Molecular Topology and Aqueous Solubility of Aliphatic Alcohols

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Abstract □ A physically based method for arriving at topological indexes is described. The derived indexes correlate with molecular surface areas and with the molecular connectivity index. The newly derived index seems to account better for the expected distinctions among primary, secondary, and tertiary alcohol aqueous solubilities. This study suggests that the Del Re method for calculating molecular charges and dipole moments also may be used, without appreciable change, to provide estimates of molecular refraction.

Keyphrases □ Alcohols, aliphatic—molecular topology, aqueous solubility, structure–activity relationships □ Topological indexes—aliphatic alcohols, molecular surface area, molecular connectivity, aqueous solubility, structure–activity relationships □ Solubility, aqueous—aliphatic alcohols, molecular topology, structure–activity relationships □ Structure–activity relationships—aliphatic alcohols, molecular topology, aqueous solubility

About 3 years ago, an approach was presented (1) for assigning a numerical index to acyclic hydrocarbons and for ranking them according to their degree of branching. To each atom (vertex) of a molecular structure (graph) was assigned a value $1/\nu^{1/2}$, where ν is the vertex valency. The valency may be taken as the number of valence electrons less the number of hydrogens associated with an atom. Each molecular bond (edge) was characterized by the product of associated atom values: $1/(\nu_i\nu_j)^{1/2}$. The branching index was obtained by summing all bond values appropriate to a molecule. Reciprocal values were used to distinguish bond types since the branching indexes thus derived parallel the ordering for branched structures arrived at from a binary representation of their connectivity (bonding or topological) matrixes.

BACKGROUND

This approach has been extended considerably (2). In particular, the treatment of cyclic aliphatics, alkenes, aromatics, and heteroatomic substances was left unspecified previously (1). The definition for ν [also termed δ (2)] was extended to include first row atoms of the periodic table (C, N, and O) irrespective of the nature of the bonding; valency values for the halogens and for sulfur were established empirically; and an adjustment to the branching index (termed χ), which is appropriate to cyclic aliphatics, was provided (2).

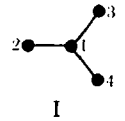
No physical definition for the branching index exists, although it appears to be related to molecular refraction or to molecular volume by the nature of its construction. The physical properties of branched aliphatic substances frequently differ from those of corresponding n-aliphatic substances. Hence, a graph of a physical property (or its logarithm) against an integer (1, 2, . . .) representing the number of carbon atoms in a side chain generally will be linear for the n-aliphatic substances, but considerable departures from this line most often will be noted for branched aliphatic substances. An index such as that described, which allows both n-aliphatic and branched aliphatic substances to lie on a line when graphed against a physical property, reflects a change due to branching in molecular refraction or to molecular volume, because these are the principal physical attributes of n-aliphatic substances.

In a sense, the derivation of branching indexes by the described approach corresponds to the determination of a molecular refraction value using bond refractions adjusted according to the nature of the immediate molecular environment. That is, molecular refractions, which are usually considered to be additive–constitutive properties, are in reality only approximately additive–constitutive; more accurate estimates require consideration of the perturbations induced by differing atomic environments. Such a perturbational approach has been taken (3, 4) for molecular dipole calculation. Bond dipoles are vectorially additive, but the effect of differing atomic environments has to be taken into account for more accurate molecular dipole estimates.

In this study, the perturbational approach described previously (3–5) was applied topologically to arrive at numerical indexes appropriate to a given molecule. The indexes obtained for a hydrocarbon series have the same general attributes as the molecular connectivity index. The indexes obtained for a series of 51 aliphatic alcohols correlate with their aqueous solubilities similarly to the correlations reported when their molecular surface areas (6) or connectivity indexes (7) were used. These results suggest that the perturbational approach may provide a means of arriving at topographically consistent molecular refraction and charge estimates.

EXPERIMENTAL

Isolated atoms, when bonded, have their properties changed. The electron affinity toward an isolated atom differs from the electron affinity for a bonded atom. Hence, depending on the bonding about an atom, the electronegativity and, consequently, the charge and polarizability characteristics of the atom will vary. For a molecule such as isobutane (I) (hydrogen atoms suppressed for simplicity), a given atomic property for a bonded atom, δ_i, may be said to be perturbed from the isolated atom value, δ_i^0, in a linear manner with respect to each similar atomic property for its immediate neighbors. Thus, a set of equations may be written (one equation for each atom of the molecule) that represents the existing perturbations within a molecule (Eqs. 1*a*–1*d*):



I

$$\delta_1 = \delta_1^0 + \gamma_{12}\delta_2 + \gamma_{13}\delta_3 + \gamma_{14}\delta_4 \quad \text{(Eq. 1}a\text{)}$$

$$\delta_2 = \delta_2^0 + \gamma_{21}\delta_1 \quad \text{(Eq. 1}b\text{)}$$

$$\delta_3 = \delta_3^0 + \gamma_{31}\delta_1 \quad \text{(Eq. 1}c\text{)}$$

$$\delta_4 = \delta_4^0 + \gamma_{41}\delta_1 \quad \text{(Eq. 1}d\text{)}$$

The coefficients γ_{ij} provide a measure of the influence of bonded atom i on bonded atom j. With numerical values for γ_{ij} and δ_i^0, one can solve the simultaneous equations represented by Eq. 2 so as to estimate the atomic properties, δ_i, appropriate to the atoms in a given molecule:

$$\begin{vmatrix} 1 & -\gamma_{12} & -\gamma_{13} & -\gamma_{14} \\ -\gamma_{21} & 1 & 0 & 0 \\ -\gamma_{31} & 0 & 1 & 0 \\ -\gamma_{41} & 0 & 0 & 1 \end{vmatrix} \begin{vmatrix} \delta_1 \\ \delta_2 \\ \delta_3 \\ \delta_4 \end{vmatrix} = \begin{vmatrix} \delta_1^0 \\ \delta_2^0 \\ \delta_3^0 \\ \delta_4^0 \end{vmatrix} \quad \text{(Eq. 2)}$$

Inspection of Eq. 2 shows that the matrix of the γ_{ij} coefficients has the form of a bonding or topological matrix. Therefore, a consistently applied set of arbitrary values for δ_i^0 and γ_{ij} may be used to arrive at topographically meaningful indexes for the atoms of a molecule. The sum of the atom indexes would then provide a branching index. In this work, the following conditions were applied: (*a*) molecular structures were represented with the hydrogen atoms suppressed; (*b*) δ_i^0 values were chosen to correspond to the number of valence electrons on an atom ($\delta_C^0 = 4$; $\delta_O^0 = 6$); and (*c*) the value of γ_{ij} ($\gamma_{ij} = \gamma_{ji}$) was taken as 0.1 for C–C and C–O bonds because such a value provides computed atom indexes, δ_i, that are all positive.

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Table I—Aqueous Solubilities of Aliphatic Alcohols and Topological Indexes

Compound	Mole Fraction Solubility, $-\log X_2$[a]	M'	A'	A'_R	TSA[a]	χ[b]
1-Butanol	1.7500	26.11	0.972	0.624	272.1	2.414
2-Methylpropanol	1.7428	26.20	0.971	0.625	263.8	2.269
2-Butanol	1.7244	26.24	0.972	0.641	264.1	2.269
1-Pentanol	2.3318	31.09	1.173	0.825	303.9	2.914
3-Methylbutanol	2.2544	31.20	1.171	0.823	291.4	2.807
2-Methylbutanol	2.2071	31.19	1.172	0.826	289.4	2.769
2-Pentanol	2.0246	31.22	1.172	0.841	295.9	2.769
3-Pentanol	1.9609	31.23	1.173	0.844	293.5	2.807
3-Methyl-2-butanol	1.9259	31.33	1.172	0.843	284.3	2.641
2-Methyl-2-butanol	1.6085	31.43	1.171	0.855	282.5	2.561
2,2-Dimethyl-1-propanol	2.0295	31.43	1.167	0.823	283.5	2.561
1-Hexanol	2.9574	36.09	1.373	1.025	335.7	3.414
2-Hexanol	2.6122	36.22	1.373	1.042	327.7	3.269
3-Hexanol	2.5419	36.23	1.373	1.044	325.3	3.307
3-Methyl-3-pentanol	2.1086	36.47	1.371	1.056	305.8	3.122
2-Methyl-2-pentanol	2.2327	36.44	1.371	1.055	314.3	3.061
2-Methyl-3-pentanol	2.4452	36.35	1.372	1.044	314.3	3.179
3-Methyl-2-pentanol	2.4585	36.35	1.371	1.042	311.3	3.179
2,3-Dimethyl-2-butanol	2.1176	36.58	1.369	1.055	301.2	2.943
3,3-Dimethylbutanol	2.8703	36.39	1.368	1.021	307.5	3.061
3,3-Dimethyl-2-butanol	2.3593	36.55	1.368	1.040	296.7	2.943
4-Methylpentanol	2.7370	36.20	1.371	1.023	323.0	3.269
4-Methyl-2-pentanol	2.5338	36.33	1.371	1.041	314.9	3.124
2-Ethylbutanol	2.9558	36.44	1.371	1.055	308.6	3.345
Cyclohexanol	2.1645	37.35	1.324	0.995	290.5	3.393
1-Heptanol	3.5545	41.08	1.573	1.225	367.5	3.914
2-Methyl-2-hexanol	2.8195	41.43	1.571	1.255	346.1	3.561
3-Methyl-3-hexanol	2.7286	41.48	1.571	1.257	337.7	3.622
3-Ethyl-3-pentanol	2.5785	41.47	1.572	1.259	324.4	3.683
2,3-Dimethyl-2-pentanol	2.6154	41.59	1.569	1.255	323.8	3.481
2,3-Dimethyl-3-pentanol	2.5875	41.58	1.570	1.257	321.8	3.504
2,4-Dimethyl-2-pentanol	2.6775	41.54	1.569	1.253	328.6	3.416
2,4-Dimethyl-3-pentanol	2.9621	41.44	1.572	1.246	331.7	3.552
2,2-Dimethyl-3-pentanol	2.8934	41.56	1.569	1.243	326.1	3.481
3-Heptanol	3.1322	41.22	1.574	1.240	357.1	3.807
4-Heptanol	3.1333	41.22	1.574	1.245	357.1	3.807
1-Octanol	4.0906	46.08	1.773	1.226	399.4	4.414
2,2,3-Trimethyl-3-pentanol	3.0184	46.84	1.766	1.461	335.2	3.811
2-Octanol	3.8105	46.21	1.773	1.435	391.0	4.269
2-Ethylhexanol	3.9150	46.22	1.722	1.427	371.3	4.345
1-Nonanol	4.7449	51.07	1.974	1.374	431.2	4.914
2-Nonanol	4.4895	51.20	1.973	1.643	423.2	4.769
3-Nonanol	4.4024	51.21	1.974	1.644	420.8	4.807
4-Nonanol	4.3298	51.20	1.974	1.644	420.8	4.807
5-Nonanol	4.2396	51.21	1.974	1.645	420.8	4.807
2,6-Dimethyl-3-heptanol	4.2534	51.41	1.972	1.643	394.0	5.517
3,5-Dimethyl-4-heptanol	4.0458	51.49	1.971	1.645	379.3	4.628
1,1-Diethylpentanol	4.1650	51.46	1.973	1.660	372.5	4.683
7-Methyloctanol	4.2396	51.20	1.971	1.623	418.7	4.769
3,5,5-Trimethylhexanol	4.2506	51.49	1.968	1.620	376.6	4.454
1-Decanol	5.4438	56.07	2.174	1.826	463.0	5.414

[a] From Ref. 6. [b] From Ref. 7.

RESULTS AND DISCUSSION

The 51 aliphatic alcohols listed in Table I were the subject of a study correlating molecular surface area with aqueous solubility (6). The same alcohols were included in an investigation correlating aqueous solubility with the molecular connectivity index, χ (7). These compounds represent a variety of *n*-aliphatic and branched aliphatic alcohols and constitute a good series for testing the relation between the newly derived branching index, M', and the molecular connectivity index. Linear regression performed on the indexes leads to the correlation equation:

$$\chi = 0.0990(\pm 0.0031)M' - 0.3981(\pm 0.1292) \qquad \text{(Eq. 3)}$$
$$n = 51 \quad s = 0.175 \quad r = 0.976 \quad F(1,49) = 982.7$$

where n is the total number of compounds, s is the standard error of the estimate, r is the correlation coefficient, and F is the computed F ratio for the correlation. The values in parentheses beside each regression coefficient are the standard errors for the regression coefficient estimates. The correlation between the two indexes is highly significant ($p < 0.01$).

A comparison of atom indexes for select molecules is instructive. In the surface area approach (6) and the molecular connectivity approach (2), hydrogen atoms bonded to carbon are taken into account either explicitly in terms of their contribution to a van der Waals radius or implicitly as the difference between the valence electron number and the number of hydrogens bonded to an atom. In the present approach, hydrogen atoms are not considered either explicitly or implicitly; a molecule is viewed as a linked chain of C and O atoms and with no other distinction.

Table II compares indexes for the methyl and methylene groups in 1-nonanol. The surface area approach shows that the terminal methyl group differs from the methylene groups and that the methylene groups nearest the terminal points of the chain differ from those more central in the chain. A similar pattern is noted for the atom indexes obtained in this work but not for the bond indexes obtained from the molecular connectivity approach. The molecular connectivity approach distinguishes a terminal methyl group from internal methyl groups since the product $(1/v_i^{1/2}v_j^{1/2})$ differs in each instance; but the methylene groups in the chain necessarily are identical as in this instance the product $(1/v_i^{1/2}v_j^{1/2})$ is the same. Since the results of this work are purely topographical in origin, methyl and methylene group distinctions apparently are a necessary consequence of both molecular topography (geometry) and atomic valency. The perturbational approach described in this work can be extended to include hydrogens. In principle, both topographical and valency effects can be taken into account.

Molecular branching or cyclization can affect the molecular physical properties by reducing the surface exposed to an external environmental influence. For example, neopentane as opposed to pentane has the central carbon atom effectively shielded from external influences by the methyl groups bonded to it. Cyclohexane as opposed to *n*-hexane has the inner

Table II—Methyl and Methylene Group Distinctions in 1-Nonanol

CH_3–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–CH_2–OH
9 8 7 6 5 4 3 2 1

Group	Atom Index: Exposed Surface Area[a]	δ_i	$1/\nu_i^{1/2}$[b]
OH	59.15	6.51	1.000
CH_2(1)	45.43	5.15	0.707
CH_2(2)	39.80	5.01	0.707
CH_2(3)	31.82	5.00	0.707
CH_2(4)	31.82	5.00	0.707
CH_2(5)	31.82	4.99	0.707
CH_2(6)	31.82	4.99	0.707
CH_2(7)	31.82	4.99	0.707
CH_2(8)	42.75	4.94	0.707
CH_3(9)	84.92	4.49	1.000

[a] From Ref. 6. [b] These atom indexes are used to derive a bond index, which is the basis of the approach in Ref. 1.

surfaces of the ring atoms shielded from external influences to a greater extent than the outer surfaces of the ring atoms. Branched or cyclic substances will be expected to have lower surface areas, molecular refractions, and molecular volumes when compared with isomeric straight-chain substances. A branching index, irrespective of its origin, seeks to mirror this expectation.

Table III compares the total surface area, the perturbationally derived index M', and the connectivity index χ for these illustrative compounds. The connectivity index for the acyclic hydrocarbons mirrors the order of their computed total surface areas, but a comparison of cyclic and straight-chain isomers shows that the order is reversed. Since the molecular connectivity approach is bond centered and cyclic hydrocarbons contain one more bond than their acyclic counterparts, an amount corresponding to the additional bond contribution should be subtracted from the computed χ value for cyclic hydrocarbons when making such comparisons (2). This adjustment properly orders χ with respect to total surface area in a comparison of cyclic with noncyclic hydrocarbons.

Since the perturbationally derived index is atom centered rather than bond centered, no adjustment for cyclic hydrocarbon indexes seems necessary. However, a comparison of M' with the total surface areas for the molecules in Table III shows that in each case the order is the reverse of that expected. This result can be traced to the fact that in the perturbational approach the more highly substituted atoms have higher derived atom indexes. Hence, atoms that are more shielded from external environmental influences are weighted more heavily in M' ($\equiv \Sigma\, \delta_i$).

An index that would weight shielded atoms less than those that are more external would be more physically realistic. For simplicity, one may make the definition $A' = \Sigma\, (1/\delta_i)$, although such a definition still will tend to overweight heavily shielded atoms. This index provides the expected surface area ordering for the compounds of Table III. When compared to the χ index, the A' index is slightly less satisfactory than M', as a statistical comparison for Eqs. 3 and 4 shows:

$$\chi = 2.573(\pm 0.088)A' - 0.317(\pm 0.138) \qquad \text{(Eq. 4)}$$
$$n = 51 \quad s = 0.197 \quad r = 0.972 \quad F(1,49) = 841.2$$

The correlation coefficients and calculated F ratios for Eqs. 5 and 6 show that the χ index has a slight statistical edge over A' in correlating the total surface areas (TSA) for the alcohols in Table I:

$$A' = 0.0060(\pm 0.0003)\text{TSA} - 0.515(\pm 0.103) \qquad \text{(Eq. 5)}$$
$$n = 51 \quad s = 0.105 \quad r = 0.943 \quad F(1,49) = 394.4$$

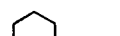
$$\chi = 0.0162(\pm 0.0006)\text{TSA} - 1.883(\pm 0.230) \qquad \text{(Eq. 6)}$$
$$n = 51 \quad s = 0.234 \quad r = 0.960 \quad F(1,49) = 579.7$$

The alcohol aqueous solubilities (Table I) have been correlated with total surface area (6) and with the χ index (7). There are four fewer alcohols in Table I than in the total surface area study (6); the four alcohols not considered are all long chain n-aliphatic alcohols and are equivalent to those in the study involving χ. The solubilities can be correlated by the respective indexes (Eqs. 7–9):

$$-\log X_2 = 0.0185(\pm 0.0006)\text{TSA} - 3.309(\pm 0.220) \qquad \text{(Eq. 7)}$$
$$n = 51 \quad s = 0.224 \quad r = 0.972 \quad F(1,49) = 832.8$$

$$-\log X_2 = 2.833(\pm 0.140)A' - 1.337(\pm 0.218) \qquad \text{(Eq. 8)}$$
$$n = 51 \quad s = 0.311 \quad r = 0.945 \quad F(1,49) = 408.2$$

Table III—Accessible Area Distinctions between Select Molecules

Compound	Structure	Molecular Index: Total Surface Area[a]	M'	χ	A'
n-Pentane		287.0	23.84	2.414	1.048
Neopentane		270.1	24.15	2.000	1.043
n-Hexane		319	28.84	2.914	1.248
Cyclohexane		279.1	29.94	3.000	1.200

[a] Reference 6.

$$-\log X_2 = 1.093(\pm 0.042)\chi - 0.961(\pm 0.155) \qquad \text{(Eq. 9)}$$
$$n = 51 \quad s = 0.248 \quad r = 0.965 \quad F(1,49) = 673.5$$

The computed correlation coefficients and F ratios for these correlations indicate that total surface area provides a better fit and A' a poorer fit of the data than does χ. All fits, however, are highly significant.

For any isomeric aliphatic alcohol series, the aqueous solubility increases in the order: primary < secondary < tertiary. The increase in solubility tends to parallel the carbonium-ion stability and suggests a distinction in the C–O bond character among primary, secondary, and tertiary alcohols. Such isomeric alcohols can be distinguished using the indexes described in the following way: (*a*) surface areas—separate the hydroxyl surface area (OHSA) from the total surface area to provide a hydrocarbon residue surface area (HYSA); (*b*) molecular connectivity—separate the C–O bond contribution (C_{CO}) from χ to provide the residual hydrocarbon index χ_R; and (*c*) perturbational—sum the atom indexes for a C–O bond (A'_{CO}) and separate the result from A' to provide the residual hydrocarbon index A'_R. A regression analysis of the alcohol solubilities using the respective hydroxyl and hydrocarbon residue indexes leads to:

$$-\log X_2 = 0.0265(\pm 0.0028)\text{OHSA} + 0.0184(\pm 0.0006)\text{HYSA} - 3.6227(\pm 0.2332) \qquad \text{(Eq. 10)}$$
$$n = 51 \quad s = 0.209 \quad r = 0.976 \quad F(2,48) = 480.7$$

$$-\log X_2 = 25.62(\pm 2.59)A'_{CO} + 2.91(\pm 0.11)A'_R - 8.94(\pm 0.88) \qquad \text{(Eq. 11)}$$
$$n = 51 \quad s = 0.230 \quad r = 0.971 \quad F(2,48) = 394.5$$

$$-\log X_2 = 3.060(\pm 0.444)C_{CO} + 1.064(\pm 0.043)\chi_R - 2.074(\pm 0.304) \qquad \text{(Eq. 12)}$$
$$n = 51 \quad s = 0.253 \quad r = 0.965 \quad F(2,48) = 323.4$$

For this analysis, the surface area values provide only slightly better correlation than do the corresponding perturbational indexes. These correlations are somewhat more significant than the correlation using molecular connectivity indexes.

A comparison of the correlation coefficients for the single-parameter and two-parameter relations (Eqs. 7–9 *versus* Eqs. 10–12) is instructive. No appreciable increase in the correlation coefficient is noted for the relations involving either the surface area index or the molecular connectivity index. However, for the correlations involving the perturbational index, the correlation coefficient is improved. Apparently, the expected hydroxyl group influence in primary, secondary, and tertiary alcohols on aqueous solubility is reflected better by the perturbational approach than by either the surface area or molecular connectivity approach.

CONCLUSIONS

The perturbational approach described previously (3–5) for the calculation of molecular charges and dipole moments contains the essential features for arriving at a topographical index[1]. The original parameterization given for the calculation of molecular charges probably can be maintained unchanged and the calculations can provide a topographical index related to molecular refraction and volume as well as charges. A

[1] Molecular connectivity indexes were derived for atoms, and these indexes were shown to correlate with CNDO/2 calculated electronic charges in alkanes. See L. H. Hall and L. B. Kier, *Tetrahedron*, 33, 1953 (1977).

combination of charge and molecular refraction indexes could extend greatly the applicability range of solubility-related correlation analyses such as have been reported for aromatic substances (8, 9). Since this approach is atom centered rather than bond centered, it appears highly suitable for arriving at molecular descriptors for pattern recognition studies (10, 11).

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Rheological and Drug Release Properties of Oil Gels Containing Colloidal Silicon Dioxide

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Abstract □ The rheological properties of oil gels prepared by dispersing colloidal silica in *n*-dodecane and 1-dodecanol were examined. The differences in gel strength using these two media were accounted for by the difference in the extent of hydrogen bond formation between the silanol groups on the silica surface. The incorporation of methyl salicylate further modified the rheological properties of the gels. The drug was capable of hydrogen bonding with silanol groups in the *n*-dodecane gels, which increase gel strength at low concentrations; at high concentrations, the drug acted as a plasticizer. In 1-dodecanol systems, the drug acted solely as a plasticizer. Adsorption studies showed that methyl salicylate was adsorbed only on the silica particles in the *n*-dodecane medium. Interaction of the drug with the silanol groups in the *n*-dodecane systems did not appear to effect methyl salicylate release from the gels.

Keyphrases □ Gels—colloidal silica in *n*-dodecane and 1-dodecanol, rheological analysis, hydrogen bonding, methyl salicylate incorporation and release □ Colloidal silica—in *n*-dodecane and 1-dodecanol gels, rheological analysis, hydrogen bonding, methyl salicylate incorporation and release □ *n*-Dodecane—gels, colloidal silica, rheological analysis, methyl salicylate incorporation and release □ 1-Dodecanol—gels, colloidal silica, rheological analysis, methyl salicylate incorporation and release □ Methyl salicylate—gels, colloidal silica, *n*-dodecane, 1-dodecanol, rheological analysis

Colloidal silicon dioxide (fumed silica), produced by the vapor-phase hydrolysis of silicon tetrachloride, is used widely in the pharmaceutical industry as a binder and glidant in tablets and as a suspending agent and viscosity modifier in suspensions, ointments, and suppositories. Its use as a viscosity modifier is largely attributable to the ability of the very small silica particles to form a network structure throughout the medium by interparticle hydrogen bonding *via* the silanol groups on the silica surface. In addition to these particle interactions, there is possible bonding between the silanol groups and other components that are also capable of hydrogen bond formation. A detailed investigation of this type of interaction was published (1).

Modification of the magnitude of the interparticle interactions and production of ointment bases of different consistencies are possible by selecting, as dispersion media, oils that differ from each other in hydrogen bonding ability. Incorporation of a drug capable of hydrogen bonding into such bases might be expected to influence not only their rheological characteristics but also their drug release properties.

The object of this work was to quantify some of these phenomena by incorporating methyl salicylate into model gel systems prepared by dispersing fumed silica in the nonhydrogen bonding *n*-dodecane and the hydrogen bonding analog 1-dodecanol. The influences of silica and drug concentration on rheological and release properties are reported.

EXPERIMENTAL

Materials—Specially pure (99%) 1-dodecanol[1], laboratory reagent grade *n*-dodecane[1] and BP quality methyl salicylate[2] were used as received. Colloidal silicon dioxide[3] was dried for 1 hr at 150° and stored in a desiccator prior to use.

Gel Preparation—The requisite amount of continuous phase, containing drug where appropriate, was added to the silica, and the system was sonicated[4] for 30 sec to obtain a uniform dispersion. The gel was transferred to a glass container, sealed, and stored at 40°.

Rheological Properties—Dynamic rheological properties were measured using a modified Weissenberg rheogoniometer[5] in conjunction with a digital transfer function analyzer[6]. This rheogoniometer is one of the few commercially available instruments with facilities for both oscillatory (dynamic) and continuous shear measurements. The viscoelastic properties of materials may be evaluated using the oscillatory technique, and its application to pharmaceutical semisolid systems was described previously (2, 3).

Parallel plate geometry (platen radius of 3.75 cm) was used, and all gels were tested over the frequency range of 0.01–25.0 Hz using two torsion strips (Nos. 6 and 7) to minimize problems associated with natural resonance (4). The measurement temperature, as monitored by a thermocouple system[7] embedded in the top platen, was 37 ± 0.5°. Samples were

[1] British Drug Houses Ltd., Poole, Dorset, England.
[2] McCarthys Ltd., Romford, Essex, England.
[3] Aerosil 300, Bush, Beach and Segner Bayley Ltd., London, England.
[4] Kerry PUL 55 ultrasonic bath, Kerry Ultrasonics Ltd., Hitchin, Herts, England.
[5] R16, Sangamo Ltd., Bogner Regis, England.
[6] JM1600/JX1606, Solartron Ltd., Farnborough, Hampshire, England.
[7] Type 1604 electronic thermometer, Comark Electronics Ltd., Littlehampton, Sussex, England.

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