Estimation of Steroid Solubility: Use of Fractional Molar Attraction Constants

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Abstract □ The fractional molar attraction constant (f_p), an empirical constant related to the solubility parameter, was defined and chosen to be related to the solubilizing capacity of solvents for a given steroid because it was thought to assess the relative polarity of solvent molecules. Experimental solubilities for two steroids are reported which indicate that f_p may be a useful parameter for solubility estimations.

Keyphrases □ Steroid solubility—estimation □ Fractional molar attraction constants—steroid solubility □ X-ray diffraction—identification □ Scintillometry—analysis

The solubility of a drug in one or more components of a pharmaceutical dosage form is valuable information which can be used to characterize its behavior in such a physical system. The solubility is usually not difficult to determine and often it is one of a few physical parameters readily available to the formulator which can aid him in the design of suitable dosage forms. This is particularly true in the case of topical dosage forms and where the solubility of the active ingredient can be related to phenomena such as thermodynamic activity, vehicle release rate, dissolution rate, and apparent penetration rate.

THEORETICAL

Methods or techniques for estimating or predicting the solubilities of drugs in various pharmaceutical solvents have obvious practical implications. One of the most useful concepts has been that of the solubility parameter (δ) as defined by Hildebrand and Scott (1) in Eq. 1 for nonelectrolytes:

$$\delta = (E/V)^{1/2} = (EV)^{1/2}/V = F/V \qquad \text{(Eq. 1)}$$

where E is the molar cohesive energy, V the molar volume, and F the molar attraction constant (2). It was originally derived for regular solutions ($\Delta H > 0$) where a good solvent for a given solute has a δ value close to that of the solute according to

$$\Delta G_m = V_m \phi_1 \phi_2 (\delta_1 - \delta_2)^2 - T\Delta S_m \qquad \text{(Eq. 2)}$$

where ΔG_m is the free energy of mixing, T the absolute temperature, S_m the entropy for mixing, V_m the volume of the mixture, and ϕ the volume fraction of component 1 or 2. This requirement corresponds to fulfilling the thermodynamic condition that ΔG_m be large and negative for good mixing. Burrell (3) has explored its potential for application in the paint and polymer coatings industry. The main limitation, however, has been that the solubility parameter concept is strictly applicable only to nonpolar systems where dispersion or London forces are predominant and other forces such as those related to hydrogen bonding and polarity are absent. In attempting to increase its applicability, these other forces and their effects have been considered by Burrell (4) and Gardon (5) and have proven to be worthwhile efforts.

In the case of steroids one encounters a somewhat specific solubility problem regarding prediction or estimation. The solubility parameter is not very useful for estimating the solubilizing capability of solvents for steroids because the circumstances are such that certain assumptions associated with δ are no longer valid; namely, that the solutes are crystalline, and specific interactions become highly significant in defining the solubility characteristics (both of these conditions tend to make $\Delta H < 0$). For steroids one finds that a proper hydrophilic-hydrophobic balance on the part of the solvent is associated with good solvent properties. That is, steroids are relatively insoluble in nonpolar solvents such as hexane and very polar solvents such as water but have appreciable solubility in solvents with partial polarity. This realization suggested that what is required is a parameter which assesses the fraction of the solvent molecule which can participate in the solubilization of a steroid and thereby hopefully place solvency on a common scale. This notion led to the defining of an empirical quantity called the fractional molar attraction constant (f_p). That is, since the presence of certain functional groups (*e.g.*, esters, ketones, ethers, alcohols) play a critical role in governing the solubility capacity of solvents for steroids and since apparently the relative abundancies of these groups are also important, the separation of δ into two components was considered according to Eqs. 3 and 4:

$$\delta = \delta_p + \delta_n = (F_p + F_n)/V \qquad \text{(Eq. 3)}$$

$$\delta_p = F_p/V;\ \delta_n = F_n/V \qquad \text{(Eq. 4)}$$

where δ_p and δ_n are the contributions made to δ by participating and nonparticipating functional groups, respectively. F_p and F_n are similarly defined for F; that is, F_p is the sum of F for all participating groups in the solvent molecule and F_n is the corresponding sum for all nonparticipating groups ($F = F_p + F_n$). The fractional molar attraction constant then was defined as in Eq. 5.

$$f_p = \delta_p/\delta = F_p/(F_p + F_n) = F_p/F \qquad \text{(Eq. 5)}$$

In order to demonstrate the possible usefulness of f_p, the solubilities of two steroids in various solvents were determined at 25°. The steroids employed in this report were fluocinolone acetonide[1] and fluocinolide.[2]

EXPERIMENTAL

Materials—Cellosolve acetate,[3] carbitol acetate,[3] *n*-butyl carbitol,[3] glyceryl triacetate,[3] methyl cellosolve acetate,[3] ethylene glycol diacetate,[3] isopropyl myristate,[4] cellosolve solvent,[3] methyl cellosolve,[3] diethylene glycol,[3] propylene glycol,[3] Ucar solvent LM,[3] 1,4-butanediol,[4] polyethylene glycol 400,[3] carbitol,[3] propylene carbonate,[5] toluene (scintillation grade),[6] PPO,[7] POPOP,[7] dioxane (scintillation grade),[6] naphthalene,[8] fluocinolone acetonide, and fluocinolide were used as received. All other materials were of analytical reagent grade. ^{14}C-labeled (acetonide label) steroids were used in all determinations and were provided by the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif. The radioactive purity was checked by developing a radioactive sample on a TLC plate with chloroform–methanol (95:5 for the acetate and 100:5 for the alcohol) and then scanning on a Vanguard model 880-D glass plate scanner. These radiochromatograms indicated that the purity was $\geq 98\%$.

Solubility Determinations—Solubilities were determined in the various solvents in duplicate by one of two methods. In the first method, an excess quantity of radioactive steroid with known spe-

[1] 6α, 9α-Difluoro-11β, 16α, 17α, 21-tetrahydroxy-1,4-diene-3,20-dione 16, 17-acetonide.

[2] 6α, 9α-Difluoro-11β, 16α, 17α, 21-tetrahydroxy-1, 4-diene-3,20-dione 16, 17-acetonide 21-acetate.

[3] Union Carbide Chemicals Co., New York, N. Y.

[4] General Aniline and Film Corp., New York, N. Y.

[5] Jefferson Chemical Co., Inc., Houston, Tex.

[6] Matheson, Coleman & Bell, Div. Matheson Co., Inc., Norwood, Ohio.

[7] Arapahoe Chemicals, Div. Syntex Corp., Boulder, Colo.

[8] Baker Analyzed Reagent Grade from J. T. Baker Chemical Co., Phillipsburg, N. J.

Table I—Solubilities of Phase I Fluocinolone Acetonide (Compd. *A*) and Fluocinolide (Compd. *B*) in Various Solvents at 25°

Solvent	f_p	Solubility (mg./ml.) at 25°: Compd. *A* Exp.	Compd. *A* Calcd.	Compd. *B* Exp.	Compd. *B* Calcd.
Isopropyl myristate	0.109	0.80[a]	0.71	0.14	0.16
n-Amyl acetate	0.244	8.65[a]	11.71	3.35	2.82
n-Butyl carbitol	0.289	51.84	21.09	5.95	5.14
Carbitol acetate	0.292	17.66	21.86	5.75	5.33
Cellosolve acetate	0.315	16.39	28.44	9.01	6.98
Polyethylene glycol 400	0.330	—	—	8.0[b]	8.23
Methyl cellosolve acetate	0.352	43.03	41.83	9.75	10.36
Ethyl acetate	0.356	20.77	43.51	7.80	10.78
Carbitol	0.364	—	—	14.0[b]	11.67
Cellosolve solvent	0.392	82.26	60.80	11.44	15.18
Ucar solvent LM	0.416	118.5	107.5	13.55	32.62
Methyl cellosolve	0.451	66.87	48.82	18.99	12.16
Propylene carbonate	0.460	—	—	14.0	9.55
Ethylene glycol diacetate	0.472	16.97	31.29	5.28	6.97
Glyceryl triacetate	0.498	24.42[a]	18.53	2.96	3.62
1,4-Butanediol	0.508	14.55[a]	15.26	—	—
Diethylene glycol	0.538	8.20[a]	8.71	1.95	1.41
Propylene glycol	0.595	—	—	0.69	0.41
Water	1.000	0.021	0.020	0.00053	0.00072

[a] The most stable phase is the clathrate; values for the solubility of Phase I were obtained by extrapolation (see text). [b] Values obtained by extrapolation to 100% of solvent in a plot of log solubility *versus* percent solvent in water.

cific activity was added to approximately 10 ml. of each solvent in a culture tube. The preparations were capped, sealed with rubber tape, and agitated on a Vibro-Mixer[9] at 25° in a thermostated bath until equilibrium was attained (2–5 days). All preparations were protected from the light. The only difference in the second method was that prior to agitation the preparations were heated to 60° to aid solubilization. Equivalent results were obtained by the two methods. Samples were withdrawn at appropriate times and passed through a suitable Gelman Metricel filter[10] (13 mm., 0.2μ). One milliliter of each filtrate was then analyzed on a liquid scintillation counter. Upon termination of the solubility experiments, the excess steroid was collected from each preparation by filtration and dried. X-ray powder diffraction patterns using copper K_α radiations on a Stoe Weissenberg goniometer system with a 57.3-mm. diameter camera were obtained on each dried sample as a means for identifying the polymorphic phase at equilibrium.

Radiochemical Assays—The specific activities of the radiochemicals were 20.7 mc./mmole for both steroids. Samples of the filtrates for each solvent were assayed for steroid utilizing a Nuclear Chicago Unilux II liquid scintillation counter. One-milliliter samples were mixed directly with either 15 ml. of scintillation fluid consisting of 13 g. of PPO (2,5-diphenyloxazol), 0.26 g. of dimethyl POPOP (1,4-bis-2-[4-methyl-5-phenyloxazolyl] benzene), 208 g. of naphthalene, 0.6 l. of methanol, 1 l. of dioxane, and 1 l. of toluene or 10 ml. of scintillation fluid consisting of 4 g. of POP, 0.1 g. of dimethyl POPOP, and 1 l. of toluene. The extent of quenching was determined from a channels ratio analysis utilizing a standard quench correction curve which included the correction factor for counter efficiency. The steroid content for each sample was calculated from the known specific activities and the disintegrations per unit time as obtained from the standard correction curve.

RESULTS

The solubilities of Phase I fluocinolone acetonide (*A*) and Phase I fluocinolide (*B*) at 25° in the various solvents are given in Table I and correspond to the mean value of two determinations. Solvents were chosen so as to give a wide range of f_p values. In the case of *B*, X-ray diffraction powder patterns of the steroid before and after equilibration indicated that no polymorphic conversion had occurred in any of the solvents. In the case of *A*, however, a polymorphic conversion to the clathrate was detected in five solvents (Table I). In these instances the solubilities for Phase I were obtained by extrapolation of a plot of solubility *versus* time (*t*) to $t = 0$ where such plots correspond to experiments employing pure Phase I as the starting material. Consequently, the reported values in these instances are approximations.

The f_p values for the various solvents in Table I were calculated according to the definition ($f_p = F_p/F = F_p/\delta V$). F_p values were calculated from structure alone by summing the *F* values corresponding to each participating group present in the solvent molecule (esters, ethers, alcohols). Such group *F* values for many functional groups have been reported by Small (6). It should be pointed out that for diols such as ethylene glycol, propylene glycol, *etc.*, the value of *F* for a single OH group is 275 as calculated from

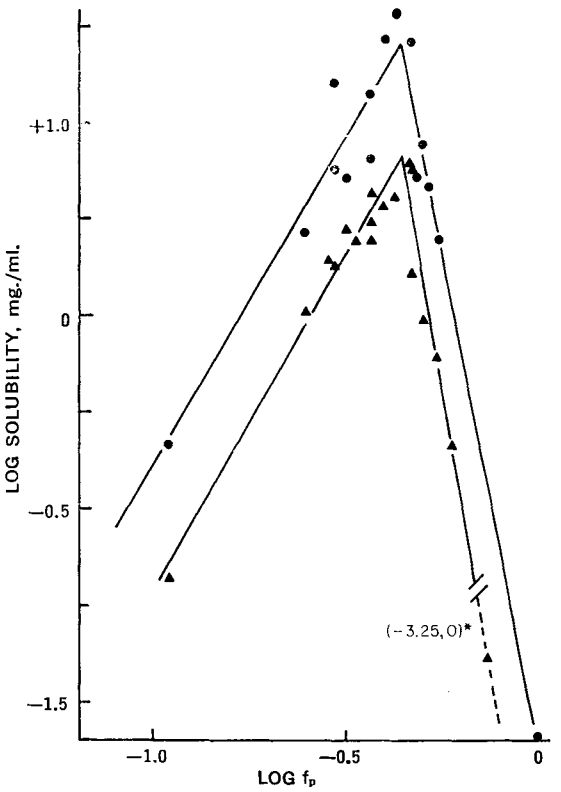

Figure 1—*Apparent linear relationship between log solubility and log* f_p *for fluocinolone acetonide* (●) *and fluocinolide* (▲) *in various solvents at 25°. * Coordinates for data point (water) which did not fit on axes.*

[9] Chemapec Corp., Hoboken, N. J.
[10] Gelman Instruments Inc., Ann Arbor, Mich.

$F = \delta V$ for the whole molecule and subtracting the reported values for the other groups, while for monofunctional alcohols such as carbitol, cellosolve, *etc.*, the corresponding value is 325 (7). To obtain $F = \delta V$, δ values taken from the technical literature of the supplier or from *Reference 2* were used and molar volumes ($V = \rho$/mol.wt.) were obtained utilizing densities (ρ) at 20° from the technical literature of the supplier or *Reference 8*. In a few instances where δ values were not available, F was calculated in the same manner as F_p. Fractional molar attraction constants so calculated are included in Table I for each solvent.

The solubility data for both steroids were found to be related to the calculated f_p values of the solvents and an optimum value of f_p was evident. For a log solubility–log f_p correlation the relationship appeared to exhibit linearity separately on each side of a maximum for both steroids. These empirical relationships are shown in Fig. 1 along with the calculated regression lines. Linear equations as determined by the method of least squares which best fit the plots in Fig. 1 are for *A*

	r	n	
$\log S = 3.474 \log f_p + 3.197$	0.939	9	(Eq. 6)
$\log S = -9.773 \log f_p - 1.691$	0.994	7	(Eq. 7)

and for *B*

$\log S = 3.554 \log f_p + 2.627$	0.989	10	(Eq. 8)
$\log S = -12.215 \log f_p - 3.139$	0.990	8	(Eq. 9)

where n is the number of data points. The correlation coefficients (r) indicated a high degree of linearity for the apparent relationships cited. Solubilities have been calculated employing Eqs. 6–9 and are included in Table I for comparison with the experimental values. A linear correlation between calculated and experimental values gave $r = 0.916$ at $p = 0.01$ for *A* and $r = 0.732$ at $p = 0.01$ for *B*. This result indicated that the relationship is significant but that much of the deviation is masked by the log–log relationship. A relationship between solubility for f_p is apparent, however, from linear plots. Perhaps a more meaningful and practical use of this relationship can be obtained by graphical estimation from linear plots and an empirical log–log relationship need not be forced or assumed.

Fractional molar attraction constants were defined with the intention of placing the solubilizing capability of solvents on a common scale in order hopefully to assess the importance of specific interactions and their relative abundance in various solvents. For strictly nonpolar solvents such as heptane, $F_p = 0$ and $f_p = 0$, while for a strictly polar solvent such as water, $F_p = F$ and $f_p = 1$. It can be shown that F values are additive on a molar basis (6, 9). They are at best only approximately additive on a constitutive and/or atomic basis but nonetheless the limited additivity of F can be useful in calculating the value of F for solvent molecules if certain limitations and rules are recognized (7). Equations 6–9 indicate the maximum solubility occurs at approximately the same solvent f_p value for *A* and *B* (0.428 and 0.431, respectively). Thus, the solvents studied are effective in solubilizing both steroids, the difference being the magnitude of their effect. An optimum in a plot of solubility *versus* f_p is in agreement with the notion that a proper hydrophobic–hydrophilic balance is required for good solvent properties.

The described techniques and relationships may be useful in estimating the solubilities of test compounds in additional solvents, once limited solubility data have been obtained. It should be pointed out that solubilities obtained utilizing these relationships can give predicted values which are substantially in error. Nonetheless, the relationships can be used to aid in the choice of solvents in appropriate situations and should find application in formulation work. In addition, it is anticipated that these relationships will be applicable to semisolid systems such as creams and ointments where solubility determinations are experimentally impractical or very difficult. Since the solubility of a topical drug in pharmaceutical solvents is necessarily required for the intelligent design of efficacious creams and ointments, additional methods for estimating solubility are an asset to the formulator.

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