The CMA test is also effective for quantitating the effects of drugs which reduce motor activity. The sensitivity of this test for the three phenothiazines evaluated is not, however, significantly greater than that of the conventional photoelectric cell method. For example, it was previously reported (4) that trifluoperazine, prochlorperazine, and chlorpromazine had oral DD_{50}'s of 1.5 (0.9–5.7), 5.3 (3.5–8.8), and 8.5 (5.2–16.5) mg./Kg. These doses were expressed in terms of the bases of these compounds and should, of course, be compared with their DD_{50}'s in terms of the base by the CMA test. Conversion of DD_{50}'s in Table IV to bases resulted in the following for the above-mentioned compounds, respectively, 1.0 (0.5–3.0), 3.6 (1.9–7.3), and 6.1 (4.0–9.3) mg./Kg. Although the DD_{50}'s by the CMA test are consistently less than the DD_{50}'s by the conventional procedure, there is no significant difference in potency for any one drug between the two tests.

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Extrapolation of Appearance of Tablets and Powders from Accelerated Storage Tests

By J. THURO CARSTENSEN, J. B. JOHNSON, W. VALENTINE*, and J. J. VANCE

A descriptive system for tablet and powder appearance utilizing tristimulus reflectances allows formal treatment of appearances. Cases are cited where responses to accelerating conditions can be treated by Arrhenius treatment.

WE HAVE, for a period of years, attempted to find a standard means of describing the appearance of a tablet in a numerical fashion, and to find "average" storage times at 55, 45, and 37° which would correspond to 2 years at 25°. Fully realizing that this will vary from compound to compound, it is nevertheless important to have a standard storage period if a large number of compounds have to be screened for compatibility with common tablet ingredients.

Several investigators (1–4) have found dyed liquid or tablet decompositions to be first order in part or *in toto*, in response to light and heat stress.

The question of whether a white tablet or powder mixture would adhere to such a scheme has been treated below by (*a*) visual observation and use of a suitable scoring system and by (*b*) reflectance measurements.

EXPERIMENTAL

As part of a routine compatibility program, the compatibility of new investigational compounds with various excipients or lubricants is tested in the following manner. The drug is mixed and ground with the excipient in question, and half of the powder mixture is transferred to glass vials which are plugged and sealed. To the other half is added 5% water, careful mixing is performed in a mortar, and the moist mix is transferred to vials as above. The plugged aluminum sealed vials are wax sealed to insure an adequate moisture barrier. As shown in Table II, 11 such two-component systems are prepared. In addition, the drug is set up *per se*. The ratio of drug to excipient is 1:5 by weight, or, in the case of lubricants, 20:1. The samples are stored at 55, 37, 25, and 5° and observed at various time intervals. The accelerated samples are stored at 5° after 10 days at 55° and 2 months at 37° to enable retrieval of the sample at later times for further comparison.

The following scoring system is used:

Degree of Color.—*1*, Unchanged; *2*, hardly noticeable darker; *3*, very slightly darker; *4*, slightly darker; *5*, darker; *6*, much darker (color change). When change toward lighter color occurs, a similar scoring system is used.

Degree of Fineness.—*1*, Unaltered; *2*, very slight particle size increase, does not adhere to glass, flow characteristics slightly altered from control; *3*, slight increase in particle size, movement not quite free flowing, and/or tendency for particles to adhere to glass; *4*, definitely increased in particle size, but still free flowing (like a granulation); *5*, caked—does not move or moves as an entity and discrete particles detectable; *6*, fluidized and solidified—no discrete particles detectable.

In the case of the photometric reflectance measurements a Color Coder[1] was used. Flat-faced bevelled tablets of two different drugs (*a*) one containing 60 mg. of active drug per 170-mg. tablet weight ($^9/_{16}$ in.) and (*b*) one containing 1 mg. of active drug per 100 mg. tablet weight ($^1/_4$ in.) were ex-

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* Present address: Vick Chemical Company.

[1] Automatic Control Devices, Bethel, Conn.

posed to (*i*) one month at 55°, (*ii*) 3 months at 45°, (*iii*) 6 months at 37°, (*iv*) room temperature, and (*v*) 5°. The samples stored at the elevated temperatures were frozen (for reference) after the prescribed periods were elapsed. Samples were retrieved after (*a*) 16 months and (*b*) 21 months and reflectance measurements taken (ten duplications) of all samples.

TABLE I.—RESULTS OF DRUGS *per se* AFTER PROLONGED ROOM TEMPERATURE STORAGE AND 10 DAYS AT 55° C.

Compd. No.	Time at Room Temp., Mo.	Room Temp. Dry	Room Temp. Wet	10 days at 55° C. Dry	10 days at 55° C. Wet
1	27	1	4	1	2
2	27	3	3	1	1
3	27	5	1	2	1
4	26	1	3	1	1
5	26	1	5	2	2
6	25	1	1	1	1
7	25	1	1	1	1
8	25	1	1	1	1
9	25	1	3	1	2
10	22	4	6	4	6
11	21	1	2	1	1
12	21	5	4	5	3
13	20	1	1	1	1
14	20	1	1	1	1
15	20	1	1	1	2
16	19	1	3	1	4
17	18	3	1	2	2
18	18	1	1	1	1
19	18	4	6	2	4
20	17	1	1	1	1
Totals		38	49	31	38

RESULTS AND DISCUSSION

Table I shows the results of the drug *per se* after prolonged room temperature storage and after 10 days at 55° for 20 chemically unrelated drugs. It is quite apparent that, on the average, 10 days at 55° is not so strenuous a test as prolonged room temperature storage.

In the case of a dry powder, *e.g.*, 100 mg. in a 10-ml. vial, the moisture loss required to saturate the space above the powder at 55° would be about 1 mg. and would, even with hermetic seals, give rise to drying of the powder. This might explain the dry phenomena in Table I, but not the wet.

In Table II each category (wet, dry, 25°, 55°) has been tabulated for the two-component systems described above. It is also apparent here that the 10 days at 55° do not adequately represent (on the average) prolonged room temperature storage. The total scores are listed in the last column. Each category (wet, dry, 25°, 55°) has a highest possible score of $12 \times 20 \times 6 = 1440$ and a minimum possible score of 240. The increases for

TABLE II.—CATEGORIES FOR TWO-COMPONENT SYSTEMS

		Identical	17–27 Mo. at 25° C. Worse	10 Days at 55° C. Worse	Total Score 25°	Total Score 55°
Drug *per se*	Dry	15	4	1	38	31
	5% H_2O	9	8	3	49	38
Drug + mag. stearate	Dry	16	3	1	34	30
	5% H_2O	15	4	1	43	35
Drug + ca. stearate	Dry	13	4	3	37	32
	5% H_2O	12	5	3	38	35
Drug + stearic acid	Dry	15	5	0	42	31
	5% H_2O	7	11	2	60	38
Drug + talc	Dry	14	5	1	38	30
	5% H_2O	10	8	2	45	34
Drug + acid washed talc	Dry	12	8	0	44	31
	5% H_2O	10	9	1	49	35
Drug + lactose	Dry	12	5	3	38	32
	5% H_2O	9	7	4	65	56
Drug + $CaHPO_4$ anhydrous	Dry	12	6	2	46	36
	5% H_2O	9	8	3	66	53
Drug + cornstarch	Dry	12	5	3	39	34
	5% H_2O	10	5	5	40	37
Drug + mannitol	Dry	10	7	3	39	31
	5% H_2O	8	7	5	47	45
Drug + terra alba	Dry	14	6	0	41	28
	5% H_2O	11	6	3	50	45
Drug + sugar 4x	Dry	12	6	2	41	34
	5% H_2O	9	7	4	63	61

TABLE III.—REGRESSION CONSTANTS

Storage, Days	Pretreatment	Total Score	Increase *d*	% Retention (*R*)	Log *R*	Regression ($days^{-1}$)
665 at 25°	Dry	447	207	83	1.919	1.22×10^{-4}
10 at 55°	Dry	380	140	88	1.944	56×10^{-4}
665 at 25°	+5% H_2O	615	375	69	1.839	2.42×10^{-4}
10 at 55°	+5% H_2O	512	272	77	1.887	113×10^{-4}

TABLE IV.—RESULTS OF TABLET A STORED FOR 6 MONTHS AT 37° C.

Test No.	X	Y	Z	$X+Y+Z$	X %[a]
1	80.8	77.0	72.8	230.6	35.04
2	83.0	79.0	74.8	236.8	35.05
3	87.0	82.8	78.0	247.8	35.11
4	83.2	79.2	75.0	237.4	35.05
5	84.2	80.0	75.2	239.4	35.17
6	85.8	81.8	76.8	244.4	35.11
7	86.0	82.0	77.5	245.5	35.03
8	84.2	80.2	75.5	239.9	35.10
9	86.8	82.5	77.8	247.1	35.13
10	86.0	82.5	77.0	245.5	35.03

[a] $\bar{x}$ = 35.08; S.D. $x \simeq 0.05$; S.D. $\bar{x} \simeq 0.02$.

The above system is subjective and the photometric measurements reported in the following were initiated in an attempt (*a*) to eliminate the subjectivity and (*b*) to allow extrapolation.

Before discussing the photometric results of Tables V and VI it might be appropriate to investigate the reproducibility of the instrument. It was found that positioning of the tablet greatly influenced the X, Y, and Z component (but not the percentages referred to below by small letters, x, y, and z) (5–7). A special holder was therefore constructed allowing precise positioning, horizontally and vertically. Since, however, rotation and tablet-to-tablet variation would also be significant, the ten tests run on each storage condition were run on

TABLE V.—DRUG B

Temp., t °C.	$10^3/T$ °K^{-1}	Mo. Stored	x-Value, %	Log x	Log x/x_0[a]	$100k$ (Mo.$^{-1}$)
5	...	21	34.44	1.53706	0.00000	...
55	3.05	1	34.59	1.53859	0.00151	1.51 ± 0.7
45	3.145	3	34.59	1.53859	0.00151	0.50 ± 0.23
37	3.225	6	34.65	1.53958	0.00252	0.42 ± 0.12
25	3.355	21	34.59	1.53895	0.00189	0.09 ± 0.03

[a] 5° value used for reference.

TABLE VI.—DRUG A

Temp., t° C.	$10^3/T$ °K^{-1}	Mo. Stored	x-Value, %	Log x	Log x/x_0[a]	$100k$ (Mo.$^{-1}$)
5	...	21	34.78	1.54133	...	...
55	3.05	1	35.06	1.54481	0.00348	3.48 ± 0.7
45	3.145	3	35.06	1.54481	0.00348	1.15 ± 0.23
37	3.225	6	35.07	0.54494	0.00361	0.62 ± 0.12
25	3.355	16	34.88	1.54258	0.00125	0.08 ± 0.04

[a] 5° value used for reference.

each category are shown as d in Table III. The per cent retention of initial appearance is expressed as $R = (1200 - d)/12.0$, and the logarithm of R is also shown. The regressions shown in the last column of Table III are $k = (1/t) \cdot (2 - \log R)$, where t is time in days.

Hence, 10 days at 55° would correspond to 560/1.22 = 459 days at room temperature (on the average) for the dry samples and 1130/2.42 = 467 days at 25° for the samples containing water. The storage period at 55° corresponding to 2 years at room temperature would be 0.089/0.0056 = 15.9 days, and for the sample containing water would be 0.177/0.0113 = 15.6 days.

Whether such a semilogarithmic treatment is justified cannot be asserted from the treatment above, but the fairly close correlation between the two correlation times, 15.9 days for the dry samples and 15.6 days for the moist samples, is an indication of its utility. It would appear that for rapid screening by the visual procedure 16 days at 55° would be the most meaningful storage time on the average. In relation to the rule of thumb that "reaction rates double to triple with each 10° increase in temperature," (8) this average rule does not give the same result as above since storage times in this case should be in an 8:1 to 27:1 ratio between 55 and 25°.

It is realized that grand averaging, as carried out above, has limitations, and that individual drugs may deviate from the calculated optimal storage periods.

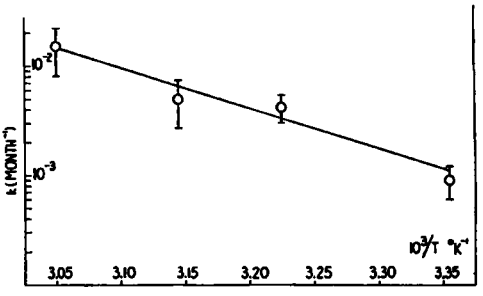

Fig. 1.—Logarithm of apparent rate constants k of drug B, taken from Table V plotted as a function of reciprocal absolute temperature.

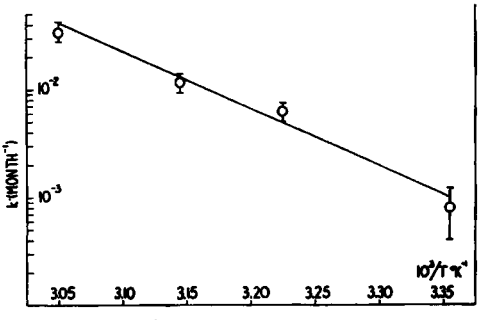

Fig. 2.—Logarithm of apparent rate constants k of drug A, taken from Table VI plotted as a function of reciprocal absolute temperature.

TABLE VII.—TABLETS OF ALGINIC ACID WITH 4% MAGNESIUM STEARATE

Days at 70°	x-Value	Initial x_0	Log x/x_0
2	35.768	35.064	0.00864
3	35.879	35.009	0.01066
4	35.876	34.890	0.01210
5	36.295	34.947	0.01644
6	36.866	34.893	0.02389
7	36.904	34.906	0.02417
8	37.457	34.942	0.03018

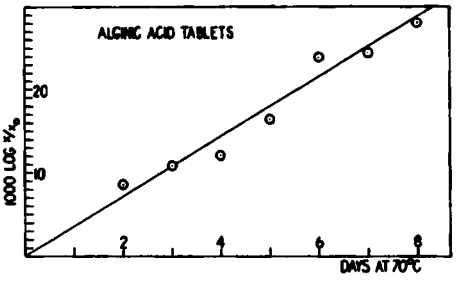

Fig. 3.—Alginic acid tablets. x-Values of reflectance are plotted as log x/x_0 *versus* days at 70°, x_0 being the original reflectance x-value.

is obeyed, (*b*) that degradation is by zero-order mathematics, and (*c*) that the sum of the X, Y, and Z components (denoted Σ below) is relatively time independent. In this case

$$\log x/x_0 = \log X - \log X_0 - \log \Sigma + \log \Sigma_0 \simeq \log X - \log X_0 = k \cdot C_d$$

where C_d is some measure of the "decomposed substance." If a first-order pattern is adhered to, then the above would also hold true in the initial stages since $\log (1 - \gamma) \simeq -\gamma$, where γ is any small number. For larger values, first-order relations would have to be tested as

$$(a) \qquad \log x/x_0 \propto C_d = \beta(1 - e^{-\alpha t}) \text{ or}$$

$$(b) \quad \frac{\partial}{\partial t}\{\log x/x_0\} = \frac{\partial}{\partial t}\{\log x\} = \beta \cdot \alpha \cdot e^{-\alpha t} = \beta \cdot \alpha \cdot 10^{-0.43\alpha t}$$

$$(c) \quad \log\left\{\frac{\partial}{\partial t}[\log x]\right\} = (\log \alpha + \log \beta) - 0.43\,\alpha t$$

Hence, if a linear relationship of type (*c*) is observed, the degradation would follow a first-order pattern. The above presupposes that the drug goes from white to some x value in degrading. The subsequent data justify this approximation.

TABLE VIII.—AVERAGE x-VALUES OF COMPOUND C TABLETS

Days at 70°	Sum of 5x Values	Av. $\bar{x}$	log $\bar{x}/\bar{x}_0$	log $\bar{x}$	Δ log $\bar{x}/\Delta t$	t, Days
4	185.06	37.012	0.02741	1.56834		
					0.00296	3.5
3	183.80	36.760	0.02445	1.56538		
					0.00402	2.5
2	182.11	36.422	0.02043	1.56136		
					0.00779	1.5
1	178.87	35.774	0.01264	1.55357		
					0.01264	0.5
0	173.74	34.748	0	1.54093		

ten different tablets. The results of tablet A stored for 6 months at 37° are shown in Table IV.

The standard deviations of this set hence are 0.02% for the average $\bar{x}$ and 0.05% for the individually measured x-value. Standard deviations for the other storage conditions are comparable and for simplicity the above values (which are in line with the reading accuracy of the instrument) have been used for the analysis below.

The results of the various storage conditions are shown in Tables V and VI. The data have been treated assuming the change in the x-value to be zero order. k is calculated from two points only, so the plots are average plots.

Since $1/t \times \log x/x_0$ is the parameter evaluated, the relative error of this term is of significance, where x is the x-value at time t. x_0 is the reference x-value (in this case the sample stored at 5°). The values are all close to 34.5 and hence log 34.54 − log 34.50 = 0.0005 would be a measure of the error on both log x and log x_0, using $2 \times 0.02\% = 0.04\%$ as the standard error of x.

The error of log x − log x_0 hence would be $10^{-4}\sqrt{25 + 25} = 0.0007$ (9). The tolerances so calculated are listed in the last column of Tables IV and V, and are also shown in the Arrhenius graphs, Figs. 1 and 2.

A provision for the above is that (*a*) Beer's law

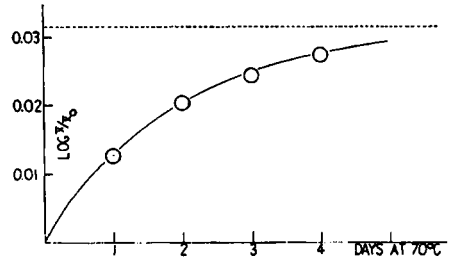

Fig. 4.—Compound C tablets. Average x-values of five lots plotted as logarithmic increase plotted *versus* days stored at 70°.

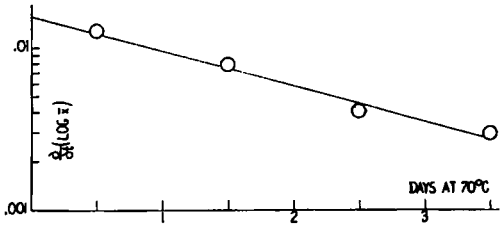

Fig. 5.—The logarithm of the slopes from Fig. 4 plotted *versus* days stored at 70°. The slope of the line is −0.4343 α, the intercept is (log α + log β). (See text for significance of α and β.)

TABLE IX.—COMPOUND C

Days at 70°	$\log \bar{x}_\infty - \log \bar{x}$	$\mu = \frac{\log \bar{x}_\infty - \log \bar{x}}{0.03166}$
4	0.00425	0.1343
3	0.00721	0.2278
2	0.01123	0.3548
1	0.01902	0.6008

Tablets were made of an alginic acid[2] containing 4% magnesium stearate. Since these tablets were difficult to make of even thickness (and hence would be difficult to position), initial values were taken of each tablet tested. Tablets were placed at 70° and withdrawn after various time periods with the results shown in Table VII (all figures being averages of 10).

These values are shown graphically in Fig. 3 and demonstrate the zero or first-order nature of the change.

As an example of a "degradation" of the first-order type, a third compound, denoted C, was tableted.

These tablets were stored at 70° for 1, 2, 3, and 4 days; the average x-values from five batches are listed in Table VIII. As Fig. 4 shows, the log x/x_0 *versus* t relationship is not linear in this case. The derivative function $(\partial/\partial t)[\log \bar{x}]$ is shown by midpoint differences in Table VIII and the log $\{(\partial/\partial t)[\log \bar{x}]\}$ is seen to be linearly related to time as shown in Fig. 5. To plot this conventionally, log x at full conversion (denoted log $\bar{x}_\infty$) would have to be known. From Fig. 5 α is 0.490 and β is calculated from the intercept to be 0.03166.

At the asymptote of graph 4 the factor $(1 - e^{-\alpha t})$ will be 1 ($t = \infty$). Thus $\log \bar{x}_\infty - \log x_0$ equals $\beta = 0.03166$, and the relations can now be expressed in a conventional manner (10), in that what appears as "fraction retained" on a first-order ordinate in this case would be

$$\mu = \frac{\log \bar{x}_\infty - \log \bar{x}}{\log \bar{x}_\infty - \log \bar{x}_0} = \frac{\log \bar{x}_\infty - \log \bar{x}}{0.03166}$$

Values of μ are tabulated for compound C in Table IX and the logarithmic relationship log $\mu = -k^*t$ is quite evident from Fig. 6.

[2] Marketed as Landalgine P 2235 by Edward Mendell Co., Inc., Yonkers, N. Y.

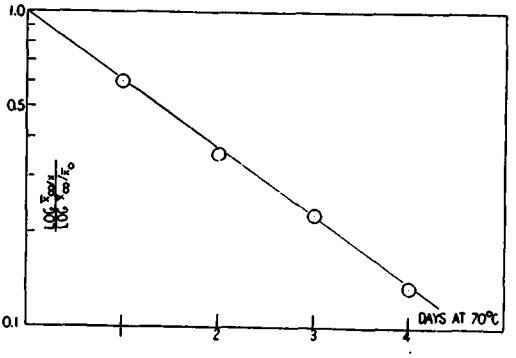

Fig. 6.—Compound C tablets. Degradation at 70° expressed as logarithm of per cent "retained" *versus* days stored at 70°.

SUMMARY

An average storage time for evaluation of tablet appearances of 16 days at 55° corresponds to 2 years at room temperature as judged by 20 different drugs.

Photometric reflectance measurements may be used to describe tablet appearances.

Photometric x, y, or z-value changes appear to be first order or zero order and may be extrapolated by formal Arrhenius treatment.

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