Comparison of Several Molecular Topological Indexes with Molecular Surface Area in Aqueous Solubility Estimation

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Abstract □ The molecular topological indexes proposed by Wiener (Wiener number), Hosoya (*Z*-value), and Randic (branching index) were correlated with computed molecular surface areas and aqueous solubilities for the monofunctional aliphatic alcohols, ethers, ketones, aldehydes, carboxylic acids, esters, and hydrocarbons. Comparison of the indexes with molecular surface area indicates that all three indexes (or simple modifications) correlate with molecular surface area and, although computed in different manners, reflect molecular topology. Comparison of the correlations of log solubility with the several indexes leads to the following conclusions: (*a*) the branching index works well for aliphatic, acyclic monofunctional compounds but not cyclic aliphatic compounds; (*b*) the square root of the Wiener number correlates less satisfactorily with log solubility than the other indexes but more correctly handles cyclic compounds (when generalized after Hosoya); (*c*) correlations of log solubility with the log *Z*-value are satisfactory, but the index is difficult to compute; and (*d*) the molecular surface area represents the single best parameter with which to correlate and estimate aqueous solubility due to its generality. However, for a restricted series of compounds, the branching index is perhaps the most useful index by virtue of its simplicity.

Keyphrases □ Topological indexes—Wiener number, *Z*-value, and branching (connectivity) index compared, correlated with molecular surface areas and aqueous solubilities, various monofunctional compounds □ Solubility, aqueous—correlated with topological indexes, various monofunctional compounds □ Wiener number—correlated with other topological indexes, molecular surface areas, and aqueous solubilities, various monofunctional compounds □ *Z*-value—correlated with other topological indexes, molecular surface areas, and aqueous solubilities, various monofunctional compounds □ Molecular connectivity—correlated with other topological indexes, molecular surface areas, and aqueous solubilities, various monofunctional compounds

The development of atomic and group "constants" that may be used in estimating the physical, chemical, and biological properties of organic compounds has been the subject of considerable research. The interest in such parameters results from the need or desire to estimate the properties of compounds that are unknown or for which the required experimental data are lacking. Examples of such parameters and approaches are numerous (1–11).

Approaches to the determination of the atomic or group parameters may be divided into two groups:

1. Those that directly reduce the molecular or bulk property to atomic contributions (*e.g.*, parachor, polarizability, refractive index, and partition coefficient).
2. Those that try to correlate the molecular or bulk property with an index computed from molecular structure (*e.g.*, correlations with computed surface areas and Wiener number).

An alternative approach, which does not necessarily imply an assumed additivity of the molecular and bulk properties from atomic contributions, is the correlation of one property with another (*e.g.*, partition coefficient with solubility and solubility with solubility parameter). There is probably no "best" parameter or approach due to the generally inevitable trade off between simplicity and accuracy. However, from an accuracy point of view, correlations between closely related physical properties are perhaps the best but require experimental data for at least one physical property.

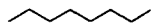
Approaches 1 and 2 have the potential (and very de-

Table I—Summary of −Log Solubility (Molal), Total Surface Area (TSA), Wiener Number (*W*), Log *W*, *Z*-Value (*Z*), Log *Z*, and Branching Index (*B*) for Saturated Hydrocarbons

Compound	Structure	−Log Solubility	TSA, Å²	*W*	$\sqrt{W}$	*Z*[a]	Log *Z*	*B*
Methane		—	152.2	—	—	1	0	0
Ethane	—	—	191.7	1	1	2	0.301	1.000
Propane		—	223.5	4	2	3	0.477	1.414
n-Butane		2.63	255.2	10	3.16	5	0.699	1.914
Isobutane		2.55	249.1	6	2.45	4	0.602	1.732
n-Pentane		3.27	287.0	20	4.47	8	0.903	2.414
2-Methylbutane		3.18	274.6	18	4.24	7	0.845	2.270
Neopentane		3.13	270.1	12	3.46	5	0.699	2.000

(*continued*)

Table I—(*Continued*)

Compound	Structure	−Log Solubility	TSA, Å²	*W*	$\sqrt{W}$	*Z*[a]	Log *Z*	*B*
Cyclopentane		2.65	—	15	3.87	11	1.04	2.500
n-Hexane		3.95	319	35	5.92	13	1.11	2.914
3-Methylpentane		3.83	300.1	31	5.57	12	1.08	2.808
2,2-Dimethylbutane		3.67	290.8	26	5.10	9	0.954	2.561
Cyclohexane		3.18	279.1	27	5.20	18	1.26	3.000
n-Heptane		4.53	351	56	7.48	21	1.32	3.414
2,4-Dimethylpentane		4.39	324.7	48	6.93	15	1.18	3.126
(*e*)-Methylcyclohexane		3.85	304.9	42	6.48	26	1.41	3.394
Cycloheptane		3.52	301.9	42	6.48	29	1.46	3.500
n-Octane		5.24	383	84	9.17	34	1.53	3.914
1-*cis*-2-Dimethylcyclohexane		4.26	315.5	60	7.75	39	1.59	3.805
Cyclooctane		4.15	322.6	64	8.00	47	1.67	4.000
2,2,4-Trimethylpentane		4.13	338.9	66	8.12	19	1.28	3.417

[a] Most tabulated values are from the compilation in Refs. 6 and 7; remaining values were computed from definitions (see text).

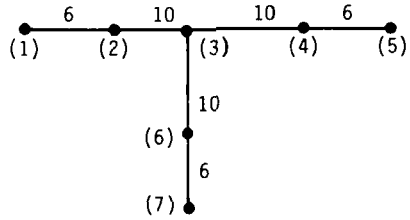
sirable) capability of estimating the physical properties of unknown compounds and, therefore, have a great attraction for "design" programs. Although they are generally limited by the additivity assumption, the nonadditivity can be at least partially accounted for by relaxing the atomic additivity to a group additivity; however, this approach causes an increase in the number of parameters required for estimation as well as a reduction in the generality and the ease of computation.

This report centers on the second approach since it was shown previously (10) that, at least in the case of molecular surface area correlations, it leads to a natural reduction in the number of parameters required for the estimation of aqueous solubilities. Molecular surface area, the Wiener number (*W*), Hosoya's *Z*-value (*Z*), and Randic's branching index (*B*) will be considered with the objective of assessing the value and limitations of the various approaches with respect to solubility estimation.

COMPUTATION OF TOPOLOGICAL INDEXES

Molecular Surface Area—Molecular surface areas were computed using the method developed by Hermann (9). An alternative method for estimating numbers related to molecular surface areas was employed by Harris *et al.* (12). This method has the advantage of not involving numerical computations but has the disadvantage of not allowing precise determination of the functional group surface areas[1].

Wiener Number—The Wiener number (*W*), called the path number by Wiener (3, 4), is defined as the sum of the distances between all pairs of carbon atoms in the molecule in terms of carbon–carbon bonds. It is computed by multiplying the number of carbon atoms on one side of any bond by the number on the other side of the bond and summing these values for all bonds. For example, for 3-ethylpentane, $W = 48$:



An alternative method of calculation of the Wiener number, suggested by Hosoya (6) and convenient for generalizing *W* to cyclic compounds, is to take *W* as one-half of the sum of the elements of the distance matrix, *D*, whose element d_{ij} is the number of bonds for the shortest path between atoms *i* and *j* with $d_{ii} = 0$. For this example, $W = 96/2 = 48$:

atom number	1	2	3	4	5	6	7	row sum
1	0	1	2	3	4	3	4	17
2	1	0	1	2	3	2	3	12
3	2	1	0	1	2	1	2	9
4	3	2	1	0	1	2	3	12
5	4	3	2	1	0	3	4	17
6	3	2	1	2	3	0	1	12
7	4	3	2	3	4	1	0	17
							total	96

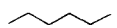
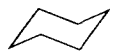
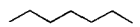
Z-Values—The topological index, *Z*, was defined by Hosoya (6, 7) as follows. Let $p(k)$ be the number of ways in which *k* bonds can be chosen from a given molecule (or graph, *G*) such that no two of them are connected. Then:

$$Z = \sum_{i=0}^{N} p(i) \qquad \text{(Eq. 1)}$$

with $p(0) = 1$ and $p(1)$ = number of bonds, *N*. This example gives $p(0)$

[1] An additional problem associated with the use of the numbers reported by Harris *et al.* (12) is that the conformations considered were not specified. Some type of averaging over possible conformations for a given compound was indicated but not precisely stated.

Table II—Normalized Solubility and Indexes

Compound	Structure	Log Solubility	−Normalized Log Solubility	Normalized TSA	Normalized W	Normalized $\sqrt{W}$	Normalized Z	Normalized Log Z	Normalized B
Methane		—	1.00	1	—	—	1	1	—
Ethane		—	2.00	2	2	2	2	2	2
Propane		—	3.00	3	3	3	3	3	3
n-Butane		−2.63	4.00	4	4	4	4	4	4
Isobutane		−2.55	3.88	3.90	2.4	3.1	3.2	3.44	3.62
n-Pentane		−3.27	5.00	5	5	5	5	5	5
2-Methylbutane		−3.18	4.86	4.78	4.5	4.74	4.38	4.68	4.70
Neopentane		−3.13	4.79	4.71	3.0	3.87	3.13	3.87	4.14
Cyclopentane		−2.65	4.05	—	3.75	4.33	6.88	5.76	5.18
n-Hexane		−3.95	−6.00	6	6	6	6	6	6
3-Methylpentane		−3.83	5.82	5.64	5.31	5.65	5.54	5.83	5.78
2,2-Dimethylbutane		−3.67	5.57	5.47	4.46	5.17	4.15	5.16	5.27
Cyclohexane		−3.18	4.83	5.25	4.63	5.27	8.31	6.8	6.18
n-Heptane		−4.53	7.00	7	7	7	7	7	7
2,4-Dimethylpentane		−4.39	6.78	6.48	6.0	6.49	5.0	6.26	6.41
Methylcyclohexane		−3.85	5.95	6.08	5.25	6.06	8.67	7.48	6.96
Cycloheptane		−3.52	5.44	6.02	5.25	6.06	9.67	7.74	7.18
n-Octane		−5.24	8.00	8	8	8	8	8	8
1-*cis*-2-Dimethylcyclohexane		−4.26	6.50	6.59	5.71	6.76	9.18	8.31	7.78
Cyclooctane		−4.15	6.34	6.74	6.10	6.97	11.06	8.73	8.18
2,2,4-Trimethylpentane		−4.13	6.31	7.08	6.29	7.08	4.47	6.69	6.98

[a]These values were computed using Eq. 4.

Table III—Results of Regression Analysis of Normalized Log Aqueous Solubility *versus* the Normalized Indexes for (*a*) Cyclic and Acyclic Hydrocarbons and (*b*) Acyclic Hydrocarbons Alone: Model N Log (Solubility) = $\theta_0 + \theta_1$ (N Index)

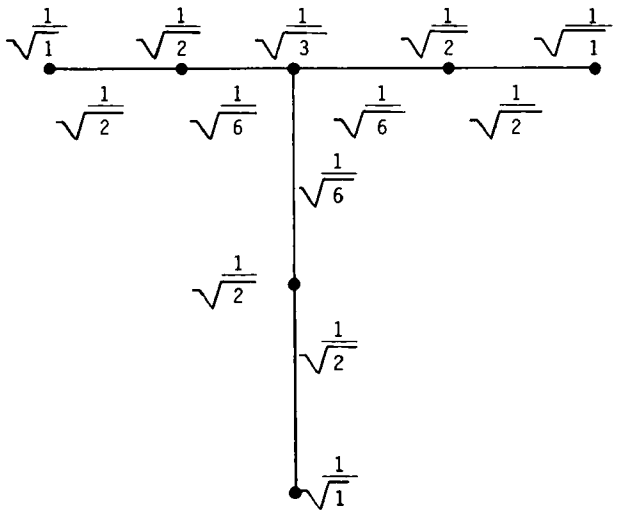
Index	θ_1	θ_0	r	s
		Acyclic and Cyclic		
NTSA	0.934	0.287	0.968	0.281
$N\overline{W}$	0.730	1.90	0.924	0.428
$N\sqrt{W}$	0.781	1.25	0.944	0.371
NZ	0.215	4.36	0.487	0.978
N log Z	0.504	2.60	0.755	0.734
NB	0.636	1.85	0.840	0.609
		Acyclic		
NTSA	0.946	0.304	0.980	0.262
$N\overline{W}$	0.714	1.98	0.932	0.471
$N\sqrt{W}$	0.811	1.20	0.965	0.343
NZ	0.720	2.08	0.848	0.688
N log Z	0.870	0.890	0.972	0.306
NB	0.887	0.722	0.975	0.288

= 1, $p(1) = 6$, $p(2) = 9$, $p(3) = 4$, and $p(i > 3) = 0$, which gives $Z = 20$. The Z-values for the various hydrocarbons considered in this study were taken directly from Ref. 6.

Branching Index[2]—The branching index, B, is defined (11) as follows. Assign to each (nonhydrogen) atom a value of $1/\sqrt{\nu}$, where ν is the number of nonhydrogen (*i.e.*, non-CH) bonds in which the atom is involved. The bond or edge index is given by the product of the values associated with the terminal atoms of that particular bond. Thus:

$$B = \sum_{\text{all bonds}} 1/\sqrt{\nu_i \nu_j} \qquad \text{(Eq. 2)}$$

and for example:

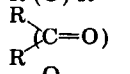
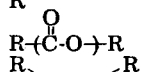
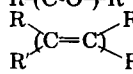


$$B = 3\left(\frac{1}{\sqrt{2}}\right) + 3\left(\frac{1}{\sqrt{6}}\right) = 3.3461 \qquad \text{(Eq. 3)}$$

RESULTS AND DISCUSSION

Comparison of Indexes—Table I presents log aqueous solubility, computed total surface areas (TSA) (with a solvent radius of 1.5 Å), W, $\sqrt{W}$, Z, log Z, and B for various hydrocarbons. Several observations can be made on inspection of Table I. First, while TSA and B increase linearly with chain length, W and Z do not. However, $\sqrt{W}$ and log Z increase in a nearly linear manner with chain length. Second, TSA and W decrease on cyclization, while Z and B increase. These trends suggest that $\sqrt{W}$ and log Z should be considered for correlation purposes and that Z (and log Z) and B will not satisfactorily treat both acyclic and cyclic compounds without a modification in their definitions.

Table IV—Atoms Contributing to Functional Group Terms

Compounds	Functional Group
Alcohols	R–(O-H)
Ethers	R–(O)–R′
Ketones, aldehydes	
Acids, esters	
Olefins	

For more detailed comparison, it is convenient to normalize the data in Table I. Each entry in Table I has been normalized in the following manner:

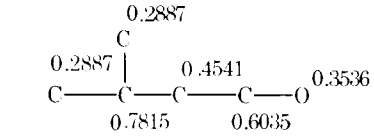
$$\text{normalized property or index} = N\left\{\frac{\text{property or index for the compound}}{\text{property or index for the corresponding normal compound}}\right\} \qquad \text{(Eq. 4)}$$

where N is the number of nonhydrogen atoms (recorded in Table II). This normalization linearizes all indexes with chain length and allows direct comparisons to be made with respect to the effect of branching on the index. The general trends in the table can be illustrated by considering the six carbon isomers. By comparing the normalized indexes with the normalized solubilities, it is observed that the TSA and B indexes more closely reproduce the solubility trends while W and Z exhibit far too dramatic decreases with branching. Log Z and $\sqrt{W}$ are considerably better in this respect. Again, only TSA and W, or $\sqrt{W}$, correctly reproduce the trend for cyclic compounds.

Table III presents the results of a regression analysis using normalized solubilities and indexes. A theoretically perfect index, in addition to giving good r and s values, would have a slope of 1.0 (θ_1 in Table III), ignoring experimental error. From the table, it is clear that, for all compounds, the TSA parameter correlates best. When restricting attention to acyclic compounds, it is observed that TSA, $\sqrt{W}$, log Z, and B all work reasonably well. In making a decision as to the "best" index, the following considerations apply. The $\sqrt{W}$ is somewhat less satisfactory overall but is relatively easy to compute and handles cyclic compounds more correctly. Log Z is reasonably good but difficult to compute and incorrectly treats cyclic compounds; B and TSA are about equally good for acyclic compounds, while TSA is definitely superior overall but requires rather involved numerical computations[3].

Branching Index *versus* Surface Area—From the preceding analysis, it appears that the surface area and the branching index methods represent the most promising approaches, one from the point of view of generality and the other from the point of view of simplicity. These two approaches will now be compared for their ability to correlate with aqueous solubilities using monofunctional aliphatic compounds. Cyclic compounds are omitted from the data sets since, as noted previously, the branching index, as presently defined, does not adequately treat ring structures[4].

In the subsequent analysis, the computed indexes are used directly rather than the normalized values. The solubility data and the treatment of functional groups using the TSA index are the same as in previous studies (10, 15). For the branching index, the edge or bond values is divided by one-half and assigned to atoms. The index for a given atom is just one-half the sum of the incident edge or bond values. For example, on 3-methyl-1-butanol:



[2] Kier *et al.* (13) referred to B as the connectivity index and gave it the symbol χ.

[3] However, an easily executable computer program is available (14).

[4] See, however, Ref. 13.

Table V—Regression Analysis Model[a]: Log Solubility = θ_1HYB + θ_2 FGB + θ_3 FGI + θ_0 for Acyclic Monofunctional Compounds

Compounds[b]	θ_1[c]	θ_2[c]	θ_3[c]	θ_0[c]	r	s
Hydrocarbons (12)	−1.15 (0.08)	0	0	−0.59 (0.23)	0.976	0.182
Alcohols (83)	−1.16 (0.02)	−4.5 (0.34)	4.5 (0.11)	−0.57 (0.05)	0.996	0.118
Ethers (39)	−1.25 (0.04)	−2.7 (0.49)	3.9 (0.26)	−0.34 (0.12)	0.997	0.135
Ketones, aldehydes (47)	−1.15 (0.04)	0.5 (0.46)	1.9 (0.33)	−0.59 (0.11)	0.994	0.171
Esters (69)	−0.98 (0.02)	0.5 (0.32)	1.4 (0.37)	−1.05 (0.07)	0.994	0.151
Acids (23)	−1.16 (0.05)	−2.0 (2.2)	4.0 (2.2)	−0.56 (0.13)	0.996	0.185
Olefins (22)	−1.20 (0.05)	−0.7 (0.53)	−0.1 (0.35)	−0.47 (0.15)	0.989	0.157

[a] HYB = hydrocarbon branching index, FGB = functional group branching index, and FGI = functional group index. [b] Value in parenthesis is the number of data points. Data sets for the monofunctional compounds included the 12 hydrocarbons. [c] Value in parenthesis is the standard error.

Table VI—Regression Model[a]: Log Solubility = θ_1 HYSA + θ_2FGSA + θ_3FGI + θ_0 for Acyclic Monofunctional Compounds

Compounds[b]	θ_1[c]	θ_2[c]	θ_3[c]	θ_0[c]	r	s
Hydrocarbons (12)	−0.0193 (0.0013)	0	0	2.1 (0.38)	0.980	0.169
Alcohols (83)	−0.0187 (0.0003)	−0.023 (0.002)	3.4 (0.11)	2.0 (0.12)	0.991	0.177
Ethers (39)	−0.0201 (0.0006)	−0.060 (0.007)	3.44 (0.09)	2.4 (0.19)	0.997	0.124
Ketones, aldehydes (47)	−0.0185 (0.0005)	−0.034 (0.003)	3.6 (0.12)	1.9 (0.17)	0.995	0.157
Esters (69)	−0.0164 (0.0004)	−0.029 (0.003)	3.6 (0.14)	1.3 (0.15)	0.991	0.188
Acids (23)	−0.0195 (0.0008)	−0.036 (0.007)	4.3 (0.50)	2.2 (0.25)	0.997	0.167
Olefins (22)	−0.0199 (0.0009)	−0.021 (0.010)	0.5 (3.5)	2.3 (0.27)	0.988	0.163

[a] HYSA = hydrocarbon surface area, FGSA = functional group surface area, and FGI = functional group index. [b] Value in parenthesis is the number of data points. Data sets for the monofunctional compounds included the 12 hydrocarbons. [c] Value in parenthesis is the standard error.

and B = 2.7701. The value of 0.3536 can now be identified with the functional group, and a value of 2.4165 can be given to the hydrocarbon part of the molecule. Functional group indexes (FGI) and hydrocarbon indexes (HYI) were computed for all monofunctional compounds in this manner. Table IV shows the atoms considered as contributing to the functional group. The results of regression analysis are presented in Table V, and the corresponding results using molecular surface area are listed in Table VI (15). These data indicate that the branching index and surface area approaches are about equally successful, with perhaps some preference given to the branching index.

A discussion of the various terms in these regression equations is essentially the same as that for surface area (15). However, one point to be noted is the low value for the FGI coefficient for ketones, aldehydes, and esters. This is a result of treating the double bond (*e.g.*, $R_1R_2C{=}O$) as contributing two edges to each vertex. If the homomorph approach (15) is chosen and the index is computed using a hydrocarbon with the same number of nonhydrogen atoms, the FGI coefficients become very similar to those values using the surface area approach.

Another point is the high standard error associated with the FGI and FGB coefficients of the fatty acids in Table V. This is a result of the high correlation between these two parameters (due to the fact the FGB is almost a constant in this series). Removing, for example, the FGB term gives essentially the same r and s values as are given in Table V and low standard errors for the remaining parameters.

From a practical point of view, the branching index is very appealing. When studies are restricted, for example, to a homologous series of aliphatic substituents, the index provides effective carbon numbers that may be used in correlations (Table II). Its simplicity, however, is a disadvantage relative to surface area on at least three counts: (*a*) its inadequate treatment of cyclic compounds, (*b*) its insensitivity to conformational and stereochemical differences, and (*c*) its inability to treat hydrophobic (intra- and intermolecular) association. A molecule that might typify all of these problems is cholesterol. The branching index would give a single value for this molecule, while its physical properties would depend markedly on the conformational and stereochemical disposition of its atoms and perhaps on intramolecular hydrophobic association (15).

If an index is to account for these effects, it must consider distances between nonbonded atoms. There is no doubt that the branching index could be modified and extended by adding additional factors and extending its definition[5]. However, care must be taken not to lose its attractive simplicity.

SUMMARY AND CONCLUSIONS

The results of these studies indicate that all of the indexes considered can be used (or easily modified) to give reasonable results. However, the parameters of choice would probably be surface area for its generality and the branching index for its simplicity. When studying homologous series effects, the branching index may be particularly useful.

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[5] See, for example, Platt's discussion of the Wiener number (5).

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Continuous Dissolution Rate Determination as a Function of the pH of the Medium

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Abstract □ A method was developed for varying the pH of the medium during dissolution rate studies of timed-release tablets with the aid of compressed, totally soluble, alkaline powder mixtures. Commercial as well as experimental timed-release capsules or tablets were used as models, and dissolution rates were determined at pH 1.1, 2.4, and 7.4. The system can be applied to other pH values or other variations of the dissolution medium (*e.g.*, ionic strength) to: (*a*) correlate *in vitro* release rates with bioavailability data, (*b*) discriminate between alternative formulations during dosage form development, or (*c*) serve as a selective control procedure for a series of sustained-release dosage forms.

Keyphrases □ Dissolution rate—timed-release tablets, continuous determination as a function of pH □ Dosage forms—timed-release tablets, dissolution rate, continuous determination as a function of pH □ Tromethamine—buffer system for dissolution rate studies of timed-release tablets as a function of pH

Among the many parameters that influence the *in vitro* release rates of pharmaceuticals from timed-release dosage forms[1], the pH of the medium is particularly important, because these forms are designed to release their active ingredient(s) for a prolonged period (usually 8–12 hr). During this time interval, solid oral pharmaceutical formulations (such as tablets or capsules) pass from the stomach to the duodenum and on through the lower intestinal tract. Throughout this passage, they are exposed to a pH gradient ranging approximately from 1 to 8. [This range is narrower for healthy adults. The average pH of gastric fluid in men is about 1.9, while it is reported to be approximately 2.6 for women (2). The pH of the duodenal secretion for both men and women varies from 5.8 to 7.6 (3).]

This study was designed to evaluate a relatively simple method for determining the dissolution rates of timed-release solid dosage forms as a function of the pH of the medium. Model capsules and tablets were selected to meet the following requirements: (*a*) good solubility throughout the tested pH range, and (*b*) availability of a rapid assay procedure compatible with the system. The basic procedure was developed to allow for adjustment of the medium to other than the initial pH values or for the introduction of further changes (*e.g.*, ionic strength, viscosity, and composition of the medium).

[1] The term "timed release" is defined in NF XIV (1).

Alkaline phosphates and tromethamine [tris(hydroxymethyl)aminomethane] have been applied or recommended for modifying the pH of the medium (4–6), particularly for testing the dissolution rates of delayed-release formulations. In this study, completely soluble compressed tablets of these agents were formulated and used as the simplest way of achieving "in process" pH changes.

EXPERIMENTAL

Apparatus—The dissolution rate apparatus was fully described previously (6). The drug substance is extracted by a continuously flowing dissolution medium from the solid dosage forms, using a flow-through dissolution cell held at constant temperature (37°). The liquid moves through a flow-through cell, and the concentration is monitored spectrophotometrically (or by another suitable instrument). A typical set of dissolution curves is shown in Fig. 1.

Dissolution Media—Hydrochloric acid (0.1 *N*) was used as the initial dissolution fluid. The pH of this medium was changed by adding increasing amounts of tromethamine[2].

Within the scope of this study, the dissolution rates were determined at pH 1.1, 2.4, and 7.4. It was found practical to formulate 3.0-g tablets containing 1.4 g of tromethamine, 1.54 g of sucrose USP, and 0.06 g of polyethylene glycol 6000[3].

The thoroughly mixed powder was compressed directly with the aid of a manual hydraulic press[4] [compression force of 2270 kg (5000 lb)]. The excipients of the tablets were selected to form a tablet that dissolves completely in an aqueous medium and does not significantly absorb light between the wavelengths of 300 and 240 nm.

By adding four or five of these tablets, which contain 5.6 or 7.0 g of tromethamine, respectively, to the initial 500 ml of dissolution medium, the desired pH value of 2.4 or 7.4 was obtained without fluid interchange of the flowing system (Table I). (The tromethamine tablets dissolve in the medium in about 90 sec.)

Pharmaceutical Preparations—Commercially available theophylline capsules contained 259.2 mg of theophylline in coated pellets. The average total weight of the pellets in the size 0 capsules was 640.0 mg.

Phenylpropanolamine hydrochloride tablets were incorporated in an experimental timed-release matrix. [Phenylpropanolamine tablets or capsules were the subjects of several recent studies (6–8) due to their increasing therapeutic importance].

Dissolution Rate Testing Procedure—A predetermined volume of 0.1 *N* hydrochloric acid was added to each of six 1-liter beakers. For the theophylline capsules, 1000 ml was used; for the phenylpropanolamine hydrochloride tablets, 500 ml was used. The beakers were

[2] Ultrapure grade, 99.9%; Aldrich Chemical Co., Milwaukee, Wis.
[3] Sentry, Union Carbide Corp., New York, N.Y.
[4] Carver laboratory press model C, Fred S. Carver, Inc., Monomonee Falls, WI 53051