Relationship Between *In Vitro* Dissolution Rates and Solubilities of Numerous Compounds Representative of Various Chemical Species

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Fifty-five sets of initial dissolution rate and solubility values covering a range of five orders of magnitude are reported. The relationship between these values is shown to support dissolution rate theory which states that the initial rate of dissolution (R) of a compound is directly proportional to its solubility (C_s). Under the experimental conditions of this investigation, $R = 2.24\ C_s$. Using this equation it is possible to predict the initial rates of dissolution of a broad range of compounds when their solubility values are known.

During the past 4 years, the authors have had the opportunity to determine the solubilities and *in vitro* rates of dissolution of a great number of compounds in various aqueous media at 37°. The purpose of this report is to present data for compounds representing many different chemical classes and to show that the initial dissolution rates of these substances are directly proportional to their respective solubilities in the same media.

EXPERIMENTAL

Dissolution Rates.—The *in vitro* rate of dissolution of each substance was determined by the method previously described in a study of the effect of agitation intensity on distinguishing differences in the rates of two polymorphic forms of methylprednisolone (1). A more adequate description of the apparatus and procedure follows. Pellets of each pure substance having dimensions of 9.5 mm. in diameter and about 2 mm. in thickness were prepared by compression in a die using a Loomis hydraulic press at a force in the range of 2,000 to 10,000 lb. In each case a maximum force consistent with the preparation of suitable pellets was employed. The initial dimensions of the pellets were measured for calculation of their initial surface areas. Then each pellet, held in a polyethylene holder, was inserted 6.3 cm. in a 4 fl. oz. oval bottle containing 120 ml. of dissolution medium at 37°. The bottle was immediately capped and fastened by a spring clip to the periphery of the wheel submerged in a water bath as described by Wruble (2). At least four pellets of each compound were rotated at 6 r.p.m. in the thermostated bath (37°) for different intervals of time selected so that the concentration of solute was always less than 10% of its solubility value. The pellets were removed, dried, and the dimensions were again measured for the calculation of the final surface area. The average of the initial and final surface areas, S, was used in each case to estimate the rate. The solutions from the rate studies were assayed by ultraviolet spectrophotometry using a Cary model 11 recording spectrophotometer.

A plot was constructed of W/S *versus* t, where W is the weight of the substance (in milligrams) dissolved in 120 ml. of medium, S is the average surface area of the pellet (in square centimeters) during exposure, and t is the time of pellet exposure in hours. Each plot was linear and was fitted with the least squares line. The slope of the regression line is the initial rate of dissolution, R, recorded in Table I.

Solubility Determinations.—The solubility of each substance was determined at 37° in the same medium as employed in the corresponding *in vitro* rate of dissolution test. Excess powdered compound was equilibrated in a thermostat by rotating a vial containing the suspension for at least 48 hr. The solution was filtered from excess solids by positive pressure at 37°. The filtrate, after appropriate dilution, was assayed spectrophotometrically. Two or more determinations were made, and the average value was the solubility, C_s (in mg. ml.$^{-1}$), recorded in Table I.

RESULTS AND DISCUSSION

The 55 sets of initial rate of dissolution and solubility data are recorded in Table I. These values cover an extraordinarily wide range of five orders of magnitude with respect to solubility and dissolution rate, the highest solubility (44.8 mg./ml.) being about 15,000 times greater than the lowest solubility (0.0029 mg./ml.) and the highest rate of dissolution (92.5 mg./cm.^{2}/hr.) being about 14,000 times greater than the lowest value (0.0068 mg./cm.^{2}/hr.). These data were evaluated to test dissolution rate theory which states that the initial rate of dissolution is directly proportional to the solubility of a compound.

The theoretical relationship, as expressed by Noyes and Whitney (3), may be written as

$$V\frac{dC}{dt} = k\,S\,(C_s - C) \qquad \text{(Eq. 1)}$$

where V is the volume of the dissolution medium, dC/dt is the rate of change of concentration with time, $V\ dC/dt$ is the rate of dissolution, k is a constant, S is the surface area, C_s is the solubility of the dissolving solid in the dissolution medium, and C is the concentration at time t. When W is the weight of substance dissolved in volume V at time t, then

$$\frac{dW}{dt} = k\,S\,(C_s - C) \qquad \text{(Eq. 2)}$$

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TABLE I.—RATE OF DISSOLUTION AND SOLUBILITY DATA OF COMPOUNDS CLASSIFIED ACCORDING TO CHEMICAL SPECIES

Compd.	Name	Test Fluid[a]	C_s (mg./ml.)[b]	R (mg./cm.²/hr.)[c]	R/C_s
	Class 1a (Neutral Compd., Steroids)				
1	17-Hydroxy-6-methyl-16-methylene pregna-4,6-diene-3,20-dione acetate	A	0.0029	0.0068	2.34
2	7α,17-Dimethyl-19-nortestosterone	A	0.0454	0.0873	1.92
3	7α,17-Dimethyltestosterone	A	0.0580	0.0952	1.64
4	1-5α-Androstene-3,11,17-trione	A	0.0784	0.152	1.94
5	7α-Methyl-19-nortestosterone	A	0.0920	0.156	1.70
6	Methylprednisolone polymorph I[d]	A	0.117	0.203	1.74
7	Methylprednisolone polymorph II[d]	A	0.141	0.265	1.88
8	Prednisolone	A	0.351	0.759	2.16
9	Fluprednisolone hydrate	A	0.586	1.41	2.41
10	Fluprednisolone	A	1.04	2.11	2.03
	Class 1b (Neutral Compd., Carbamates)				
11	*p*-Phenylphenol, methylcarbamate	B	0.0268	0.0650	2.43
12	Salicylanilide, methylcarbamate	B	0.0464	0.0923	1.99
13	4-Hydroxybenzophenone, methylcarbamate	B	0.104	0.214	2.06
14	3-(α,α,α-Trifluoro-*m*-tolyloxy)-1,2-propanediol, 1-carbamate	A	1.08	2.07	1.92
15	3-(*p*-Chlorophenoxy)-1,2-propanediol, 1-carbamate	B	3.64	8.48	2.33
		C	3.84	9.11	2.37
	Class 2 (Sulfonylureas)				
16	1-(*p*-Acetylphenylsulfonyl)-3-cyclohexylurea	B	0.0111	0.0258	2.32
17	1-Cycloheptyl-3-*p*-tolylsulfonylurea	D	0.0117	0.0254	2.17
18	Tolbutamide	D	0.142	0.319	2.25
17	1-Cycloheptyl-3-*p*-tolylsulfonylurea	E	0.536	1.18	2.20
16	1-(*p*-Acetylphenylsulfonyl)-3-cyclohexylurea	C	2.22	5.51	2.48
18	Tolbutamide	E	2.73	7.06	2.59
	Class 3 (Salt of Sulfonylurea and Strong Base)				
19	Potassium salt of 1-cycloheptyl-3-*p*-tolylsulfonylurea	D	0.0132	0.0312	2.36
		E	0.563	1.06	1.88
	Class 4 (Sulfonylsemicarbazides)				
20	1-(*p*-Chlorophenylsulfonyl)-3-(hexahydro-1-azepinyl)-urea	C	0.435	1.19	2.74
21	1-(4-Methylpiperidino)-3-*p*-tolylsulfonylurea	C	0.742	1.49	2.01
22	1-Piperidino-3-*p*-tolylsulfonylurea	C	0.974	1.47	1.51
23	1-(*p*-Tolylsulfonyl)-3-(hexahydro-1-azepinyl)-urea	C	1.09	2.19	2.01
24	1-(4,4-Dimethylpiperidino)-3-*p*-tolylsulfonylurea	C	1.34	2.88	2.15
25	1-(1,2,3,6-Tetrahydro-1-pyridyl)-3-*p*-tolylsulfonylurea	C	2.92	8.15	2.79
26	1-(*p*-Acetylphenylsulfonyl)-3-hexahydro-1-azepinyl)-urea	C	4.09	7.55	1.85

When $C \ll C_s$, as exemplified by Parrott *et al.* (4) and Nelson (5), the initial rate of dissolution per unit surface area, R, will be

$$R = \frac{dW}{Sdt} = k\,C_s \qquad \text{(Eq. 3)}$$

For a single component solid dissolving in a non-reactive medium

$$k = \frac{D}{h} \qquad \text{(Eq. 4)}$$

where D is the diffusion coefficient of the solute in the solvent, and h is the thickness of the diffusion layer. Hence, as shown by Higuchi *et al.* (6), the initial rate of dissolution per unit surface area, R, should be directly proportional to the solubility, C_s, when all the diffusion coefficients may be set to the same value. According to Eq. 3, a plot of R *versus* C_s should pass through the origin and have a slope equal to k. In addition to the requirement that the line go through the origin, it is plausible to assume that the standard deviation of R is proportional to the level of C_s. The data support this assumption much better than the assumption of equal variation. Since a plot of the data shows linearity is not in doubt, the method of analysis can then be that of model IA of Snedecor (7). For our experimental conditions,

$$R = (2.24 \pm 0.10)C_s \qquad \text{(Eq. 3}a\text{)}$$

when R has units of mg. cm.$^{-2}$ hr.$^{-1}$, C_s has units of mg. ml.$^{-1}$, and the constant k (2.24) has units of cm. hr.$^{-1}$. The 95% confidence interval for the constant k is indicated.

The individual ratios, R/C_s, which are shown in Table I, have an average of 2.24, range from 1.51 to 3.03, and have a standard deviation of 0.37. It is noted that much of this variation can be attributed to the fact that the diffusion coefficients of the compounds are not exactly equal. Although there appears to be considerable variation in these individual ratios, it should be borne in mind that the solubility and rate data are representative of many different classes of chemical compounds covering a range of five orders of magnitude.

Apparent exceptions, although not noted here, have been observed and will be the subject of future reports. It is sufficient to point out that in many

TABLE I.—(*continued*)

Compd.	Name	Test Fluid[a]	C_s (mg./ml.)[b]	R (mg./cm.²/hr.)[c]	R/C_s
	Class 5 (Weak Acids Other than Sulfonylureas)				
27	*p*-Isobutylphenylacetic acid	B	0.184	0.444	2.41
28	8-Cylorotheophylline	B	0.652	1.87	2.87
29	Pamoic acid	C	2.35	4.24	1.80
30	Methylene-bis-salicylic acid	C	3.28	9.00	2.74
27	*p*-Isobutylphenylacetic acid	C	3.68	9.59	2.61
31	Acetylsalicylic acid U.S.P.	B	3.73	11.3	3.03
28	8-Chlorotheophylline	C	4.96	13.6	2.74
	Class 6 (Basic Amino Compd.)				
32	3-(1-Methyl-2-pyrrolidinyl)-indole	A	0.703	1.89	2.69
33	2-Purin-6-ylaminoethanol	C	0.744	1.98	2.66
32	3-(1-Methyl-2-pyrrolidinyl)-indole	C	2.36	6.35	2.69
34	1,1,3-Tricarbonitrile-2-amino-1-propene	B	14.8	32.2	2.18
		C	15.5	27.6	1.78
	Class 7 (Amphoteric Compd. Other than Sulfonylsemicarbazides)				
35	6-Amino-*s*-triazine-2,4-dithiol	B	0.196	0.508	2.59
		C	3.60	8.27	2.30
36	*N*-(3-Amino-2,4,6-triiodobenzoyl)-*N*-phenyl-β-alanine[e]	C	4.86	11.0	2.26
37	*N*1(4,5-Dimethyl-2-oxazolyl)-sulfanilamide[f]	B	6.10	13.1	2.15
38	5-Methylpyrazole-3-carboxylic acid	B	7.53	17.3	2.30
39	6-Amino-4-(diallylamino)-1,2-dihydro-1-hydroxy-2-imino-*s*-triazine	A	30.1	59.5	1.98
	Class 8 (Salt of Weak Base and Strong Acid)				
40	2,2′-Methylene-bis-5-methoxybenzimidazole dihydrochloride	B	44.8	92.5	2.06
	Class 9 (Salts of Weak Base and Weak Acid)				
41	*N*-(3,3-Diphenylpropyl)-α-methylphenylethylamine lactate[g]	D	0.247	0.515	2.08
42	(+)-*N*-Benzyl-*N*,α-dimethylphenethylamine pamoate	E	0.354	0.658	1.86
43	α-Diethylamino-2,6-aceto-xylidide pamoate	C	1.00	2.76	2.76
44	3-(2-Aminobutyl)-indole-8-nitrotheophyllinate	C	1.42	3.96	2.79
45	Morphine pamoate	C	4.00	6.70	1.68

[a] A, water, deionized; B, pH 1.3, 0.05 *N* HCl (μ = 0.1 with NaCl); C, pH 7.2 phos., 0.0209 *M* K_2HPO_4, 0.0091 *M* KH_2PO_4, 0.0282 *M* NaCl; D, pH 1.0, 0.1 *N* HCl; E, pH 7.2 Tham, 0.2 *M* Tris(hydroxymethyl)aminomethane adjusted with HCl. [b] The average of two or more solubility determinations of the compound in the designated test fluid at 37°C. Solubility values within each classification of compounds increase in a descending order. [c] The initial dissolution rate of the compound from the surface of pellets under the given *in vitro* test conditions. [d] Experimental data reported previously (1), but not used in the same context as this report. [e] Osbil. Brand of Byk-Gulden-Lomberg, Chem. Fabrik GmbH, Konstanz, West Germany. [f] Sulfuno. Brand of Nordmark-Werke GmbH, Hamburg, Germany. [g] Segontin lactate. Brand of Farbwerke Hoechst, Frankfurt am Main, Germany.

cases the compounds have undergone reaction with the dissolving medium. For example, the dissolution behavior of self-coating pellets of benzphetamine pamoate in acidic media, described by Higuchi and Hamlin (8), for a different *in vitro* procedure would undoubtedly be an exceptional case in this system. Likewise, it is expected that the behavior of aluminum aspirin in an alkaline medium, reported by Levy and Procknal (9), would also fall in the same category.

One of the important aspects of the solubility rate of dissolution relationship reported here is that for many types of compounds, such as included in this investigation, the solubility data may be used as a basis for making decisions of practical purpose concerning whether the absorption of a drug from a formulation may be a problem. Of course, the final *in vitro* performance test of the formulation is the rate of dissolution of the drug from the dosage form.

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