89	1.89	1.89
XIII	2.45	2.41	2.40
XIV	2.45	2.31	2.41
XV	1.85	2.11	1.97
XVI	2.03	2.08	2.04
XVII	2.60	2.76	2.69

[a] Calculated from Ref. 18.

were computed; they are shown in Tables II–IV together with the D_b/D_f values observed.

The slope of Eqs. 10–12 is a measure of the sensitivity of the protein binding system to the hydrophobicity of each series of disopyramide derivatives (4). The value of the intercept (Eqs. 10–12) will be a function of the sensitivity of the system and the intrinsic thermodynamic activity (Eqs. 9*a* and 9*b*) of a given series of drugs. It will also depend on the ratio of active sites to substrate molecules in position to react with these sites, $(\bar{n} - \bar{v})P$.

If the binding of disopyramide derivatives to plasma protein is nonspecific, as reported for most drugs (7), and the difference in plasma binding extent is only due to the change in their lipophilicity, then a good correlation should be found when disopyramide and all 20 derivatives (Tables I–IV) are submitted to the same multiple-regression analysis as in Eqs. 10–12, neglecting the differences in their sites of structural variation. The following correlation was obtained:

$$\log\left(\frac{D_b}{D_f}\right) = -0.388 + 0.577 \log(\text{p.c.}) \qquad \text{(Eq. 13)}$$

n	γ	s^2
21	0.955	0.018

Both the high correlation coefficient ($\gamma = 0.955$) and low residual variance ($s^2 = 0.018$) indicated that the extent of plasma binding of disopyramide and the 20 derivatives was highly correlated with their lipophilicity. The values of $\log (D_b/D_f)$ estimated from Eq. 13 were also determined; they are shown in Tables II–IV together with those values observed and computed from Eq. 10, 11, or 12. A comparison made between Eq. 13 and Eqs. 10–12 pointed out that the interaction of disopyramide derivatives with plasma protein is nonspecific in nature and is slightly dependent on the sites of structural variation (compare the data estimated to those observed in Tables II–IV). Overall, any modification in the molecular structure of disopyramide derivatives that leads to a higher lipophilicity will result in enhanced binding with plasma protein. In the practice of drug design, this fact should be considered when the pharmaceutical chemist attempts to improve the tissue permeability of a given drug by enhancing its lipophilic nature.

The values of log (p.c.) (Tables I–IV) for all of the disopyramide derivatives were obtained in an *n*-octanol–phosphate buffer (pH 7.4) system. The relative lipophilicity (π) of a given derivative (x) may be calculated as follows:

$$\pi(x) = \log(\text{p.c.})\,x - \log(\text{p.c.})_H \qquad \text{(Eq. 14)}$$

The magnitude of π values may also be estimated from information on the partition coefficient of the parent compound and the group contribution of the substituents added onto the derivative by using the rule of addition (8, 18). For example, Compound XIII (Table III) is the *m*-tolyl derivative of Compound II. Its relative lipophilicity may be estimated as follows:

$$\begin{aligned}\sum\pi(\text{XIII}) &= \pi(\text{disopyramide}) + \pi(m\text{-CH}_3)\\ &= \pi(\text{II}) + \pi(\text{phenyl}) + \pi(m\text{-CH}_3)\\ &= 0 + 1.89 + 0.56\\ &= 2.45\end{aligned} \qquad \text{(Eq. 15)}$$

By using this approach, the π values were calculated (Table V) for the other derivatives of II in reference to three systems, benzene, benzoic acid, and phenoxyacetic acid (18), and were quite close to each other.

The correlation of the extent of plasma binding of these disopyramide derivatives (Column 4 in Table III) with these three sets of estimated π values was also submitted to multiple-regression analysis. The results are represented by the following correlations:

With the benzene system as a reference source:

$$\log(D_b/D_f) = -1.352 + 0.462\,\pi \qquad \text{(Eq. 16)}$$

n	γ	s^2
7	0.948	0.016

With the benzoic acid system as a reference source:

$$\log(D_b/D_f) = -1.337 + 0.444\,\pi \qquad \text{(Eq. 17)}$$

n	γ	s^2
7.	0.923	0.024

With the phenoxyacetic acid system as a reference source:

$$\log(D_b/D_f) = -1.350 + 0.456\,\pi \qquad \text{(Eq. 18)}$$

n	γ	s^2
7	0.941	0.018

A comparison made among Eqs. 11 and 16–18 indicates that the extent of plasma binding, $\log (D_b/D_f)$, of disopyramide derivatives is not only highly correlated to their lipophilicity, log (p.c.), measured experimentally but also to the magnitude of π estimated from literature data. The magnitude of the correlation coefficients (r) obtained only shows the trend on the change of $\log (D_b/D_f)$ as a function of the variation of the lipophilicity of a drug species. On the other hand, the residual variance (s^2) demonstrates the magnitude of difference between the observed $\log (D_b/D_f)$ value from that predicted.

The magnitude of the residual variances in Eqs. 16–18 is found to be three- to fourfold greater than that in Eq. 11. The results are illustrated and compared in Table VI. It was noted that Eqs. 16–18 failed to give good estimates of $\log (D_b/D_f)$ values when the phenyl ring contained methoxy, fluoro, and chloro groups, *i.e.*, electron-

Table VI—Comparison of the Observed and Calculated Extent of Plasma Binding of Disopyramide Derivatives

Compound	$\log (D_b/D_f)$				
		Calculated			
	Observed	Eq. 11	Eq. 16	Eq. 17	Eq. 18
II	−1.317	−1.209	−1.352	−1.337	−1.350
Disopyramide	−0.425	−0.485	−0.480	−0.498	−0.489
XIII	−0.343	−0.257	−0.222	−0.268	−0.256
XIV	−0.203	−0.220	−0.222	−0.312	−0.251
XV	−0.745	−0.874	−0.499	−0.401	−0.452
XVI	−0.294	−0.315	−0.416	−0.414	−0.420
XVII	−0.015	−0.018	−0.152	−0.112	−0.124

withdrawing substituents. The measurement of lipophilicity, using experimental partition coefficient data, was more dependable than an estimation from literature data collected in a different system. The preference for actual measurement over the estimation of lipophilicity is even more obvious when one deals with drug molecules having a complicated molecular structure.

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Selecting Key Parameters in Pharmaceutical Formulations by Principal Component Analysis

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Abstract □ The role of principal component analysis in the selection of pharmaceutical formulations is presented. The objective and the procedure of the analysis are discussed in detail. The technique was successfully applied to a system consisting of 10 response variables (tablet properties). Analysis of the results showed that the first component (dissolution) and components one and two together (dissolution and disintegration) contributed 95.4 and 99.3%, respectively, to the overall information about the formulations and that eight of 10 response parameters contributed nothing further to the overall information. The results obtained from this method of analysis may be found useful for achieving economy in both cost and time of measuring responses. Principal component analysis also provides a basis for understanding the underlying mechanism of the system under consideration.

Keyphrases □ Pharmaceutical formulations—selecting key parameters by principal component analysis, examples □ Formulations, pharmaceutical—selecting key parameters by principal component analysis, examples □ Principal component analysis—selecting key parameters in pharmaceutical formulations

In the development of a drug delivery system, a research pharmacist usually measures several response parameters. For instance, 10 or more parameters were considered in the development of a pharmaceutical tablet formulation (1). Based on all of these parameters, one attempts to find those levels of the formulation factors (diluent ratio, compressional force, *etc.*) for which the system is considered optimum. Since a large number of interrelated response variables is generally involved, it is relevant to ask how the interrelation and covariation of these measurements might be represented and whether fewer measurements might not carry all the necessary information for accomplishing a specific objective.

When several formulations are available, the developmental pharmacist must determine how best to distinguish between them. When one is choosing between two or three, the trend may be obvious. For example, the formula changes made may cause no difference in tablet hardness but considerable difference in disintegration characteristics. But when a long list of formulations is available or, more precisely, when one has infinite possibilities (as in computer optimization) and is dealing with many parameters, the trend is less obvious.

One may have certain basic constraints, such as a minimum hardness value, but it is nevertheless important to know which property or properties can be used to distinguish between choices. Generally, an educated guess is made, based on experience with the system and with pharmaceutical systems in general.

But there is a mathematical method to select those variables that best distinguish between formulations and those variables that change most drastically from