Dissolution of a Soluble Drug Substance from Vinyl Polymer Matrices

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Abstract □ It was shown that vinyl polymers form good bases for *in vitro* sustained-release matrices, and that the character of the release curves is basically in line with their pH–solubility profiles. For a flow cell, the release curves may be approximated by the equation: $\ln (m/m_0) = -K(t - t_i)$, where m is the amount not dissolved, m_0 is the initial drug content, K is a dissolution constant, t is time, and t_i is a lag time. Furthermore, it was shown that K is a function of tablet hardness (H) and polymer content (Q, percent). This functionality is well represented by the equation: $\ln K = \alpha H + \gamma \ln Q + \epsilon$, where α, γ, and ϵ are polymer-dependent parameters. Matrix erosion is represented by an exponential decay: $(p/p_0) = \exp(-Dt + a)$, where p is the amount not eroded, p_0 is the initial weight, D is an erosion constant, and a is a soluble polymer-dependent parameter. In the case of these soluble polymers, K is not solely a function of D.

Keyphrases □ Dissolution—soluble drug substances from vinyl polymer matrices □ Polymers—vinyl polymer matrices, dissolution of a soluble drug substance □ Matrices—vinyl polymer, dissolution of a soluble drug substance

The fundamental dissolution relationship from sustained-release preparations have been studied extensively. Matrix formulations are based on a published model (1), and the ensuing square root law has been well established (2). In these formulas, the matrix is completely insoluble.

BACKGROUND

Several reports (3–13) have appeared describing dissolution from rapidly disintegrating dosage forms. The dissolution frequently appears to follow an exponential decay law. It would be expected that the dissolution should adhere to a cube root law; that it does not is due to the effect of disintegration of the tablet in the dissolution apparatus. This effect (3) gives rise to a dissolution equation of the form:

$$\ln (p/p_0) = -Dt \qquad \text{(Eq. 1)}$$

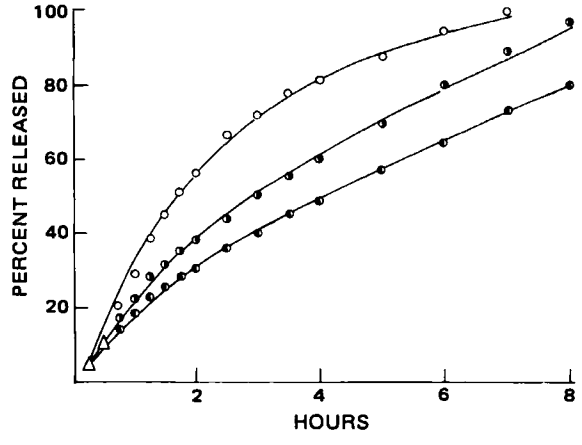

Figure 1—*Example of release curves by half-change method in flow cell under sink conditions of polyvinyl phthalate acetate, 60% directly compressed. Key: (○) 5-kg hardness; (◑) 10-kg hardness; (◐) 15-kg hardness; (△) points that are graphically indistinguishable between the three hardnesses.*

where p is the amount not disintegrated at time t (p_0 at time zero) and D is a disintegration constant. For a tablet where disintegration is rapid, Eq. 1 in conjunction with a cube root equation leads to a dissolution curve of the type:

$$\ln (m/m_0) = -K(t - t_i) \qquad \text{(Eq. 2)}$$

where m is the amount not dissolved, m_0 is the amount of drug present in the tablet, K is a dissolution constant, and t_i is a lag time. The parameter is frequently a function of D by the relation:

$$\ln K = a' + n \ln D \qquad \text{(Eq. 3)}$$

where a' and n are constants.

Contrary to previous studies, many sustained-release preparations can be formulated where the matrix is not completely insoluble, *i.e.*, the tablets disintegrate or erode to some extent during the dissolution process. The word erosion is preferred over the word disintegration, although at times a sharp distinction between the two is not possible.

One of the purposes of the present report is to examine matrices that are not completely insoluble, and to (*a*) elucidate the general dissolution profile, (*b*) estimate the effect of formulation and processing parameters on the dissolution profile, and (*c*) estimate the disintegration or erosion profile in the dissolution apparatus to assess its effect on the dissolution profile.

The conditions of study are such that a half-change method is used. Long-acting tablets were prepared with polymers of different types such that they: (*a*) are acid soluble, but alkali insoluble (giving an initial phase where dissolution is correlated to disintegration and where the final phase should be by diffusion), (*b*) are alkali soluble but acid insoluble (giving the reverse effect), (*c*) are soluble over the entire pH range, and (*d*) are insoluble over the entire pH range.

Since flow methods (11) are commonly used in Europe, one of the purposes of the work reported in this study was to investigate erosion and dissolution behavior in such an apparatus. Erosion profiles in flow cells are not well understood. Some reports on disintegration time (6) have appeared, but elucidation of erosion time curves have not been attempted previously.

The present investigation also reports on formulas that possess *in vitro* release characteristics making them good candidates for sustained-release preparations. The empirical equations serve as a means of obtaining optimum operating conditions for producing the sustained-release tablets and for obtaining the most desirable tablet formula for a given set of specifications for the amount released at two time points.

The drug selected was especially chosen because its solubility is not particularly pH dependent. This allows study of the dissolution behavior to be aimed at the effect of the matrix. The rationale for sustained-release preparations of the compound and its biopharmaceutical characteristics have been described (13).

Table I—Formulas Used [a]

	Direct Compression			Wet
	I	II	III	Granulation
Dyphylline	20	20	20	20
Polymer[b]	15	30	60	15
Dicalcium phosphate[c]	60	45	15	62
Talc	3	3	3	1
Magnesium stearate	1.5	1.5	1.5	2
Pyrogenic silica[d]	0.5	0.5	0.5	
Solvent[e]				(22.5)[c]

[a] Quantities listed are percent by weight, and quantities in parentheses are the percent lost on drying. [b] See Table II. [c] Encompress, Edward Mendell Co., Carmel, NY 10512, (S.P.C.I., 93212, La Plaine-St. Denis, France). Encompress was used in the direct compression formula only. [d] Aerosil 200, Degussa-France, 92100, Neuilly, France. [e] The solvents used are listed in Table II.

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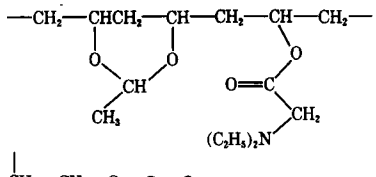
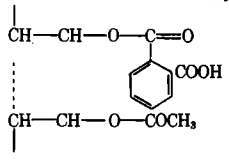
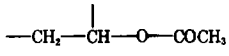
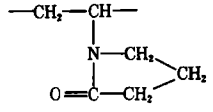
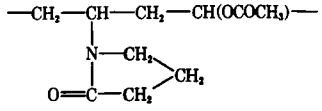
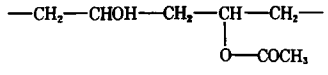
Table II—Polymers Used

Polymer	Formula (Monomer Unit)	Solvent for Granulation	Characteristics
Polyvinyl acetal diethylamino acetate[a] (I)		Absolute ethanol	Acid soluble; alkali insoluble; *pK* 5.8–6.1; Mol. wt., 20,000
Polyvinyl acetate phthalate[b] (II)		Absolute ethanol	55–65% phthalate groups; 1.2% free acid; acid insoluble, alkali soluble
Polyvinyl acetate[c] (III)		Water	Insoluble at low and high pHs
Povidone[d] (IV)		Water	Soluble at all pHs; Mol. wt., 40,000
Povidone–vinyl acetate[e] (V)		Water	Povidone–vinyl acetate (60:40); soluble at all pHs; Mol. wt., 60,000 ± 15,000
Polyvinyl alcohol–acetate[f] (VI)		Water	Soluble at all pHs; 12% acetate groups

[a] Sankyo, Marcel Quarré, 75009, Paris, France, designation PADAA 5. [b] Colorcon, Seppic, Elysées, 75008 Paris, France. [c] Rhodopas, BB_3 used for direct compression. Emulsion A 010 Rhodopas readymade aqueous suspension used for wet granulation. Rhône-Poulenc polymères, 92408 Courbevoie, France. [d] Plasdone K 29-32, General Aniline and Film, 95380, Louvres, France. [e] PVP/VA S-630, General Aniline and Film, 95380, Louvres, France. [f] Mowiol, 4-88, Hoechst—France, 75008 Paris, France.

The use of polyvinyl polymers for sustained-release matrices has been reported in general (14–17). Polyvinyl alcohol has been used extensively for pharmaceutical purposes: in coating (18–23) and as a binder in granulation (24). Povidone has also been used extensively for coating (18, 21, 24–27), as a binder in granulation (28–31), and for sustained-release matrices (32). Polyvinyl acetate has been used in coating (18, 33–37), in matrices (17, 38–40), and in sustained-release capsule beads (41, 42). Povidone–vinyl acetate has been used in coating (43, 44) in granulations (45), and in cast films (46–48). Polyvinyl acetate phthalate has been used for coating (49–53), and polyvinyl acetal diethylaminoacetate has been used in coating (54, 55), studied in cast films (56, 57), and used in matrices (14).

EXPERIMENTAL

Dyphylline was selected for study in the sustained-release preparations because of its high solubility (~25% w/v in water at 25°) and the ease of assay (spectrophotometric). Tablets were made by both direct compression and wet granulation.

Direct Compression—The formulas used for direct compression are shown in Table I. The polymer and dyphylline were sieved, and the fraction finer than 315 μm was used. The powders were mixed in a turbulent action mixer[1] for 10 min and were compressed at three pressures, giving hardnesses of 5, 10, and 15 kg.

The experimental conditions (punch pressures) giving these conditions had been established, and hardness was within 5%. All experiments were carried out immediately after manufacture of the tablets. Tablets were compressed on a single-punch tablet machine[2], at a tablet weight of 500 mg using a flat, nonbeveled punch, 12-mm diameter. The machine was instrumented with strain gauges to record upper and lower punch forces.

Wet Granulation—The chemical properties and the granulation solvents are listed in Table II. The general formula for the wet granulation

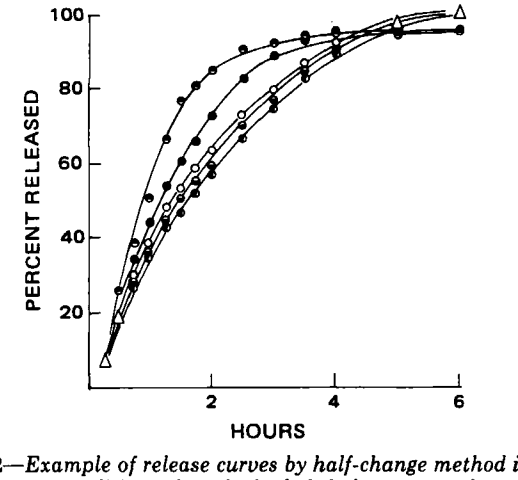


Figure 2—*Example of release curves by half-change method in flow cell under sink conditions of a polyvinyl phthalate acetate formulation (15%) made by wet granulation and compressed to three hardnesses. Key: (○) 5 kg; (◒) 10 kg; (◐) 15 kg; (△) points that are graphically indistinguishable; (◓) povidone–vinyl acetate, 15% at 10 kg; (●) polyvinyl acetate, 15% at 15 kg.*

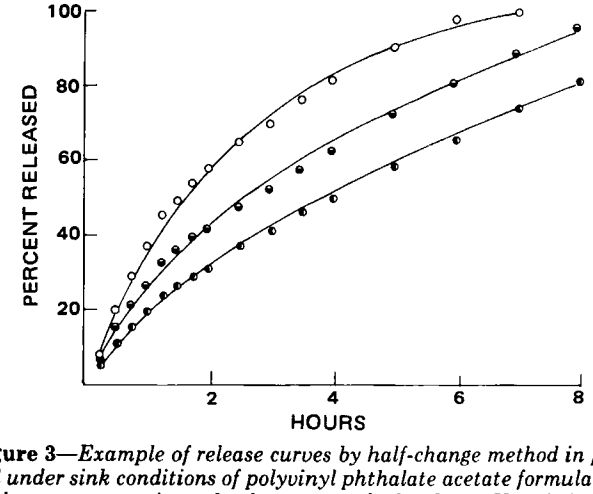


Figure 3—*Example of release curves by half-change method in flow cell under sink conditions of polyvinyl phthalate acetate formulation at three concentrations of polymer at 15-kg hardness. Key: (○) 15%; (◒) 30%; (◐) 60%. All formulas were directly compressed.*

[1] Turbula mixer, Prolabo, 75011 Paris, France.
[2] Model AO Machine, Frogerais, 94400, Vitry-sur-Seine, France.

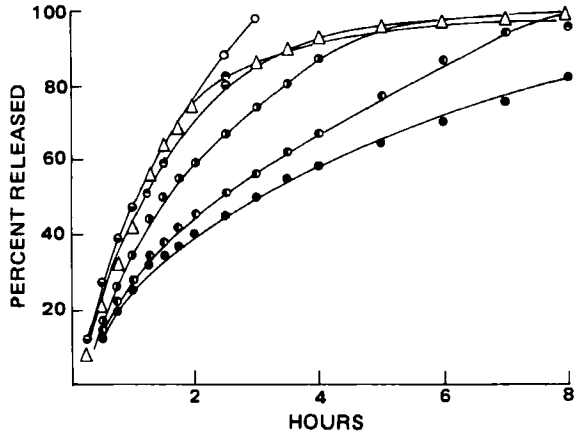


Figure 4—*Release curves at a particular pressure for each of the directly compressed polymer formulas tested, shown for general comparison. Key: (○) polyvinyl alcohol–acetate, 60% at 5 kg; (◒) povidone–vinyl acetate, 15% at 10 kg; (◒) povidone, 30% at 15 kg; (◑) polyvinyl acetal diethylamino acetate, 60% at 15 kg; (◐) polyvinyl acetate phthalate, 30% at 10 kg; (●) polyvinyl acetate, 60% at 5 kg, (△) graphically indistinguishable points.*

is in the last column of Table I. The sieved dyphylline was mixed with the dibasic calcium phosphate for 5 min in a planetary mixer[3]. A 50% w/w solution of the polymer in the solvent was added to the mixture in the planetary mixer, and kneading was carried out for 5 min. The remaining solvent was added and kneading was performed for an additional 5 min. The wet mass was passed through an oscillating granulator[4] equipped with a 2-mm screen. The granulation was dried at 60° in a fluid bed dryer[5] to a moisture content of 2% (loss on drying in an IR moisture balance[6]). Drying time was ~30 min for alcohol wet granulations and ~1 hr for water wet product. The dried granulation was passed through an oscillating granulator with a 1-mm screen, lubricated for 5 min in the turbulent action mixer, and compressed.

Testing—Dissolution was carried out at 37° in a continuous flow apparatus with a flow cell[7], under sink conditions, using the half-change method. One tablet was placed in the cell, and simulated gastric fluid without enzymes was added; after 1 hr this was changed to a 50% mix of simulated gastric fluid and simulated intestinal fluid, both without enzymes. After 2 hr the acid concentration was reduced to 25%. The pH values recorded were: 0–1 hr, 1.2; 1–2 hr, 2.0; 2–3 hr, 6.4; 3–4 hr, 7.0; 4–5 hr, 7.2; 5–6 hr, 7.3; 6–7 hr, 7.4; and 7–8 hr, 7.5. The test was carried out under sink conditions, *i.e.*, fluid was not returned to the cell once it had passed. The assays were carried out spectrophotometrically at 274 nm. The results were converted to amount of drug, m (in milligrams or percent), not released at time t. The testing intervals were typically as shown in Figs. 1 and 2. The hardness of the tablets was tested using a moving-stationary anvil fracture strength tester[8].

The disintegration mode was studied by a described method (4, 9) and yielded the weight of tablet, p (on a dry basis), not disintegrated at time

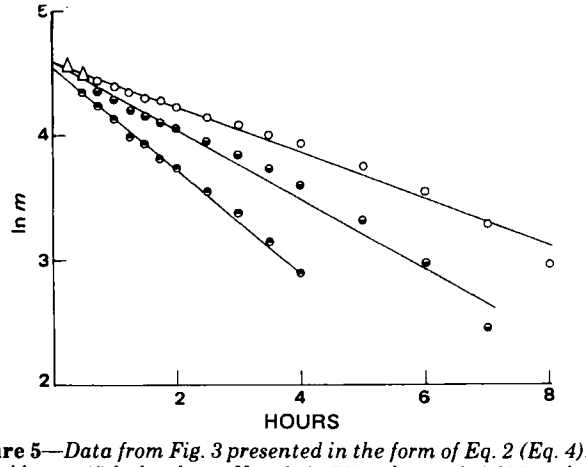


Figure 5—*Data from Fig. 3 presented in the form of Eq. 2 (Eq. 4). All are tablets at 15-kg hardness. Key: (◒) 15% polymer; (◒) 30% polymer; (○) 60% polymer; (△) graphically indistinguishable points.*

Table III—Least-Squares Fit Values for All Dissolution Data Treated According to Eq. 4

Polymer	Percent	Hardness, kg	Correlation Coefficient, r^2	Intercept a	Negative Slope K
I	15	5	0.988	4.89	1.23
	15	10	0.996	4.80	1.01
	15	15	0.998	4.74	0.89
	15g[a]	5	0.999	4.71	0.82
	15g[a]	10	0.998	4.78	0.96
	15g[a]	15	0.998	4.76	0.82
	30	5	0.999	4.69	0.75
	30	10	0.999	4.63	0.57
	30	15	0.995	4.60	0.53
	60	5	0.987	4.84	0.77
	60	10	0.997	4.68	0.61
	60	15	0.991	4.68	0.50
II	15	5	0.999	4.69	0.71
	15	10	0.985	4.59	0.45
	15	15	0.996	4.56	0.45
	30	5	0.997	4.63	0.45
	30	10	0.982	4.61	0.30
	30	15	0.978	4.62	0.27
	60	5	0.997	4.67	0.44
	60	10	0.971	4.69	0.30
	60	15	0.977	4.61	0.18
	15g[a]	5	0.993	4.60	0.58
	15g[a]	10	0.988	4.73	0.56
	15g[a]	15	0.973	4.74	0.54
III	15	5	0.989	4.80	0.90
	15	10	0.975	4.77	0.81
	15	15	0.984	4.73	0.76
	30	5	0.990	4.75	0.62
	30	10	0.988	4.76	0.65
	30	15	0.995	4.71	0.59
	60	5	0.993	4.51	0.19
	60	10	0.990	4.50	0.15
	60	15	0.981	4.48	0.12
	15g[a]	5	0.996	4.78	1.18
	15g[a]	10	0.997	4.66	0.75
	15g[a]	15	0.990	4.74	0.76
IV	15	5	0.961	4.76	0.90
	15	10	0.973	4.72	0.76
	15	15	0.976	4.77	0.74
	30	5	0.958	4.99	1.32
	30	10	0.984	4.85	0.98
	30	15	0.994	4.67	0.70
	60	5	0.974	4.77	1.03
	60	10	0.987	4.91	1.17
	60	15	0.984	4.97	1.31
	15g[a]	5	0.992	4.73	0.79
	15g[a]	10	0.983	4.78	0.81
	15g[a]	15	0.996	4.76	0.88
V	15	5	0.999	4.69	0.70
	15	10	0.999	4.61	0.65
	15	15	0.996	4.73	0.85
	15g[a]	5	0.978	4.91	1.27
	15g[a]	10	0.987	4.81	1.08
	15g[a]	15	0.989	4.74	0.98
	30	5	0.990	4.91	1.41
	30	10	0.997	4.85	1.35
	30	15	0.994	4.59	0.76
	60	5	0.992	4.75	1.80
	60	10	0.975	5.00	1.58
	60	15	0.981	4.89	1.51
VI[b]	15	5	0.989	4.92	1.55
	15	10	0.991	4.87	1.15
VI[b]	30	5	0.992	4.86	1.06
VI[b]	60	5	0.960	4.86	0.85
	15g[a]	5	0.978	4.84	0.91
	15g[a]	10	0.992	4.74	0.84
	15g[a]	15	0.992	4.81	0.95

[a] g stands for wet granulated. [b] Even at very high compression pressures it was not possible to make tablets harder than those shown.

[3] Hobart Mixer, 1-kg capacity, Hobart Manufacturing Co., Troy, Ohio.
[4] Erweka, model F.G.S., Euraf, 75018 Paris, France.
[5] Glatt, model TR2, Chimie-Plastique, BP 664, 95004, Cergy, France.
[6] Mettler, LP12, Sofranie, Levallois-Perret, France.
[7] Desaga flow cell.

[8] Heberlein Hardness Tester, Grogerais, 94400 Vitry-sur-Seine, France.

Table IV—Least-Squares Fit Parameter Values According to Eq. 5

Polymer	Percent	α	β	Correlation Coefficient, r
I	15	−0.032	+0.357	−0.992
I	15g[a]	−0.031	+0.273	−1.0
I	30	−0.035	−0.148	−0.948
I	60	−0.043	−0.051	−0.999
II	15	−0.055	−0.127	−0.935
II	15g[a]	−0.007	−0.509	−0.999
II	30	−0.051	−0.593	−0.947
II	60	−0.089	−0.353	−0.997
III	15	−0.018	−0.018	−0.996
III	15g[a]	−0.091	+0.618	−1
III	30	−0.019	−0.237	−1
III	60	−0.046	−1.434	−0.999
IV	15	−0.020	−0.031	−0.922
IV	15g[a]	+0.011	−0.300	+0.955
IV	30	−0.063	+0.602	−0.999
IV	60	0.024	−0.089	0.999
V	15	0.054	−0.969	1.0
V	15g[a]	−0.026	+0.358	−0.990
V	30	−0.062	+0.741	−0.896
V	60	−0.018	0.662	−0.962
VI	15	−0.060	0.736	−1.0
VI	15g[a]	−0.016	−0.014	−1.0

[a] g is wet granulated.

t. Testing intervals were typically 1, 2, 3, 4, 6, and 8 hr, except for periods during dissolution in particular cases where disintegration was rapid. In these cases the intervals were shortened.

RESULTS AND DISCUSSION

The dissolution curves obtained are all of the shape shown in Figs. 1–4, which is a type profile frequently encountered in dissolution work. The general, mutual position of the curves is in good agreement with the physical characteristics of the polymers, the most soluble giving rise to the most rapid release and the least soluble giving rise to the slowest. This is illustrated in Fig. 4, where all formulas are shown at one hardness (per polymer). It is seen from Fig. 2 that wet granulation causes a marked increase in dissolution rate.

It is to be expected that hardness (H) and polymer content (Q) would affect the rate of release. Figures 1–3 demonstrate this in a qualitative way. In a more quantitative fashion, the dissolution constant (K, hr^{-1}) would have to be a function of both Q and H.

To establish a function that could describe this dependence, the effect of hardness will first be examined, and then the effect of both hardness and polymer concentration will be scrutinized.

It is conventional to fit dissolution data to one of several types of functions (11), an exponential decay (Eq. 2) being one such relationship. In this case the plotting should follow:

$$\ln (m/m_0) = -Kt + a \qquad \text{(Eq. 4)}$$

where m_0 is the initial drug content. Figure 5 shows this type of plotting to be well adhered to, and the least-squares fit parameters for all the preparations are shown in Table III. From the correlation coefficients, the empirical choice of Eq. 4 is well justified.

Table V—Amount Disintegrated as a Function of Time for Three Polymers

Polymer	Percent	Hardness	Fraction Not Disintegrated at Time t, hr			
			0.5	1.0	1.5	2
IV	15	15	0.55	0.36	0.40	0.40
	30	15	0.50	0.30		
	60	15	0.36	0.10	0.05	
	15g[a]	15	0.65	0.47	0.50	0.46
V	15	15	0.56	0.43	0.51	0.37
	30	15	0.45	0.14		
	60	15	0.46	0.19	0.04	
	15g[a]	15	0.49	0.29	0.11	0.14
VI	15	10	0.45	0.24	0.20	
	30	5	0.44	0.24	0.21	0.07
	60	5	0.66	0.46	0.37	
	15g[a]	15	0.47	0.32	0.24	0.20

[a] g is wet granulated.

Table VI—Multiple Regression Treatment of the Data According to Eq. 7 (Direct Compression Formulas)

Polymer	ϵ	α	γ	Average α from Table IV for Direct Compression Formulas
I	1.32	−0.037	−0.37	−0.037
II	1.04	−0.065	−0.41	−0.065
III	3.36	−0.011	−1.22	−0.027
IV	−0.77	−0.020	+0.27	−0.019
V	−1.93	−0.034	+0.683	−0.009
VI	+1.86	−0.054	−0.434	−0.048

It was mentioned earlier that K decreases with increasing hardness, H, and inspection of Table III leads to the plausibility of a relation of the type:

$$\ln K = \alpha H + \beta \qquad \text{(Eq. 5)}$$

The least-squares values for K for all the preparations in Table III have been treated according to Eq. 5, and for each polymer (i), the least-squares fit parameters β_i and α_i are listed in Table IV. A dimensionless plot, as described previously (10, 12), is shown in Fig. 6; the ordinate values are the individual values of $y = \ln K_i - \beta_i$, and the abscissa values are $x = \alpha_i H_i$, and since according to Eq. 5:

$$(\ln K_i) - \beta_i = \alpha_i H \qquad \text{(Eq. 6)}$$

a line with unity slope and zero intercept should follow. Figure 6 indicates that this is the case, showing that Eq. 5 is a reasonable choice of function representing the dependence of K on H, and all values for all the preparations are included.

Table IV shows that the wet granulated preparations are less sensitive to hardness (tableting pressure) than the directly compressed tablets.

The parameter K is not only a function of H but also of the drug content, Q (percent), of the polymer. There are four of the cases where K decreases with increasing polymer concentration, and two cases (povidone and povidone–vinyl acetate) where K increases with increasing polymer concentration. These latter two cases are in accord with previously reported findings where povidone (58–61) and providone–vinyl acetate (45) have been found to increase dissolution rates. However, as seen in Table V, erosion rates also increase with increasing concentration of these two polymers, so that dissolution (diffusion) rate increase or erosion rate increase (or both) could account for the increase in K with an increase in the polymer concentration. Table V shows that K probably approaches a limiting value (K') as Q increases. This requires four parameter fits (*i.e.*, $K = F(H,Q,K')$, where F denotes function of. Since K' would have to be obtained by iteration, the resulting statistics would be of questionable robustness. Instead, it has been assumed here that K for a given hardness

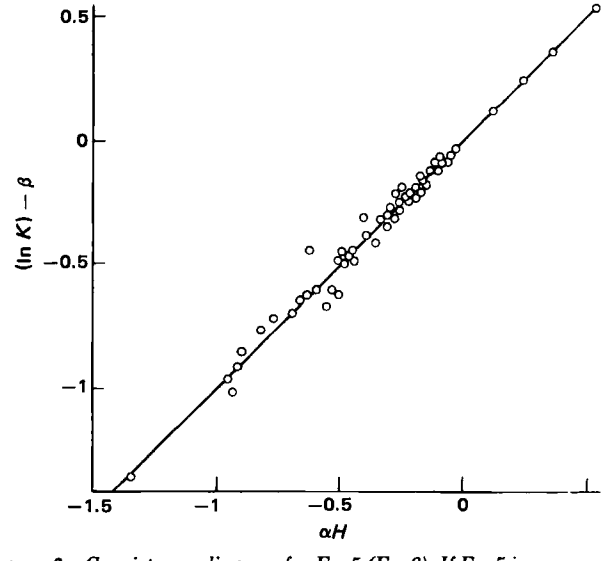


Figure 6—*Consistency diagram for Eq. 5 (Eq. 6). If Eq. 5 is a reasonable fit, then* y = x, *where* x = αh *and* y = ln K − β. *The least-squares fit of the line is* y = 1.002x − 0.0004, i.e., *the slope is close to unity, the intercept is close to zero, and the equation is close to* y = x.

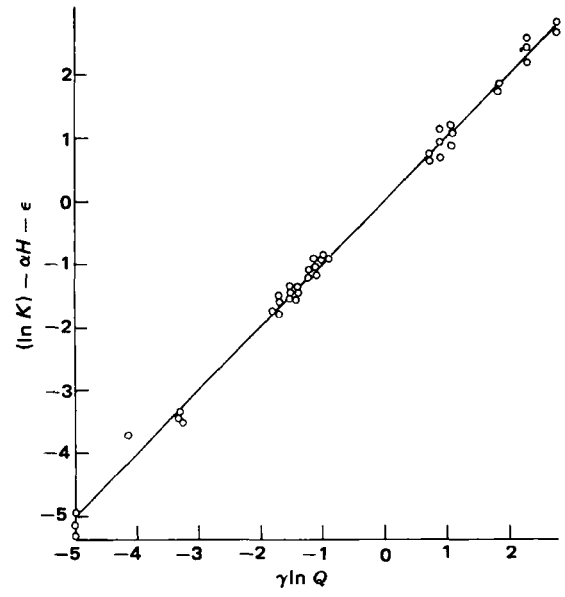


Figure 7—*Data treated according to Eq. 7. The abscissa is* x = γln Q *and the ordinate is* y = (ln K) − αH − ϵ. *The least-squares fit is* y = $(1 \times 10^{-5})x + 5 \times 10^{-4}$, *so that the slope is close to unity and the intercept close to zero as required for Eq. 7 to be a reasonable function* (r = 0.997).

changes in log–log fashion with Q, *i.e.*, retaining the format of Eq. 5 for the H-dependence:

$$\ln K = \alpha H + \epsilon + \gamma \ln Q \qquad \text{(Eq. 7)}$$

The data have been treated by multiple regression, and the least-squares fit values are shown in Table VI. The data are shown in dimensionless presentation in Fig. 7. The ordinate is $y = \ln K - \alpha_i H - \epsilon_i$, where the subscript i is the individual parameter values for the ith polymer. The abscissa is $\gamma_i \ln Q$, so the line, $y = x$, should have unity slope and zero intercept, which is the case. Equation 7, therefore, is a reasonable overall empirical function for the data. The values of α in Tables IV and VI should be close to one another, and as shown in the last column of Table VI, they are.

The value of the phenomonological approach is as follows. For development of sustained-release products, it is usually the intent to obtain a certain *in vitro* release curve. This is often of the military specification type with a range of percent release after (for example) 1 hr, and a range of percent released after 4 hr. At this starting point there is already a benefit from knowing the release equation. If the specifications were, *e.g.*, 25–30% after 1 hr and 40–60% after 4 hr, then the type release found here

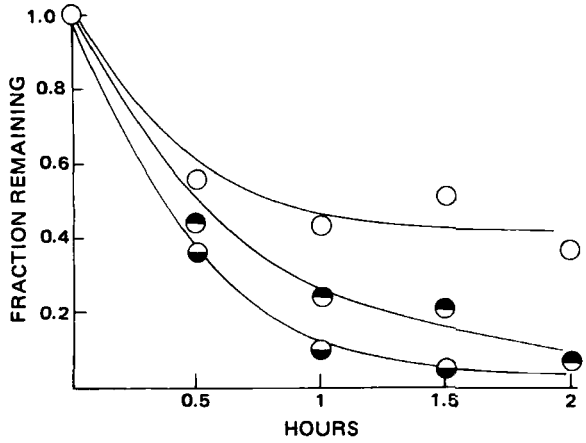


Figure 8—*Disintegration data for polymers with non pH-dependent solubilities. The ordinate is fraction not disintegrated (eroded) at time* t. *Key: (○) providone–vinyl acetate, 15%, 15-kg hardness; (◒) povidone, 60%, 15-kg hardness; (◓) polyvinyl alcohol–acetate, 30%, 5-kg hardness.*

Table VII—Disintegration Data for Tablets Made with Polyvinyl Acetal Diethylaminoacetate

Polymer, %	Parameters for Eq. 15			
	P_∞ (Fraction)	a	D	Correlation Coefficient, r
15g[a]	0.16	−0.318	1.076	−0.98
15	0.18	−0.244	−0.973	−0.99
30	0.26	−0.30	−1.36	−1.0
60	0.33	−0.40	−1.50	−1.0

[a] g is wet granulated.

Table VIII—Values of (p/p_0) for Polyvinyl Acetate Phthalate Formulations

Time, hr	Formula (Polymer, %; Hardness, kg)				
	15%, 15 kg	30%, 15 kg	60%, 15 kg	60%, 10 kg	60%, 5 kg
0	1	1	1	1	1
1	0.7	0.81	0.97	0.98	0.96
2	0.7	0.79	0.97	0.98	0.97
4	0.62	0.66	0.93	0.81	0.77
6	0.34	0.55	0.78	0.63	0.63
8	0.27	0.39	0.54	0.47	0.39
D	0.208	0.130	0.138	0.135	0.170
a	0.289	0.126	0.512	0.340	0.470
$t_i = a/D$	1.39	1.97	3.72	2.49	2.75
r	−0.97	−0.98	−0.97	−0.99	0.97

(Eq. 2) would not be adequate[9]. It should be pointed out that most sustained-release patterns are of this type. That it would not be adequate is seen from the following. The K-value calculated from the 4- and 1-hr restrictions must be in the range:

$$\text{1 hr: } -\ln 0.75 < K < -\ln 0.70 \text{ or } 0.29 < K < 0.35 \qquad \text{(Eq. 8)}$$

$$\text{4 hr: } -0.25 \ln 0.6 < K < -0.25 \ln 0.4 \text{ or } 0.13 < K < 0.23 \qquad \text{(Eq. 9)}$$

Since the two intervals do not overlap, it is not possible to meet the specification range requirements. Without knowing the dissolution pattern, it would be possible to spend considerable time attempting to obtain a formulation which could not possibly meet the given requirements.

If, instead, the required release ranges were 25–35% after 1 hr and 55–75% after 4 hr, then similar calculations would give:

$$\text{1 hr: } 0.29 < K < 0.43 \qquad \text{(Eq. 10)}$$

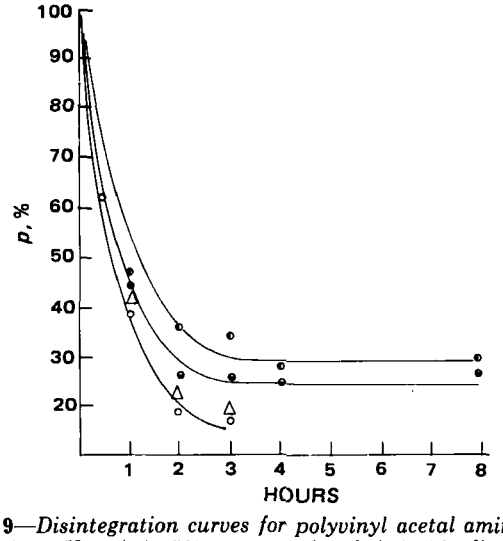


Figure 9—*Disintegration curves for polyvinyl acetal aminoacetate preparations. Key: (○) 15% wet granulated; (△) 15% directly compressed; (◒) 30% directly compressed; (◐) 60% directly compressed. The parameter* p *is the amount not disintegrated in percent.*

[9] It should be noted that an immediate release component in the formulation might solve this. An extension of the argument is that if a specification is set in addition at, *e.g.*, 8 hr, a similar impossible situation might arise.

Table IX—Disintegration Data Treated According to Eq. 17

Polymer	Percent (Q)	Hardness (H)	Correlation Coefficient, r	a	D	ln D	ln K^c
V	15	15	−0.92	−0.408	0.365	−1.01	0.162
	30	15	−1.0[b]	0.243	1.832	0.605	−0.274
	60	15	0.98	0.644	2.455	0.898	0.412
	15g[a]	15	−0.95	−0.208	0.987	−0.013	−0.020
IV	15	15	−0.84	−0.489	0.270	−1.309	−0.301
	30	15	−1.0[b]	−0.155	0.860	−0.151	−0.357
	60	15	−0.99	0.079	1.837	0.608	0.270
	15g[a]	15	−0.93	−0.320	0.307	−1.181	−0.128
VI	15	10	−0.99	−0.267	0.910	−0.094	0.140
	30	5	−0.97	−0.069	1.138	0.129	0.058
	60	5	−0.99	−0.105	0.586	−0.534	−0.163
	15g[a]	15	−0.99	−0.343	0.661	−0.414	−0.051

[a] g is wet granulated. [b] Only two points were available and were not included in Fig. 12. [c] From Table III.

$$4 \text{ hr: } 0.20 < K < 0.35 \qquad \text{(Eq. 11)}$$

i.e., K must be in the interval: $0.29 < K < 0.35$.

If polymer II is used, and a 8–11-kg hardness is required, then (Table VI, line 2):

$$\ln K = -0.065\,H - 0.41 \ln Q + 1.04 \qquad \text{(Eq. 12)}$$

Inserting lower limits for K and H gives:

$$\ln 0.29 + (0.065 \times 8) - 1.04 = -0.41 \ln Q \text{ or } Q = 73 \qquad \text{(Eq. 13)}$$

and inserting upper limits for K and H:

$$\ln 0.35 + (0.065 \times 11) - 1.04 = -0.41 \ln Q \text{ or } Q = 29 \qquad \text{(Eq. 14)}$$

Therefore, in this case, Q must be between 30 and 73, and narrowing the specification limits or the hardness limits would produce a narrower range of Q, but the example gives a starting point for the final phase of product development for a product of this type. Other factors may affect release (*e.g.*, moisture content and machine speed) and such factors can (at increased experimentation) be included in a multivariable phenomonological equation. Preliminary factorial experimentation on two levels may sort out the variables of importance prior to model experimentation. If many variables are included, then it is best, as suggested previously (62) to assume that all the relations can be described by two-power polynomials and approach the problem by fractional factorials. In this case there is no experimental testing of the actual functionality: it is assumed to be a two-power polynomial.

Erosion Curves—Disintegration is presumably erosion due to dissolution of the polymer. If this is so, then the erosion is a function of polymer solubility. It should follow a cube root law if the solubility is absolutely pH independent; as pointed out previously (63), cube root relations often resemble exponential decays. Because of the differences in solubility profiles as a function of pH, the cases will be discussed individually in the following, but typical examples of disintegration patterns for polymers with pH-insensitive solubility are shown in Fig. 8, and the erosion figures are given in Table V.

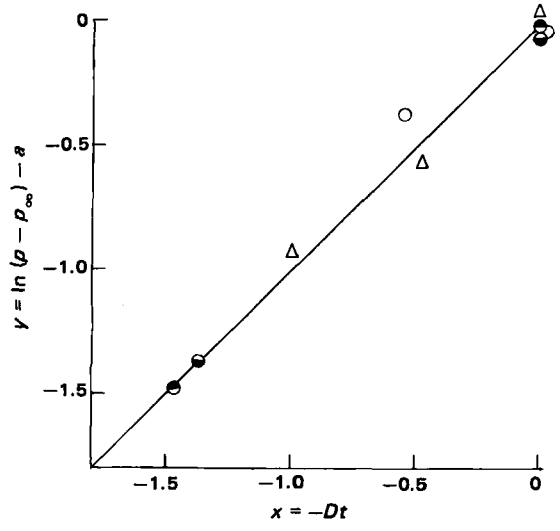


Figure 10—*Consistency diagram in dimensionless units for Eq. 8, using data in Table VII. The parameter* p *is here in fraction. For Eq. 8 to be a reasonable function, the data should be linear and the line should go through the origin (*y = x *as shown). Key: (Δ) 15% wet granulated; (○) 15% directly compressed; (◒) 30% directly compressed; (◓) 60% directly compressed.*

Table X—Disintegration Data (p/p_0) for Polyvinyl Acetate Preparations

Time, hr	Fraction disintegrated at the time indicated (Polymer, %; Hardness, kg)			
	15%, 15 kg	30%, 15 kg	60%, 15 kg	15%, 15 kg, g[a]
0	1	1	1	1
0.5				0.8
1	0.77	0.81	0.94	0.75
1.5				0.74
2	0.69	0.77	0.96	0.72
4	0.74	0.81	0.95	
6	0.76	0.79	0.93	
8	0.69	0.78	0.91	

[a] g is wet granulated.

Polyvinyl Acetal Diethylaminoacetate (I)—Polyvinyl acetal diethylaminoacetate is acid soluble and alkali insoluble; therefore, it should be subject to erosion (dissolution) only in the first 2 hr, as seen in Table VII. The value of p in Eq. 2 should approach an asymptotic value different from zero (unless erosion were complete within 2 hr, which is not the case). The erosion equation should reflect this as:

$$\ln (p - p_\infty) = -Dt + a \qquad \text{(Eq. 15)}$$

where p_∞ is the amount of matrix not disintegrated at infinite time, p is the matrix, and the data in Table VI, referring to polyvinyl acetal diethylamino acetate have been subjected to this adjustment. The data are shown in Fig. 9. Reasonable asymptote values can be estimated from the figure, and the data have been subjected to dimensionless plotting in Table VII. The dimensionless plot is shown in Fig. 10 and establishes that Eq. 8 is a reasonable function for treating the erosion data.

The erosion constant is of the same order of magnitude in the first 2

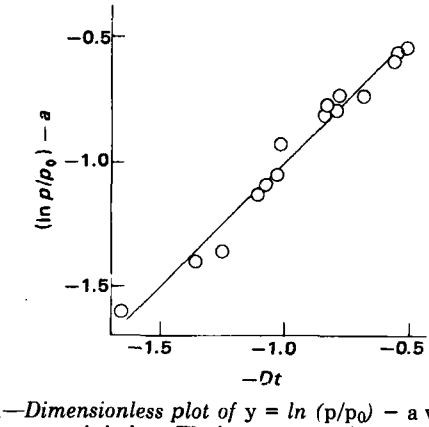


Figure 11—*Dimensionless plot of* y = *ln* (p/p0) − a versus −Dt *for polyvinyl acetate phthalate. The least-squares fit is* y = *0.998*x − *0.002, i.e., a straight line with close to unity slope and close to zero intercept, showing applicability of Eq. 1 to this system (*r = *0.99).*

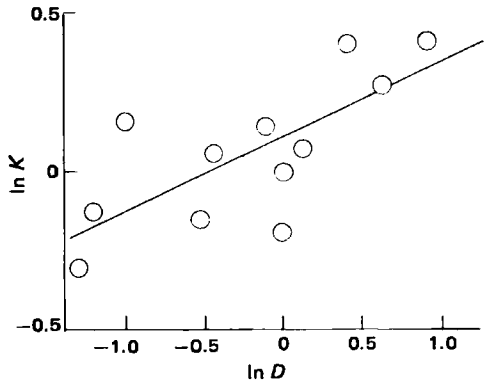


Figure 12—*ln* K *as a function of ln* D *(Table IX). The least-squares fit line is ln* K = *0.229 ln* D + *0.105 (r = 0.79).*

hr as the dissolution constant in the remainder of the dissolution period, so that the overall dissolution curve will be well represented by Eq. 4. It may be concluded that the rate-controlling process is twofold: erosion in the first 2 hr and diffusion in the remainder of the dissolution period (during this latter period the matrix weight remains constant and the dissolution is log-linear).

Polyvinyl Acetate Phthalate—In this case the polymer is acid insoluble and alkali soluble. Dissolution of the polymer should not occur until after the second hour. It is seen in Table VIII that in the case of the two lower polymer concentrations (15 and 30%) there is a certain amount of erosion immediately. Apparently this is an effect of the excipients and does not occur at the high concentration. After this immediate erosion the weight remains constant for 2 hr (during which time the pH is low and the polymer does not dissolve), and after 2 hr the increase in pH causes the solubility of the polymer to increase and erosion to begin. It is seen in Table VIII that the erosion after the 2-hr point appears to follow Eq. 1, and the least-squares fit values are listed. Since the disintegration actually does not occur substantially until a certain time, t_i (presumably between 2 and 4 hr), the correct form of Eq. 1 would be:

$$\ln (p/p_0) = -D(t - t_i) \qquad \text{(Eq. 16)}$$

so that a is equal to Dt_i. Values of t_i calculated in this fashion are shown in Table VIII and are in the correct range for the higher concentration.

The data in Table VIII are shown in dimensionless presentation in Fig. 11, and the adherence of this plot to linearity with unity slope and zero intercept shows that the disintegration is well represented by Eq. 16.

Povidone, Povidone–Vinyl Acetate, and Polyvinyl Alcohol–Acetate—These three polymers have solubilities that are not pH dependent. The disintegration of the formulas follow Eq. 1 fairly well, and the least-squares fit parameters are shown in Table IX. The effect of flow cells on disintegration has been reported for povidone (6).

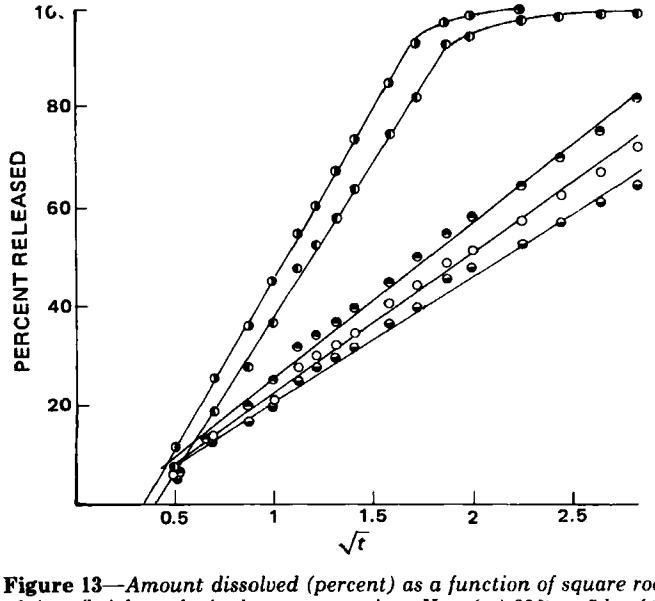


Figure 13—*Amount dissolved (percent) as a function of square root of time (hr) for polyvinyl acetate matrices. Key: (●) 60% at 5 kg; (○) 60% at 10 kg; (◒) 60% at 5 kg; (◐) 30% at 15 kg; (◑) 15% at 15 kg.*

In addition, the disintegration behavior in rotating baskets (2–5, 64–66) has been shown to lead to exponential decay dissolution profiles (Eq. 2) with lag time when disintegration is the rate-limiting factor. Therefore, correlations between K and D frequently occur in rotating dissolution apparatuses (4, 9–11) when rapidly disintegrating formulas are tested. Such a correlation is not necessarily to be expected in the case of the polymers reported here; however, the data in Table IX imply a correlation of the type:

$$\ln D = q \ln K + j \qquad \text{(Eq. 17)}$$

where q and j are constants. The data in Table IX are shown by a dimensionless representation in Fig. 12 using Eq. 17. There is fair linearity, the slope is close to unity, and the intercept is close to zero, so that Eq. 17 is not an unacceptable function, but the scatter about the line is such that other effects might be expected. Presumably, the amount, m, not released at time t, would be a complex function of both K and D, where K and D are not entirely independent of one another.

Polyvinyl Acetate—In this case there should be insolubility throughout the pH range. As shown earlier, only the 60% preparation is free from some initial disintegration (erosion). In the case of the two lower concentrations, the amount of weight lost is in excess of drug released, *e.g.*, for the 30% polymer concentration 30 mg (6% of the tablet weight) of drug is dissolved after 1 hr as opposed to the fact that the weight loss is 23%. In the case of polyvinyl acetate, the matrix should be insoluble, and the release pattern should come close to being a square root of time dependence (1). Figure 13 and Table X shows this to be the case, although the deviations from the line are first negative, then positive, then negative (+ − +) so that [Durbin–Watson statistics (67)] the fit is not exact. The initial lag time and the end effect is to be expected (2). It is apparent that the release is also well represented by a semilogarithmic relationship (Eq. 2). These latter frequently simulate square root in time functions (68).

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Evaluation of Mosquito Repellent Formulations

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Abstract □ *N,N*-Diethyl-*m*-toluamide was formulated with several acrylate polymers in ethanol solution and various silicone polymers in 2-propanol suspension; the ratio of polymer to *N,N*-diethyl-*m*-toluamide (I) was varied. Formulations that had drying times of <10 min were evaluated for film hardness and elasticity. Contact angles made by water on films cast from the formulations were measured when such films were uniform. For the acrylate formulations, containing polymers that are solid at room temperature, the presence of I increased drying times; decreased film hardness and elasticity resulted from decreasing the ratio of polymers to I. Lower contact angle with water resulted from decreasing the ratio of acrylate polymer to I. However, this effect was less pronounced with the lower molecular weight acrylate polymer formulations. Films cast from the silicone formulations had low contact angles with water. In addition, formulations of repellents, ethohexadiol and *N,N*-diethyl-*p*-toluamide, each in combination with a silicone polymer, were evaluated. Films with short drying times, high contact angle, and measurable hardness could be cast from the *N,N*-diethyl-*p*-toluamide–silicone formulations due to the film-forming ability of the repellent itself. The physical properties of the ethohexadiol–silicone formulations were similar to the I–silicone formulations. Selected formulations received preliminary evaluation for duration of effectiveness against *Aedes aegypti* mosquitoes *in vitro* and in animal test systems. Except for one formulation of I with a lower molecular weight acrylate polymer, these formulations did not enhance the duration of effectiveness of I on hairless dogs. The *in vitro* ED_{50} of the test repellent for *A. aegypti* was significantly enhanced in 5 of 15 formulations tested. The 4-hr ED_{50} of the test repellent on white mice was significantly enhanced in 6 of 15 formulations tested.

Keyphrases □ Repellents, mosquito—film hardness and elasticity evaluation for *N,N*-diethyl-*m*-toluamide–acrylate polymer formulations □ *N,N*-Diethyl-*m*-toluamide—formulation with acrylate polymer, evaluation for film hardness and elasticity in mosquito repellents □ Polymers—*N,N*-diethyl-*m*-toluamide formulations, evaluation for film hardness and elasticity in mosquito repellents

The duration of protection afforded by a mosquito repellent is limited by the ways it can be lost from the skin surface, such as abrasion and removal by water immersion (1) and excessive evaporation and penetration into the skin (2, 3). Many efforts have been made to improve the persistance of mosquito repellents by incorporating the active ingredient (usually *N,N*-diethyl-*m*-toluamide, I) with a variety of materials such as polysaccharide esters or silicone and acrylic polymers (4), clay (5), zinc oxide (6), vanillin (7), and others. However, there remains to be found a repellent formulation which has acceptable cosmetic and toxicologic properties and has significantly

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