Quantitative Structure–Selectivity Relationships: Selective Drug Design

ALDO GARZIA *, ALBERTO VILLANTI ˣ, and GIANFRANCO TUCCINI

Received July 21, 1978, from *Tecnofarmaci S.p.A., Via Ardeatina Km. 21,000, 00040 Pomezia, Italy.* Accepted for publication February 23, 1979. *Present address: Istituto Chemioterapico Italiano, S. Grato, 20075 Lodi, Italy.

Abstract □ The concept of complex selectivity (S_c^n) permits the investigation of quantitative structure–selectivity relationships in the presence of n side effects; S_c^n permits differentiation of the most selective molecules rather than the most active ones in a congener series. Selectivity quantification in the presence of n side effects facilitates molecular comparisons. The information provided by S_c^n and its changes with increasing n is discussed. The proposed mathematical model is applied to the study of the selectivity of some antibiotics and antibacterial agents.

Keyphrases □ Structure–selectivity relationships—penicillins, alkylchlorophenols, drug design, bioavailability, structure–activity relationships □ Penicillins—structure–selectivity relationships, bioavailability □ Alkylchlorophenols—structure–selectivity relationships, bioavailability □ Drug design—structure–selectivity relationships, penicillins, alkylchlorophenols □ Antibacterials—structure–selectivity relationships, penicillins

Researchers working on quantitative structure–activity relationships have been mainly examining the most active compound, the one that produces the highest activity characteristic of a series of congeners. Insufficient care has been given to rational drug design.

Identification of the most active molecule is insufficient for therapeutically useful drug design. The ideal compound must be as specific and selective as possible, with minimal side effects. This aim can be achieved by generalizing some results obtained by previous investigators (1–3). These studies extended the multiparameter Hansch analysis (4) to the study of selectivity, taking only one side effect into account.

The purpose of this work was to extend this approach to the study of n side effects considered simultaneously with the main effect. With the proposed method, isolation of the most selective compounds rather than the most active ones in a series of molecules is possible.

This work is a contribution to the development of a general mathematical model for forecasting overall drug action and for quantifying biopharmacological activities in order to direct, *a priori*, the synthetic work toward molecules with optimal therapeutic characteristics.

THEORETICAL

In a series of pharmacologically active congener molecules, all producing the same range of effects but having different intensities from molecule to molecule, the overall effect, E_o, of each molecule can be expressed as a function of the combined single effects:

$$E_o = f(E_m, E_1, \ldots E_i, \ldots E_n) \qquad \text{(Eq. 1)}$$

where E_m is the main effect and E_i represents the n undesirable side effects.

The application of the Hansch approach to each single effect for the whole series gives:

$$E_m: \quad \log \frac{1}{C_m} = a_{0m} + \sum_{j=1}^{r_m} a_{jm}x_{jm} \qquad \text{(Eq. 2)}$$

$$E_1: \quad \log \frac{1}{C_1} = a_{01} + \sum_{j=1}^{r_1} a_{j1}x_{j1} \qquad \text{(Eq. 3)}$$

$$E_i: \quad \log \frac{1}{C_i} = a_{0i} + \sum_{j=1}^{r_i} a_{ji}x_{ji} \qquad \text{(Eq. 4)}$$

$$E_n: \quad \log \frac{1}{C_n} = a_{0n} + \sum_{j=1}^{r_n} a_{jn}x_{jn} \qquad \text{(Eq. 5)}$$

where $1 < i < n$ and r_i is the number of parameters in the ith equation.

The therapeutic index or selectivity, S_i, of each molecule relative to the ith side effect usually is described (5) as the quotient between a standard concentration, C_i, that produces a side effect, E_i, with a given intensity and an effective standard concentration, C_m, relative to the main effect, E_m:

$$S_i = \frac{C_i}{C_m} \qquad \text{(Eq. 6)}$$

A high selectivity, *i.e.*, a high S_i value, depends on a relatively large numerator and a small denominator of Eq. 6. By taking the logarithms, Eq. 6 becomes:

$$\log S_i = \log \frac{C_i}{C_m} \qquad \text{(Eq. 7)}$$

Enlarging a summation to the n selectivities gives:

$$\sum \log S_i = \sum_{i=1}^{n} \log \frac{C_i}{C_m} \qquad \text{(Eq. 8}a\text{)}$$

or:

$$\sum \log S_i = \log \frac{\prod_{i=1}^{n} C_i}{(C_m)^n} \qquad \text{(Eq. 8}b\text{)}$$

where the logarithmic fraction on the right side is the "complex selectivity" and is indicated by the symbol S_c^n where n is the number of side effects studied contemporaneously with the main effect. In this way, one can speak of first-, second-, . . . , nth-order complex selectivity according to the number of side effects simultaneously considered. Therefore, Eq. 8*b* can be rewritten:

$$\log S_c^n = \log \frac{\prod_{i=1}^{n} C_i}{(C_m)^n} \qquad \text{(Eq. 9}a\text{)}$$

or:

$$\log S_c^n = n \log \frac{1}{C_m} - \sum_{i=1}^{n} \log \frac{1}{C_i} \qquad \text{(Eq. 9}b\text{)}$$

If the various C_i's and C_m's in Eq. 9*b* are substituted by their functional expressions as represented by Eqs. 2–5, the following is obtained:

$$\log S_c^n = n\left(a_{0m} + \sum_{j=1}^{r_m} a_{jm}x_{jm}\right) - \sum_{i=1}^{n}\sum_{j=1}^{r_i} a_{ji}x_{ji} - \sum_{i=1}^{n} a_{0i} \qquad \text{(Eq. 10)}$$

The series of values of physicochemical parameters that maximizes $\log S_c^n$ should identify the molecule whose action is the best compromise between therapeutic activity and side effects. This calculus method of complex selectivity is based on the linear combination of the single linear combinations that correlate the main effect and the side effects with their relative physicochemical parameters. In synthesis, this calculus method of quantitative structure–selectivity relationships presumes knowledge of the structure–activity relationships.

A different approach may consist in direct analysis of the eventual correlation between all of the experimental data properly combined according to Eq. 9*a* or 9*b* in a series of $\log S_c^n$ values and the physicochemical parameters:

$$\log S_c^n = a_0 + \sum_{1}^{r} a_r x_r \qquad \text{(Eq. 11)}$$

Equation 11 is a generalization of Eq. 10.

0022-3549/79/0900-1081$01.00/0

Table I—Penicillins: Compounds, Constants, Activities, and Observed and Calculated Values of Log S_c^n

	Compound	R_m^a	Activity[b] against *S. aureus*	Activity[b] against *E. coli*	Activity[b] against *T. pallidum*	Log S_c^2, Eq. 12[c] Obs.[f]	Log S_c^2, Eq. 12[c] Calc.	Log S_c^1, Eq. 13[d] Obs.[f]	Log S_c^1, Eq. 13[d] Calc.	Log S_c^1, Eq. 14[e] Obs.[f]	Log S_c^1, Eq. 14[e] Calc.
I	Dicloxacillin	1.63	4.23	0.66	4.89	2.91	3.43	3.57	3.95	−0.66	−0.52
II	Nafcillin	1.39	3.72	0.72	4.54	2.18	2.95	3.00	3.58	−0.82	−0.63
III	Cloxacillin	1.34	4.10	0.86	4.85	2.49	2.85	3.24	3.50	−0.75	−0.65
IV	Oxacillin	1.05	3.98	0.93	4.84	2.19	2.27	3.05	3.05	−0.86	−0.78
V	Phenethicillin	1.03	4.80	1.06	5.10	3.44	2.23	3.74	3.02	−0.30	−0.79
VI	Penicillin V	0.89	5.14	1.72	5.78	2.78	1.95	3.42	2.81	−0.64	−0.85
VII	Benzylpenicillin	0.55	4.85	2.09	5.76	1.85	1.27	2.76	2.28	−0.91	−1.01
VIII	Methicillin	0.47	3.15	0.85	4.50	0.95	1.11	2.30	2.15	−1.35	−1.04
IX	Ampicillin	0.08	4.35	3.10	5.43	0.17	0.33	1.25	1.55	−1.08	−1.22
X	Methylenampicillin	−0.29	3.87	2.94	5.14	−0.34	−0.41	0.93	0.98	−1.27	−1.38
XI	Carbenicillin	−0.46	3.45	3.12	5.16	−1.38	−0.75	0.33	0.71	−1.71	−1.46

[a] Chromatographic parameters. See Ref. 6, p. 513. [b] The biological activity is expressed as log $1/C$, where C is the molar (mM × 10^{-2}) concentration of each antibiotic that gives an inhibition diameter of 20 mm. See Ref. 6, p. 513. [c] Equation 12: log S_c^2 = 2.00 (±0.67) R_m + 0.17 (±0.65). [d] Equation 13: log S_c^1 = 1.55 (±0.47) R_m + 1.43 (±0.45). [e] Equation 14: log S_c^1 = 0.45 (±0.25) R_m − 1.25 (±0.24). [f] Equation 9*b*.

Table II—Alkylchlorophenols: Compounds, Constants, Activities, and Observed and Calculated Values of Log S_c^n

	Compound	Log P^a	Activity[b] Against *S. aureus*	Activity[b] Against *S. typhosa*	Activity[b] Against *S. hemolyticus*	Log S_c^2, Eq. 15[c] Obs.[b]	Log S_c^2, Eq. 15[c] Calc.	Log S_c^1, Eq. 17[d] Obs.[f]	Log S_c^1, Eq. 17[d] Calc.	Log S_c^1, Eq. 19[e] Obs.[b]	Log S_c^1, Eq. 19[e] Calc.
XII	4-Chloro	2.39	0.77	0.77	0.78	−0.01	0.16	0.00	0.08	−0.01	0.08
XIII	4-Chloro-2-methyl	2.89	1.28	1.28	1.23	0.05	−0.03	0.00	−0.08	0.05	0.05
XIV	4-Chloro-2-ethyl	3.39	1.76	1.68	1.72	0.12	−0.07	0.08	−0.09	0.04	0.02
XV	4-Chloro-2-*n*-propyl	3.89	2.23	2.23	2.15	0.08	0.06	0.00	0.05	0.08	0.01
XVI	4-Chloro-2-*n*-butyl	4.39	2.70	2.44	2.69	0.27	0.34	0.26	0.33	0.01	0.01
XVII	4-Chloro-2-*n*-amyl	4.89	3.03	2.52	3.07	0.47	0.79	0.51	0.77	−0.04	0.02
XVIII	4-Chloro-2-*sec*-amyl	4.69	2.82	2.00	2.82	0.82	0.59	0.82	0.58	0.00	0.01
XIX	4-Chloro-2-hexyl	5.39	3.45	1.72	3.48	1.70	1.39	1.73	1.35	−0.03	0.04
XX	2-Chloro	2.15	0.60	0.53	0.43	0.24	0.31	0.07	0.21	0.17	0.10
XXI	2-Chloro-4-methyl	2.65	1.06	0.98	0.93	0.21	0.04	0.08	−0.02	0.13	0.06
XXII	2-Chloro-4-ethyl	3.15	1.42	1.46	1.40	−0.02	−0.07	−0.04	−0.10	0.02	0.03
XXIII	2-Chloro-*n*-propyl	3.65	1.77	1.83	1.80	−0.09	−0.02	−0.06	−0.04	−0.03	0.02
XXIV	2-Chloro-4-*n*-butyl	4.15	2.27	2.23	2.24	0.07	0.19	0.04	0.18	0.03	0.01
XXV	2-Chloro-4-*n*-amyl	4.65	2.78	2.22	2.67	0.67	0.55	0.56	0.54	0.11	0.01
XXVI	2-Chloro-4-*tert*-amyl	4.33	2.42	1.83	2.47	0.54	0.30	0.59	0.29	−0.05	0.01
XXVII	4-Chloro-3-methyl	2.95	1.24	1.21	1.24	0.03	−0.04	0.03	−0.09	0.00	0.04
XXVIII	4-Chloro-3,5-dimethyl	3.51	1.63	1.70	1.66	−0.10	−0.05	−0.07	−0.07	−0.03	0.02
XXIX	4-Chloro-6-ethyl-3-methyl	3.95	1.96	2.07	2.00	−0.15	0.08	−0.11	0.07	−0.04	0.01
XXX	4-Chloro-6-*n*-propyl-3-methyl	4.45	2.60	2.42	2.54	0.24	0.39	0.18	0.38	0.06	0.01
XXXI	4-Chloro-6-isopropyl-3-methyl	4.25	2.47	2.32	2.43	0.19	0.25	0.15	0.24	0.04	0.01
XXXII	4-Chloro-2-ethyl-3,5-dimethyl	4.51	2.32	1.96	2.27	0.41	0.43	0.36	0.42	0.05	0.01
XXXIII	4-Chloro-6-*sec*-butyl-3-methyl	4.77	2.86	1.96	2.85	0.91	0.66	0.90	0.65	0.01	0.02
XXXIV	4-Chloro-2-isopropyl-3,5-dimethyl	4.81	2.82	2.24	2.82	0.58	0.70	0.58	0.69	0.00	0.02
XXXV	4-Chloro-6-diethylmethyl-3-methyl	5.25	3.19	1.78	3.10	1.50	1.20	1.41	1.17	0.09	0.03
XXXVI	4-Chloro-6-isopropyl-2-ethyl-3-methyl	5.25	2.66	2.11	2.60	0.61	1.20	0.55	1.17	0.06	0.03
XXXVII	4-Chloro-2-*sec*-butyl-3,5-dimethyl	5.31	3.11	1.81	3.10	1.31	1.28	1.30	1.25	0.01	0.03

[a] Octanol-water partition coefficients. See Ref. 7, p. 432. [b] The biological activity is expressed as log PC', where PC' is the phenol coefficient converted to a molar basis. See Ref. 7, pp. 431, 432. The biological activity is the minimum concentration effective in 10 min. See Ref. 8, p. 2577. [c] Equation 15: log S_c^2 = −2.07 (±0.81) log P + 0.32 (±0.10) (log P)^2 + 3.30 (±1.51). [d] Equation 17: log S_c^1 = 1.89 (±0.82) log P + 0.30 (±0.11) (log P)^2 + 2.90 (±1.52). [e] Equation 19: log S_c^1 = −0.18 (±0.20) log P + 0.02 (±0.03) (log P)^2 + 0.39 (±0.37). [f] Equation 9*b*.

Table III—Penicillins: Regression Equations Generated from Table I Data According to Eq. 11

	Equation[a]	r	s	EV	F	p
Main effect: against *S. aureus*	12. log S_c^2 = 2.00 (±0.67)R_m + 0.17 (±0.65)	0.91	0.66	0.81	43.82	<0.01
Side effect: against *E. coli*	13. log S_c^1 = 1.55 (±0.47)R_m + 1.43 (±0.45)	0.93	0.46	0.84	53.60	<0.01
Side effect: against *T. pallidum*	14. log S_c^1 = 0.45 (±0.25)R_m − 1.25 (±0.24)	0.80	0.25	0.60	15.68	<0.01

[a] n = 11.

When one considers only one side effect, *i.e.*, when n = 1, the meaning of log S_c^n is obvious; it expresses the relationship between the main effect and the side effect in a qualitative and quantitative way. If log S_c^n is positive, it means that the main effect prevails over the side effect and the value of log S_c^n indicates on a logarithmic scale to what extent the former is superior to the latter. If, on the contrary, log S_c^n is negative, the side effect is stronger than the main effect. When the value of log S_c^n is near zero, the effects are of similar intensities and, therefore, the molecules are hardly selective. The larger the absolute value of S_c^n, the greater is the prevalence of one effect over the other.

If $n > 1$, *i.e.*, if more than one side effect is considered at a time, the question becomes more complicated. If $n = 2$ and log $S_c^2 > 0$ starting from Eq. 9*b*, the following is obtained:

$$2 \log \frac{1}{C_m} > \left(\log \frac{1}{C_1} + \log \frac{1}{C_2} \right)$$

This relationship holds for three different situations. In Case A:

$$\log \frac{1}{C_m} > \log \frac{1}{C_1}$$

$$\log \frac{1}{C_m} > \log \frac{1}{C_2}$$

In Case B:

$$\log \frac{1}{C_m} > \log \frac{1}{C_1}$$

$$\log \frac{1}{C_m} < \log \frac{1}{C_2}$$

with:

$$\log \frac{1}{C_m} < \log \frac{1}{C_2} < \left(2 \log \frac{1}{C_m} - \log \frac{1}{C_1} \right)$$

Table IV—Alkylchlorophenols: Regression Equations Generated from Table II Data According to Eq. 11

	Equation[a]	r	s	EV	F	P
Main effect: against *S. aureus*	15. $\log S_c^2 = -2.07\ (\pm 0.81) \log P + 0.32\ (\pm 0.10)(\log P)^2 + 3.30\ (\pm 1.51)$	0.91	0.21	0.81	55.63	<0.01
	16. $\log S_c^2 = 0.39\ (\pm 0.15) \log P - 1.16\ (\pm 0.63)$	0.73	0.35	0.51	27.28	<0.01
Side effect: against *S. typhosa*	17. $\log S_c^1 = 1.89\ (\pm 0.82) \log P + 0.30\ (\pm 0.11)(\log P)^2 + 2.90\ (\pm 1.52)$	0.91	0.22	0.81	54.68	<0.01
	18. $\log S_c^1 = 0.40\ (\pm 0.15) \log P - 1.25\ (\pm 0.61)$	0.75	0.33	0.55	31.91	<0.01
Side effect: against *S. hemolyticus*	19. $\log S_c^1 = -0.18\ (\pm 0.20) \log P + 0.02\ (\pm 0.03)(\log P)^2 + 0.39\ (\pm 0.37)$	0.42	0.05	0.11	2.49	>0.1
	20. $\log S_c^1 = -0.02\ (\pm 0.02) \log P + 0.09\ (\pm 0.10)$	0.26	0.06	0.03	1.77	>0.1

[a] $n = 26$.

In Case C:

$$\log \frac{1}{C_m} < \log \frac{1}{C_1}$$

$$\log \frac{1}{C_m} > \log \frac{1}{C_2}$$

with:

$$\log \frac{1}{C_m} < \log \frac{1}{C_1} < \left(2 \log \frac{1}{C_m} - \log \frac{1}{C_2}\right)$$

Case A is the situation of a molecule whose main effect is stronger than the two side effects. In Cases B and C, the main effect is stronger than one side effect but not the other. Nevertheless, under the given conditions, the value of $\log S_c^2$ is greater than zero. In these cases, the sign of $\log S_c^2$ indicates that the main effect prevails over the sum of the two side effects. However, it is not possible to establish with certainty if the main effect is greater than one single side effect or if it is greater than both of them.

In an analogous way, it can be stated that the undesired side effects in their totality are more intense than the main effect when $\log S_c^2 < 0$, but the latter could be stronger than one of the former.

These considerations can be extended to cases where $n > 2$. Generally, with increasing n, one will obtain less information from $\log S_c^n$. Nevertheless, the absolute value and the sign of $\log S_c^n$ can give useful information about the prevalence of the main effect or of the total of the side effects.

During drug design such information should be able to direct the synthetic work toward molecules with the highest forecasted $\log S_c^n$ values. However, more detailed knowledge of the molecular action may require comparing each effect with the main effect by studying the trend of the corresponding series of $\log S_c^1$ values.

EXPERIMENTAL

The applicability of the proposed model was tested using literature data regarding a group of penicillins (6) and a larger group of alkylchlorophenols (7). Data on the activities of the pencillins against *Staphylococcus aureus, Escherichia coli,* and *Treponema pallidum* and of the alkylchlorophenols against *S. aureus, Salmonella typhosa,* and *Streptococcus hemolyticus* were available.

Methods—None of the activities produced by the two series of molecules could be considered strictly as side effects. Nevertheless, these examples were chosen because exact quantitative data on undesired side effects are often unavailable.

Moreover, the definition of a pharmacological activity as a side effect is not always univocal and absolute but can depend on contingent research requirements. Furthermore, the aim of this study was to focus on the separability of the single effects more than on their specific characteristics. Therefore, the cases illustrated have essentially a paradigmatic value and show how the mathematical model can be applied and what conclusions can be deduced from it.

In both cases, one of the activities was taken arbitrarily as the main effect and the others as side effects. By comparing contemporaneously the main effect with the two side effects, the observed $\log S_c^2$ and the relative regressions were obtained. The observed values of $\log S_c^1$ and the corresponding regressions were obtained by comparing the main effect with each single side effect.

Penicillins—The experimental data on the activities against *S. aureus, E. coli,* and *T. pallidum* and the values of the chromatographic parameter R_m were those published previously (6). The same paper (6) reported the methods of culturing and preparing the microorganisms for the tests. The activity arbitrarily considered as the main effect was the one against *S. aureus*. These data are given in Table I together with the observed and calculated values of $\log S_c^n$.

Alkylchlorophenols—The data on the activities aginst *S. aureus, S. typhosa,* and *S. hemolyticus* and the values of the physicochemical parameter $\log P$ were those provided in the literature (7, 8). The bacteriological techniques were the same as those used by the U.S. Department of Agriculture (9) and have been reported (10). As in the preceding example, the activity against *S. aureus* was arbitrarily chosen as the main effect. The biological data are given in Table II, together with the relative values of $\log S_c^n$.

Regression Analysis—The regression equations were generated by the least-squares method (11). The relative calculations and the statistics were performed by an HP-97 desk minicomputer.

The values of R_m and $\log P$ are given in Tables I and II, respectively. The reported statistics are r, s, the explained variance EV, F values, and p levels. The significance of the regression coefficients was tested at the $p < 0.05$ level by the t test.

RESULTS

The observed values of $\log S_c^n$ were obtained from Eq. 9*b*. These values were correlated directly with the physicochemical parameters according to Eq. 11.

The regressions used to calculated $\log S_c^n$ were generated from the data of Tables I and II are are reported in Table III for the penicillins and in Table IV for the alkylchlorophenols. In this last case, since the introduction of $(\log P)^2$ improved the statistics, the calculated values of $\log S_c^n$ reported in Table II are from Eqs. 15, 17, and 19 of Table IV.

DISCUSSION

The first point that can be deduced from the results is the possibility of correlating directly the selectivity of congener molecules, expressed as $\log S_c^n$, and the structural physicochemical parameters. This was clear from the regression statistics.

Second, the observed $\log S_c^2$ values identified the most selective molecules, even if they were not the most active ones. In fact, from Table I it is evident that I and V are the most selective compounds in their action against *S. aureus* whereas the most active molecule is VI, which is not as selective as the first two. Similarly, the least selective molecule is XI, whereas the least active one is VIII.

The values of $\log S_c^2$ calculated according to Eq. 12 confirm these conclusions with good approximation, even if there is some contradiction with the observed values. This example belongs to Case B (see *Theoretical*), where the main effect is stronger than one of the side effects but not as intense as the other one. This is indicated clearly by the trend of the observed and calculated values of $\log S_c^1$ relative to Eqs. 13 and 14. The values relative to Eq. 14 are all negative, indicating that the side effect against *T. pallidum* is more intense than the main effect against *S. aureus*.

Similar considerations may be deduced regarding the alkylchlorophenols, but in this example the set of the most selective molecules is the same as the most active ones. The less selective compounds, however, do not coincide with the less active ones.

The statistics of Eqs. 14, 19, and 20 indicated a significant worsening of the quality of these regressions compared with the others. This result could be explained by the fact that in these cases the compared activities were carried out on pairs of Gram-positive microorganisms. *S. aureus* and *S. hemolyticus* are Gram-positive; *T. pallidum,* although lacking a cell wall, is sensitive to the antibiotics in an analogous way to Gram-positive bacteria. The R_m and $\log P$ values express the lipophilicity of molecules and, therefore, their ability to cross the cell wall. It is, therefore, likely that these parameters do satisfactorily explain selectivity and its variance in the case of Gram-dissimilar bacteria but that they lead to worse results with Gram-similar bacteria.

CONCLUSIONS

In conclusion, within the limits discussed, the use of log S_c^n should make easier and faster the search for, and the identification of, the therapeutically best molecules. Log S_c^n permits selectivity forecasting by methods and techniques analogous to the ones (quantitative structure-selectivity relationships) utilized to forecast biological activity. Moreover, log S_c^n makes it easier and faster to compare the therapeutic characteristics of different molecules since it permits selectivity quantification in the presence of many side effects.

REFERENCES

(1) C. Hansch, A. R. Steward, and J. Iwasa, *Mol. Pharmacol.*, **1**, 87 (1965).

(2) A. Fujinami, A. Mine, and T. Fujita, *Agr. Biol. Chem.*, **38**, 1399 (1974).

(3) A. Fujinami, T. Satomi, A. Mine, and T. Fujita, *Pestic. Biochem. Physiol.*, **6**, 287 (1976).

(4) W. P. Purcell, G. E. Bass, and J. Clayton, "Strategy of Drug Design: A Guide to Biological Activity," Wiley, New York, N.Y., 1973.

(5) E. Fingl and D. M. Woodbury, in "The Pharmacological Basis of Therapeutics," 4th ed., L. S. Goodman and A. Gilman, Eds., Macmillan, London, England, 1970, pp. 21, 22.

(6) G. L. Biagi, M. C. Guerra, A. M. Barbaro, and M. F. Gamba, *J. Med. Chem.*, **13**, 511 (1970).

(7) E. J. Lien, C. Hansch, and S. M. Anderson, *ibid.*, **11**, 430 (1968).

(8) E. Klarmann, V. A. Shternov, and L. W. Gates, *J. Am. Chem. Soc.*, **55**, 2576 (1933).

(9) G. L. A. Ruehle and C. M. Brewer, "United States Food and Drug Administration Methods of Testing Antiseptics and Disinfectants," Circular 198, U.S. Department of Agriculture, Dec. 1931.

(10) E. Klarmann, V. A. Shternov, and L. W. Gates, *J. Lab. Clin. Med.*, **19**, 835 (1934).

(11) G. W. Snedecor and W. G. Cochran, "Statistical Methods," 6th ed., Iowa State University Press, Ames, Iowa, 1967.

ACKNOWLEDGMENTS

The authors thank Dr. William P. Purcell, University of Tennessee, Memphis, Tenn., for helpful comments.

Hydrodynamic Characterization of a Spin-Filter Dissolution Device

J. W. MAUGER ˣ, S. A. HOWARD, and A. KHWANGSOPHA

Received December 26, 1978, from the *School of Pharmacy, West Virginia University, Morgantown, WV 26506.* Accepted for publication March 1, 1979.

Abstract □ The spin-filter dissolution device was characterized using a two-dimensional convective diffusion model. Experimental model testing involved analysis of dissolution rates from nondisintegrating salicylic acid disks. The disks were prepared as double-layer tablets, with an ethylcellulose layer as a nondissolving surface. For each dissolution run, the disk was positioned so that the dissolving salicylic acid surface was parallel to the flow of the circulating fluid. Experimental variables included the stirring speed, the tablet radius, and the distance of the tablet from the stirring source. At the farthest distance from the stirring source, the average numerical exponents for stirring speed and tablet radius were 0.58 and 1.54, respectively, which compare favorably with the values of 0.50 and 1.50 from the model. When the dissolving salicylic acid surface was positioned closer to the stirring source, the numerical exponent for the stirring speed increased significantly, while the average numerical exponent for the tablet radius was lowered to 1.07, indicating a change in dissolution mechanism as a function of distance from the stirring source. These data indicate that dissolution rates are not necessarily proportional to surface area as predicted by the Nernst equation and that distance from the stirring source is significant.

Keyphrases □ Hydrodynamics—dissolution devices, spin filter, salicylic acid disks □ Models, hydrodynamic—dissolution devices, spin filter, salicylic acid disks □ Dissolution devices—spin filter, hydrodynamic analysis, models

Knowledge of critical operating variables for a dissolution device is important to the pharmaceutical scientist interested in product development, quality control, and research applications. A recent paper (1) discussed certain operating variables for the spin-filter dissolution device developed by Shah *et al.* (2). The results of this investigation indicate that the dissolution of a tablet placed in a basket is much more rapid from the face of the tablet resting on the bottom of the basket than from the face inside the basket. This effect was duplicated at stirring speeds of 300 and 500 rpm.

Understanding and predicting the dissolution performance for a given dissolution instrument require evaluating the instrument with a justifiable model. The purpose of the present study was to continue an evaluation of the spinning-filter device *via* a convective diffusion model based on a physically realistic and mathematically sound development.

THEORY

The model chosen is a classical one involving the flow of incompressible fluids past immersed bodies. For a nondissolving plate immersed in a fluid where the free stream velocity is U (centimeters per second), the velocity of the fluid in contact with the surface of the plate ($y = 0$) is assumed to be zero and frictional resistance retards the moving fluid in a thin layer near the wall. A property of the hydrodynamic boundary layer, h_1 (centimeters), is that its thickness is a function of the length of the plate. It is assumed that h_1 is zero at the leading edge of the plate ($x = 0$). A functional relationship between the hydrodynamic boundary layer, h_1, the free stream velocity, U, and the length of the plate, x, is:

$$h_1 = 4.64\left(\frac{\nu x}{U}\right)^{1/2} \qquad \text{(Eq. 1)}$$

Thus, h_1 increases as a function of the square root of the distance along the x axis of the plate and diminishes by a factor equal to the reciprocal square root of the free stream velocity. As Levich (3) emphasized, in reality h_1 is not a distinct distance. Instead, it represents a transition from viscous flow in the hydrodynamic boundary layer to inviscid flow in the main stream and is smooth and gradual. The thickness is commonly defined as the distance from the wall ($y = 0$) to a point where the velocity in the x direction is 90% of the free stream velocity.

A mass transfer model under conditions of forced convection can now be evaluated. Once again, visualize a plate immersed in a fluid stream.

0022-3549/79/0900-1084$01.00/0