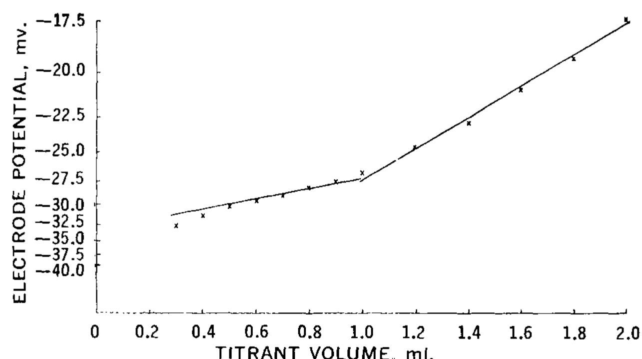

Figure 1—*Grans plot titration of 20 ml. of 10^{-3}* M *potassium phenethyl-β-D-glucopyranosiduronate with 10^{-2}* M *$CuCl_2$. Background: 10^{-1}* M *potassium acetate.*

addition of the calculated amount of potassium sulfate (4.35 g., 0.025 mole, in 40 ml. of water) and filtering. By evaporating the filtrate and crystallizing from methanol and ethanol, 8.81 g. of crystalline potassium salt was obtained. It was characterized by analysis and specific IR absorption peaks. The presence of the β-glucopyranosido grouping was indicated by the triplet at 796, 875, and 928 $cm.^{-1}$.

By using a monovalent cation electrode[1], the product was checked for complexing of potassium ion at pH 7.8 in the concentration range of 2.36×10^{-4} to 2.36×10^{-2} *M* but no complexing was found. A portion was converted to the sodium salt by ion exchange and examined similarly but no complexing was found. Grans plots[2] were then made using a divalent cation electrode[3], a 10^{-3} *M* solution of the glucuronide potassium salt containing a background of 10^{-1} *M* potassium acetate to act as pH and ionic strength adjuster, and 10^{-2} *M* titrants of Ca^{+2}, Mg^{+2}, Fe^{+2}, Zn^{+2}, Cu^{+2}, Co^{+2}, and Mn^{+2} (all as the chlorides). Negative results for complex formation were found in every case except Cu^{+2}, which showed a break in the titration curve (Fig. 1) at a ratio of 1:1 Cu^{+2}–phenethyl-β-D-glucopyranosiduronate. Complex formation was confirmed (after isolation from a 10^{-3} *M* solution at pH 7.65) from the IR spectrum of the green glass complex and analytical data for the ratio of copper to carbon. Thus, among the major biological cations, copper is specifically bound by this glucuronide in dilute solution at a pH close to that of blood.

Glucuronides as a class may be favorable materials for manipulating cations in living systems, because they are reported to be not metabolized and not rapidly excreted (1). Other indications for complex formation in this group may be stilbestrol glucuronide (an unusually insoluble sodium salt) and euxanthic acid (isolated as a magnesium salt). Finally, it should be pointed out that phenethyl alcohol is a natural antibiotic (2) active against bacteria and molds in the concentration range of 0.25–0.30% (3). It has been shown (4) to inhibit RNA and protein synthesis. There is a possibility that phenethyl alcohol *in vivo* is converted to its glucuronide which, in turn, inhibits a key copper-dependent enzyme such as cytochrome oxidase.

[1] Catalog No. 476220, Corning Glass Works.
[2] A 10% volume corrected paper was used; Catalog No. 90-00-90, Orion Research Inc.
[3] Model 92-32, Orion Research, Inc.

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Prediction of Dissolution Rates of Slightly Water-Soluble Powders from Simple Mathematical Relationships

Keyphrases □ Dissolution rates, slightly water-soluble powders—prediction from simple mathematics □ Powders, slightly water soluble—dissolution rates predicted from simple mathematics

Sir:

Recently, several articles in the literature reported sophisticated, expensive, and complex methods for determining the dissolution rates of slightly water-soluble powders (1–3). Aside from the fact that these and similar methods require the development of sensitive analytical procedures, the results obtained are often unpredictable. For example, Ullah and Cadwallader (1) were unable to detect differences in the rate of dissolution of salicylic acid ranging in particle size from 60 to 230 mesh. This is contrary to the fact that the rate of dissolution depends on the exposed surface area of the drug. I wish to report that one can predict, with high accuracy, the rate of dissolution of powders from simple mathematical relationships. The only required information is: (*a*) the surface area of the powder, and (*b*) the solubility of the compound in the dissolution media.

The amount of drug dissolved under sink conditions

Table I—Diffusion Coefficients of Weak and Nonelectrolytes in Water at 25°

Solute	$D \times 10^5$ cm.²/sec.
Glucose	0.67
Pentaerythritol	0.76
Glycolamide	1.14
α-Alanine	0.91
β-Alanine	0.93
o-Aminobenzoic acid	0.84
Aminobenzoic acid	0.84

Table II—Percentage of Hydrocortisone (60–80 Mesh) Dissolved in Water as a Function of Time at 25° and 55 r.p.m.[a]

Dissolution Time, min.	Percent Dissolved Found	Percent Dissolved Calculated
8.5	8	7
23	20	19
26	26	23
40	40	36
59.6	50.8	50.5
70.1	57.3	60

[a] The weight of the sample is 22 mg., and the volume of the dissolution medium is 500 ml.

Table III—Percentage of Levodopa (80–100 Mesh) Dissolved in Water as a Function of Time at 25° and 55 r.p.m.[a]

Dissolution Time, min.	Percent Dissolved Found	Percent Dissolved Calculated
1	15.4	15.1
1.3	20	20
2	30.8	30
3	45	45
4	60	62

[a] The weight of the sample is 43.5 mg., and the volume of the dissolution media is 500 ml.

as a function of time can be calculated from Fick's first law:

$$Q = \frac{A \cdot S \cdot D \cdot t}{h} \qquad \text{(Eq. 1)}$$

where:

Q = amount of drug (in grams) dissolved in time t
A = surface area occupied by the total weight of the sample
S = solubility of the drug (in grams/milliliter) in the dissolution media
D = diffusion coefficient of the drug (in cm.^{2}/sec.)
h = thickness of the diffusional layer (in centimeters)

All this information can either be easily determined or obtained from the literature. For example, the surface area can either be measured directly for W grams of the powder or can be calculated from the average particle size, assuming the particles are spherical in shape:

$$V \text{ of sphere} = \tfrac{4}{3}\pi r^3 \qquad \text{(Eq. 2)}$$

$$\text{number of particles in } W \text{ grams of powder} = \frac{W}{\tfrac{4}{3}\pi r^3} \qquad \text{(Eq. 3)}$$

$$\text{area of sphere} = 4\pi r^2 \qquad \text{(Eq. 4)}$$

The total surface area occupied by W grams of the powder is the product of Eqs. 3 and 4 and is equal to $(W \times 3)/r$ cm.^{2}.

The value for the diffusion coefficient D is almost the same for a wide range of molecules. Since D varies only with the cube root of molecular weight, large variations in molecular weight and shape result in only small changes of D. Table I shows the value of D for several compounds of different molecular weight and shape (4). A value of 9×10^{-6} cm.^{2}/sec. is a close average value for a wide range of molecules.

The thickness of the diffusional layer, h, varies with the stirring rate. However, at 55 r.p.m., where Levy (5) and Cressman *et al.* (6) found a close correlation between *in vitro* dissolution rates and *in vivo* absorption rates, the thickness of the diffusional layer was estimated to be approximately 50×10^{-4} cm.

The following example illustrates the utility of these relationships. The weight of hydrocortisone is 22 mg., the average particle size is 212 μ (60–80-mesh fraction), and the solubility of hydrocortisone in water is 0.28 mg./ml. If one wishes to calculate the time required for 50% of the drug to dissolve, then:

$$Q = 11 \text{ mg.} \qquad \text{(Eq. 5a)}$$

$$A = \frac{22 \times 10^{-3} \times 3}{212/2 \times 10^{-4}} = 6.2 \text{ cm.}^2 \qquad \text{(Eq. 5b)}$$

$$11 = \frac{6.2 \times 9 \times 10^{-6} \times 0.28 \times t}{50 \times 10^{-4}} \qquad \text{(Eq. 5c)}$$

$$t = 3530 \text{ sec.} = 58.7 \text{ min.} \qquad \text{(Eq. 5d)}$$

Tables II and III show the experimentally determined and the theoretically calculated percent hydrocortisone and levodopa dissolved as a function of time.

Table IV shows the correlation between the experimentally determined dissolution times and the calculated values for several compounds.

The data in Table IV indicate that one can actually calculate an approximate, if not an exact, value for t_{20}, t_{50}, *etc.*, of dissolution. Since, in many instances, one cannot exactly correlate between *in vitro* dissolution rates and *in vivo* absorption rates, an approximate and easily calculated value for the t_{50} of dissolution is all that is needed. The described method assumes complete dispersion of the powder to obtain a maximum surface area. In reality, this assumption may or may not be valid. However, the error obtained by this method is of the same magnitude as that obtained experimentally if the powder is not wetted and dispersed in the dissolution media (7).

(1) T. Ullah and D. E. Cadwallader, *J. Pharm. Sci.*, **59**, 979(1970).
(2) *Ibid.*, **60**, 230(1971).

Table IV—Correlation between Experimentally Determined 20 and 50% Dissolution Times and the Calculated Values

Compound	Average Particle Size, μ	Solubility, mg./ml., in Dissolution Media	Weight of Drug Used, mg.	t_{20} Exp.	t_{20} Calc.	t_{50} Exp.	t_{50} Calc.
Hydrocortisone	212 (60–80 mesh)	0.28	22	20[a]	19	58[a]	58
Benzoic acid	212 (60–80 mesh)	3.4	102.5	1.5[a]	2	5[a]	5.4
Levodopa	162 (80–100 mesh)	3.78	43.5	1.3[a]	1.3	3.3[a]	3.3
Griseofulvin	5	0.013	5	—	—	30–40[b]	30

[a] Determined in this laboratory by the method described by Poole (7). [b] *Reference 8.*

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Screening Nornuciferine Derivatives for Apomorphine-Like Activity

Keyphrases ☐ Nornuciferine derivatives—screened for apomorphine-like activity, dogs, pigeons, mice ☐ Apomorphine-like activity, potential—nornuciferine derivatives screened, dogs, pigeons, mice

Sir:

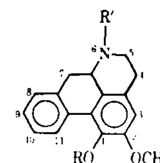
A substantial number of apomorphine analogs and derivatives were examined in an attempt to define the chemorphological requisites for biological activity, notably activity relating to emesis and behavioral stereotypy (1–3). In a continuing study of apomorphine derivatives having "potential" emetic activity, Vavrek *et al.* (4) prepared a series of 1,2-dimethoxylated noraporphines (nornuciferines) for biological evaluation. These compounds recently were screened for several apomorphine-related activities: (*a*) emesis in dogs, (*b*) compulsive pecking in pigeons, and (*c*) compulsive gnawing in mice. Gross acute toxicity in mice, in terms of convulsions and lethality, were also evaluated.

The method for assessing emetic activity was described previously (2) and involves comparison of the threshold emetic dose of a compound with the threshold emetic dose of apomorphine reference standard in the same animals. Compounds that do not provoke emesis in doses 100 times the apomorphine threshold emetic dose are judged to be inactive. Cumulative pecking responses in birds were recorded with an electromechanical monitor (5), and gnawing activity in mice was assessed as a dose-related quantal response. Drugs were administered as hydrobromide or hydrochloride salts in saline by the following routes: dogs and pigeons, intramuscular; and mice, intraperitoneal.

All of the nornuciferine derivatives were inactive as emetics and exerted no overt behavioral effects in either mice or pigeons. They were devoid of all ability to generate compulsive behavioral responses so characteristic of apomorphine.

The compounds, however, do provoke intense clonic convulsions as does apomorphine. Estimates of convulsant and lethal potencies are presented in Table I. Sparingly soluble compounds, VI–VIII and XIII–XVI, could not be administered in sufficiently high doses to

Table I—Comparative Toxicities of Nornuciferine Derivatives in Mice[a]



Compound	Number[b]	R	R′	CD_{50}[c], μmoles/kg.	LD_{50}[d], μmoles/kg.
Apomorphine	—	—	—	328 ± 13	559 ± 33
Nornuciferine	I	CH_3	H	123 ± 4	323 ± 18
Nuciferine	II	CH_3	CH_3	70 ± 2	142 ± 6
(−)-Nuciferine	(−)II	CH_3	CH_3	237 ± 9	280 ± 9
N-Ethylnornuciferine	III	CH_3	$CH_2—CH_3$	164 ± 12	291 ± 3
N-*n*-Propylnornuciferine	IV	CH_3	$CH_2—CH_2—CH_3$	363 ± 24	851 ± 60
N-Cyclopropylmethylnornuciferine	V	CH_3	CH_2—◁	212 ± 15	385 ± 8
N-Allylnornuciferine	VI	CH_3	$CH_2—CH{=}CH_2$	>1010	>1010
N-Propargylnornuciferine	VII	CH_3	$CH_2—C{\equiv}CH$	>1010	>1010
N-Benzylnornuciferine	VIII	CH_3	$CH_2—C_6H_5$	>900	>900
1-Hydroxy-2-methoxynoraporphine	IX	H	H	339 ± 29	469 ± 32
1-Hydroxy-2-methoxyaporphine	X	H	CH_3	217 ± 3	235 ± 4
1-Hydroxy-2-methoxy-*N*-ethylnoraporphine	XI	H	$CH_2—CH_3$	227 ± 8	272 ± 8
1-Hydroxy-2-methoxy-*N*-*n*-propylnoraporphine	XII	H	$CH_2—CH_2—CH_3$	404 ± 27	>650
1-Hydroxy-2-methoxy-*N*-cyclopropylmethylnoraporphine	XIII	H	CH_2—◁	>650	>650
1-Hydroxy-2-methoxy-*N*-allylnoraporphine	XIV	H	$CH_2—CH{=}CH_2$	>650	>650
1-Hydroxy-2-methoxy-*N*-propargylnoraporphine	XV	H	$CH_2—C{\equiv}CH$	>650	>650
1-Hydroxy-2-methoxy-*N*-benzylnoraporphine	XVI	H	$CH_2—C_6H_5$	>650	>650

[a] Female Harlan ICR. [b] Code as designated in *Reference 4*. [c] Median convulsant dose ± *SE* in μmoles of base/kg. body weight, intraperitoneal. [d] Median lethal dose.