

The kinetics of dissolution for a non-disintegrating standard substrate

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The dissolution profiles for a 1 cm sodium chloride cube, which was considered to represent a standard non-distintegrating substrate, were obtained in seven kinds of dissolution apparatus. The results were used to assess experimental reproducibility and apparatus variables and to examine the adherence of the kinetics of the dissolution process to theoretical rate laws.

The dissolution rate of a solid dosage form may be the rate limiting step in the pharmacodynamic processes controlling the physiological availability of a drug (see Wagner, 1961 for references).

Hixson & Crowell (1931) examined the dissolution kinetics for a solid, the surface area of which changed predictably with mass transfer into solution. Their "cube root law" was derived by assuming that: (a) dissolution takes place normal to the surface of the dissolving solid; (b) the same agitation effect is observed on all parts of the surface; (c) no stagnation of the liquid in any region within the volume of the solvent takes place; (d) solid particles remain intact throughout dissolution.

Meaningful dissolution kinetic coefficients, which are representative of the entire dissolution process, can be obtained only if the apparatus and the solid solute satisfy the stringent conditions laid down by Hixson & Crowell (1931). In addition, for any apparatus used to follow the progress of dissolution, dimensions, geometry and energy input should be rigidly specified if reproducible results are to be obtained.

The variation in physical properties between tablets which control dissolution, even from the same batch and lot number, is well recognized. Thus it has not been possible to differentiate between apparatus and vehicle (tablet) variables which may both contribute to observed variations in dissolution rate measurements for tablets with different formulations. In this paper a single cubic crystal of sodium chloride of one cm edge was used to distinguish intra and inter apparatus variables in seven kinds of apparatus. Dissolution profiles have been kinetically analysed and the conformation of the observed data from each apparatus to mathematical models has been tested.

MATERIALS AND METHODS

Apparatus

Seven types of dissolution apparatus were used. No attempt was made to examine the effect of changing variables like agitation intensity, solvent volume, geometry for a given apparatus. Similarly, test conditions were not selected to accentuate any advantages or disadvantages of a particular apparatus. Distilled water was used as solvent throughout. All dissolution studies were made at $37.0 \pm 0.1^\circ$. Precise descriptions are given because designs permit some variation.

(1) *The stationary basket (S.B.)* (Fig. 1) described in part, by Cook, Chang & Mainville (1966) consisted of a 3-litre jar (Fisher, catalogue number 11-823) containing 2 litres of solvent, a T-shaped glass stirrer and a suspended basket constructed of stainless steel wire mesh. A sodium chloride cube was placed in the basket after thermal equilibrium had been achieved between the beaker, its contents and the temperature controlled bath. The stirrer was rotated clockwise (from above) at constant rate of 150 rev/min.

(2) *Food and Drug Directorate disintegration apparatus (F.D.D.)* (1965) (with the discs and plungers removed). A sodium chloride cube was placed in one of the cylinders of the tablet holder and the reciprocal motion of the latter was used to effect dissolution by agitation of 2.5 litres of solvent.

(3) *United States Pharmacopeia disintegration apparatus (U.S.P.)*. The apparatus which has been described in detail elsewhere (Withey & Mainville, 1969), and method were similar to that described in (2) except that the volume of solvent was 800ml and that of the container was 1 litre as in the U.S.P. 1965.

(4) *The Levy Beaker (L.B.)* (Levy & Hollister, 1964). The three-bladed impeller was rotated clockwise (from above) at 60 rev/min and the volume of the solvent was 350 ml contained in a 400 ml beaker.

(5) *Resin kettle method (R.K.)*. This was essentially the same as the apparatus described in (4) except that the container was a 1 litre resin kettle (Corning Glass Co., catalogue number 6947) and 900 ml of solvent was used.

(6) *Rotating basket method (R.B.)*. Details are in the 1970 U.S.P. and N.F. The apparatus consisted of a cylindrical 40 mesh stainless steel wire basket (height 3.6 cm outside diameter, 2.5 cm) attached by spring clips to a 6 mm diameter stain-

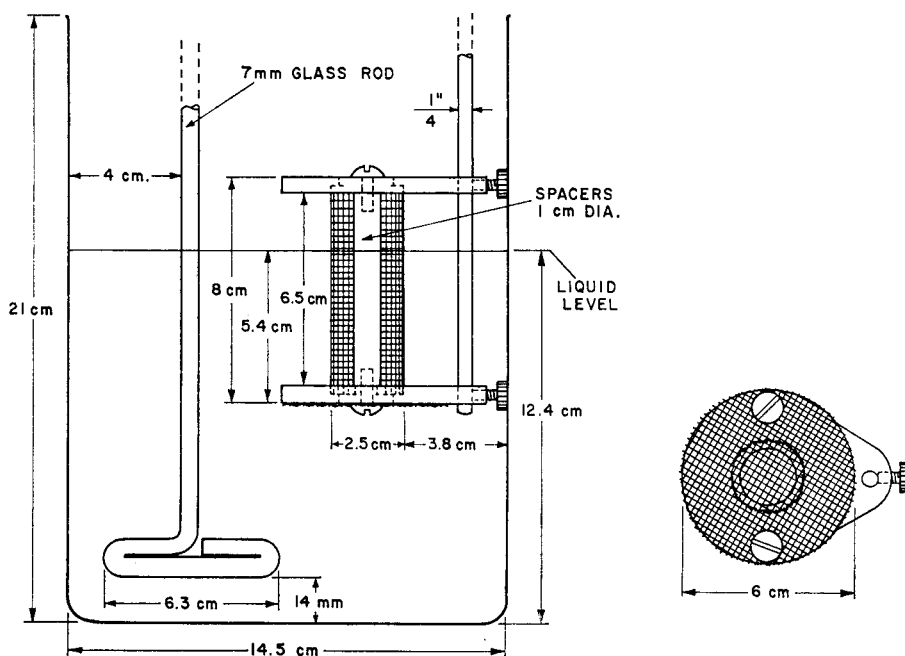


FIG. 1. Stationary basket dissolution apparatus.

less steel rod which fitted into a chuck attached to a constant speed motor (no impeller was used). A sodium chloride cube was placed in the basket which was then immersed in 900 ml of solvent, contained in a one litre resin kettle jar (as in 5 and rotated at 50 rev/min. The bottom of the wire mesh basket was 2 cm from the centre of the container bottom.

(7) *Tumbling cylinder method (T.C.)* (Withey & Mainville, 1969) (Fig. 2). This consisted of a lucite cylinder of equal height and internal diameter with a volume of 2 litres. A removable top (A) facilitated cleaning and the filling of the cylinder with solvent and a subsidiary access port (B) allowed the rapid insertion of the solid being examined. A liquid seal was effected by means of a 6 inch i.d. "O" ring (D). The cylinder was mounted in a U-shaped jig (C) and rotated about an axis at right angles to its height by means of a motor and drive shaft attached to the mid-point of the cylinder length. A second fixed, hollow support shaft (E) mounted opposite to the drive shaft was connected to the cylinder by means of a rotary seal¹ fabricated of stainless steel. In this study an electrolytic conductivity cell, G, was inserted through the hollow shaft and positioned in the body of the solvent. The whole apparatus was immersed in a bath at $37.0 \pm 0.001^\circ$.

The rate of rotation of the cylinder (60 rev/min) was chosen because the solid remained intact and was bathed in solvent on all sides throughout the dissolution process. At <20 rev/min the cube rolled around the inside surface of the cylinder and at >100 rev/min the motion of the cube was erratic and unpredictable.

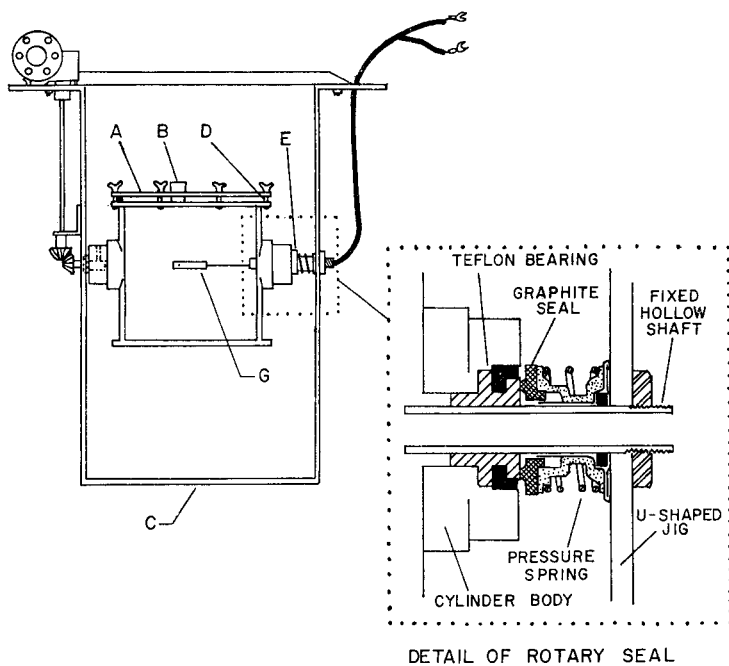


FIG. 2. Tumbling cylinder dissolution apparatus (labels refer to description which is given in the text).

¹ Beatty Pump Rotary Seal, catalogue No. 2000, Beatty Pumps, Chicago, Ill.

The sodium chloride cube of 1 cm edge with faces cut along the 100 axes² used for the test was considered an ideal non-disintegrating substrate. The mean and standard deviation of the weights of 50 of these were 2.5681 ± 0.350 g. The dissolution of a single cube was followed in each apparatus with four replicates by measuring the specific electrical conductivity of the solution using a platinum electrode probe³ of cell constant 1.00 in the solution and connected to an automatic conductivity bridge⁴. As the temperature coefficient for the conductivity of salt solutions is large, the temperature was controlled to $\pm 0.001^\circ$ (Tronac⁵ controller). The bridge was operated in a manual-hold condition which allowed the displayed conductance reading at any instant to be held. Initially readings were recorded every 5 s; for most runs about sixty readings were taken.

The apparatus giving the highest final concentration (i.e. having the smallest volume of solvent) was the Levy beaker (0.1056M) in which the dissolved cube gave a solution that was 17% saturated. Since the specific conductance of a solution of sodium chloride does not vary linearly with concentration above 1×10^{-3} M (Robertson, 1967), calibration curves of conductance against concentration between 1×10^{-3} and 150×10^{-3} M were constructed and the concentration of solutions were obtained from these by interpolation. The specific conductivity of solutions could be read to $\pm 0.1 \mu$ mhos which allowed the concentration of sodium chloride solutions to be assessed to at least $\pm 1 \times 10^{-5}$ mol.

In any apparatus, the sodium chloride cube was dissolved within 30 min. Kinetic runs were therefore followed for at least 30 min or until identical readings had been obtained over a 5 min period. Thus "infinity readings" which were used in the kinetic analysis were asymptotic values.

ANALYSIS OF RESULTS

For each kinetic run, plots were made of % dissolved, of log (% dissolved) and of $(\% \text{ dissolved})^{1/3}$ against time, using a Calcomp 663 Digital Incremental plotter.

Mean dissolution curves were calculated from the data of the five runs in each apparatus. The $(\% \text{ undissolved})^{1/3}$ and log (% undissolved) mean curves are shown in Figs. 3 and 4. The means and standard deviations were also calculated after the logarithmic and cube root transformations had been applied. These calculations were done only for times at which each of the five runs had yielded data. To clarify the presentation every other datum point was omitted.

Two least squares lines were calculated for each of the 35 runs, one to the log (% undissolved) data and the other to the $(\% \text{ undissolved})^{1/3}$ data. In these calculations it was assumed that the times were recorded without error and no weighting was introduced. Parameters resulting from these analyses are presented in Table 1.

DISCUSSION

The Noyes-Whitney equation (1897) has frequently been quoted where the theoretical aspects of the dissolution of a solid have been discussed. In some cases (Levy & Sahli, 1962; Nelson, 1962; Gibaldi & Weintraub, 1968; Tawashi, 1968) an attempt has been made to keep the surface area, S , constant in which case the

² Optovac, Inc., North Brookfield, Mass.

³ Yellow Springs Instrument Corp., catalogue No. 3417.

⁴ General Radio (Canada) Ltd., Toronto, type 1681, Impedance comparitor bridge.

⁵ Type P.T.C.-1000, Tronac Inc., Provo, Utah, U.S.A.

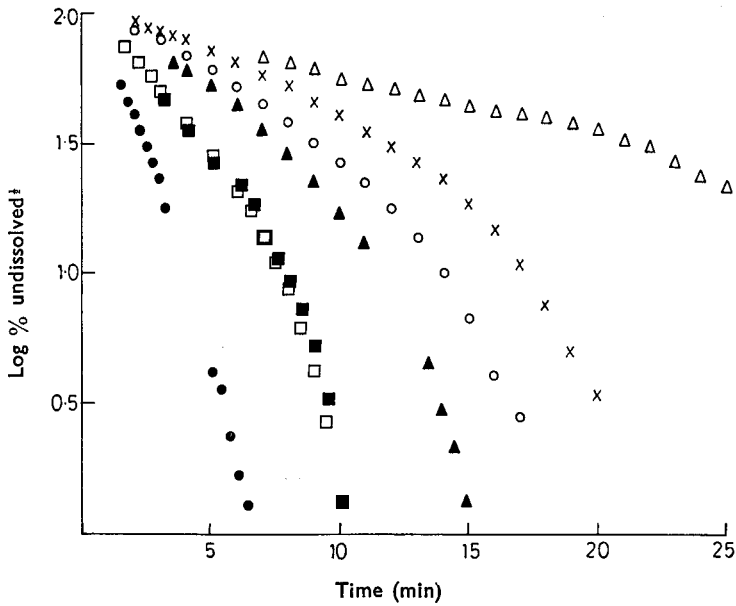


FIG. 3. Mean curves for the logarithm of % undissolved against time for the dissolution of a sodium chloride cube by different methods. × Levy beaker. ▲ stationary basket. △ Rotary basket. ■ F.D.D. □ U.S.P. ● Tumbling cylinder. ○ Resin kettle.

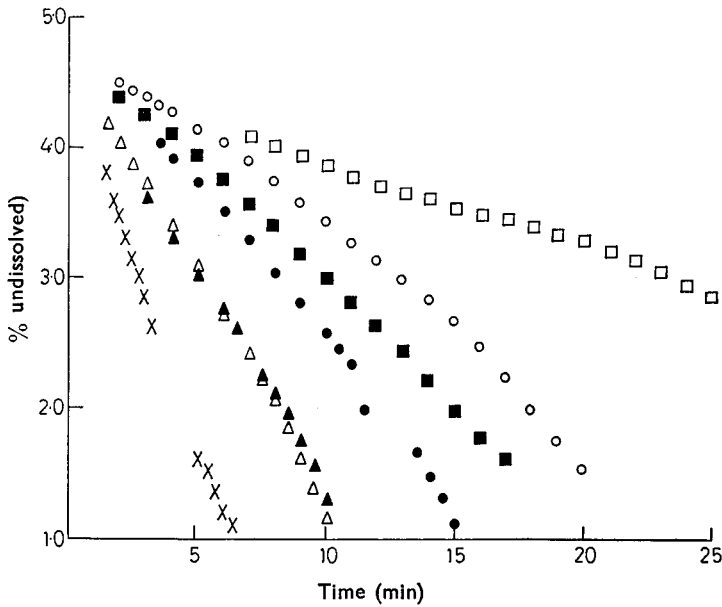


FIG. 4. Mean curves for the cube root of % undissolved against time for the dissolution of a sodium chloride cube by different methods. × Tumbling cylinder. ▲ F.D.D. △ U.S.P. ■ Resin kettle. □ Rotating basket. ● Stationary basket. ○ Levy beaker.

dissolution rate, in a sufficient volume of solvent to maintain sink conditions, becomes zero order. In other cases (Levy & Hollister, 1964), a first-order rate law has been assumed in the analysis of dissolution data although, as Wagner (1969) has pointed out, conformation of a dissolution process to a first-order law is usually an artifact.

It is usual to follow the dissolution of a solid by monitoring the concentration of substrate that appears in solution. Since the theoretical rate of dissolution of a solid is proportional to the area of the solid which is exposed to the solvent, it is necessary to predict the rate of change of surface area as the mass is transferred to solution.

For a perfect cube, of edge length x , the initial mass M_t , is equal to:

$$M_t = x^3 \rho \quad \dots \quad \dots \quad \dots \quad \dots \quad (1)$$

where ρ is the density.

Thus, if M_0 is the initial mass then:

$$x = \left(\frac{M_0}{\rho} \right)^{1/3} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

The total surface area, S , of a cube is $6x^2$ so that:

$$S = 6 \left(\frac{M_t}{\rho} \right)^{2/3} \quad \dots \quad \dots \quad \dots \quad \dots \quad (3)$$

Substitution of (3) in the modified Noyes-Whitney equation (1897) yields the differential rate equation:

$$-\frac{dm}{dt} = 6k C_s \left(\frac{M_t}{\rho} \right)^{2/3} \quad \dots \quad \dots \quad \dots \quad (4)$$

If M is the mass which remains undissolved at a time t , integration of (4) between the limits 0 and t gives:

$$\frac{3\rho^{2/3}}{6C_s} \left(M_0^{1/3} - M_t^{1/3} \right) = -kt \quad \dots \quad \dots \quad \dots \quad (5)$$

which conforms to Hixson and Crowell's cube root dissolution law. A plot of $M_t^{1/3}$ against t should therefore give a linear relation of slope $-2C_s k / \rho^{2/3}$.

Three factors were considered in assessing the results of this investigation. These were: (a) Whether the observed dissolution rate followed an exponential (first-order) or cube root law; (b) The reproducibility of the results obtained by using a specific method and apparatus; (c) The relative order of magnitude of the overall rate of the dissolution process in a particular apparatus.

The data plotted on the cube root scale were found to be as or more linear than those plotted logarithmically (Figs 3 and 4) implying that the cube root law for the dissolution of a sodium chloride cube is more closely followed than the exponential first order law even for conditions which do not comply with the assumptions made by Hixson & Crowell (1931). It would appear that deviations of dissolution behaviour from a cube root law would better reflect formulation differences in a commercial tablet especially if Hixson and Crowell's conditions are met by the apparatus.

The foregoing conclusion is also supported by the analysis of individual curves which is presented in Table 1. The figures for the ratio of root mean squares r.m.s.

Table 1. *Derived parameters for data fitted to cube root and logarithmic functions.*

Apparatus	$y^{1/3} = a_1 + b_1x$			$\log y = a_2 + b_2x$			$\frac{r.m.s._1}{r.m.s._2}$	n
	a_1	$-b_1$	$r.m.s._1 \times 10^2$	a_2	$-b_2 \times 10^2$	$r.m.s._2 \times 10^3$	$r.m.s._2$	
Levy beaker ..	4.87	0.117	4.179	2.09	4.01	22.45	1.86	51
	4.85	0.139	3.242	2.09	4.87	20.22	1.60	48
	4.72	0.161	1.546	2.06	5.84	7.28	2.12	42
	4.78	0.135	3.726	2.07	4.76	22.63	1.65	49
	4.86	0.142	4.574	2.10	5.07	24.96	1.83	40
c.v.		11.5%						
Rotating basket	4.55	0.024	2.234	1.98	0.78	7.75	2.88	57
	4.50	0.069	6.776	1.99	2.55	17.44	3.89	57
	4.44	0.052	3.786	1.96	1.88	20.71	1.83	53
	4.63	0.071	3.102	2.04	2.59	13.04	2.38	39
	4.71	0.115	5.342	2.08	4.34	13.15	4.06	39
c.v.		49.7%						
Resin kettle ..	4.65	0.165	2.733	2.04	6.07	7.42	3.68	41
	4.96	0.176	1.826	2.14	6.39	13.67	1.34	18
	4.84	0.184	2.107	2.11	6.59	10.25	2.06	9
	4.86	0.172	3.918	2.12	6.31	19.39	2.02	17
	4.85	0.208	3.959	2.12	7.66	21.35	1.85	31
c.v.		9.0%						
Stationary basket	4.80	0.229	1.069	2.11	8.58	11.66	0.92	28
	4.91	0.214	1.704	2.15	7.97	13.34	1.28	21
	4.83	0.217	1.706	2.11	8.06	14.46	1.18	27
	4.81	0.226	1.400	2.12	8.73	12.61	1.11	27
	4.82	0.229	1.253	2.12	8.58	11.14	1.12	25
c.v.		3.2%						
F.D.D.	4.21	0.276	2.406	1.90	10.55	8.60	2.80	31
	4.26	0.276	3.398	1.92	10.75	10.68	3.18	30
	4.41	0.223	4.111	1.97	8.53	18.60	2.21	23
	4.59	0.343	2.319	2.04	13.14	6.63	3.50	23
	4.69	0.280	4.631	2.08	10.71	15.13	3.06	31
c.v.		15.2%						
U.S.P.	4.68	0.327	1.269	2.05	11.97	8.43	1.51	33
	4.68	0.328	1.972	2.05	11.86	9.27	2.13	33
	4.70	0.312	1.190	2.05	11.21	7.07	1.68	34
	4.68	0.317	2.572	2.06	11.79	6.16	4.18	32
	4.68	0.330	1.726	2.05	12.11	9.90	1.74	33
c.v.		2.4%						
Tumbling cylinder ..	4.61	0.599	5.220	2.07	23.98	16.73	3.12	20
	4.43	0.577	4.452	2.02	23.81	18.03	2.47	18
	4.70	0.597	2.099	2.11	23.97	8.72	2.41	22
	4.90	0.673	6.910	2.17	26.27	28.12	2.46	18
	4.60	0.544	3.122	2.08	21.94	12.33	2.53	25
c.v.		7.9%						

The following abbreviations are used in this table:

r.m.s. = Root mean square $\sqrt{(\text{observed} - \text{fitted})^2 / n - 2}$

n = Number of observations used in the analysis,

c.v. = Coefficient of variation $100 s/\bar{x}$, where s is the standard deviation.

of the cube root and log data ($r.m.s._1/r.m.s._2$) are generally smaller than the expected⁶ range of between 2.1 and 3.6. The r.m.s. values for data of individual curves are compounded of a random component and a non-linear component (curvature). Part of the reason why the rms ratios fall below the calculated range is probably due to an unusually large curvature component in the logarithmic fit.

A comparison of the derived zero-time coefficients (a_1 and a_2 in Table 1) with the theoretical values of 4.64 for the cube root and 2.00 for the logarithmic function, shows little difference for the F.D.D. apparatus, the logarithmic coefficient to be closer for the rotating basket, and the cube root coefficient to be superior for the remainder.

Reproducibility within a given apparatus may be assessed from the coefficients of variation of the slope, b (Table 1). The magnitude of the coefficients of variation given in Table 1 indicate that the ranking in order of decreasing reproducibility was U.S.P., stationary basket, tumbling cylinder, Levy beaker, resin kettle, F.D.D. and rotating basket.

A comparison of the relative overall rates of dissolution for the different methods reveals that if the rate coefficient of dissolution is considered to be proportional to the slope of the cube root plot, then the ranking, in an order of increasing dissolution rate, is: rotating basket, Levy beaker, resin kettle, F.D.D., stationary basket, U.S.P. and tumbling cylinder.

If the sodium chloride cube is considered to be a standard substrate it is reasonable to conclude that this order is also the ranking for the agitation intensity of the dissolution medium in the various apparatus. The intensity of agitation has been considered as an important factor that can affect the rank order of dissolution rate for pharmaceutical dosage forms (Wurster & Taylor, 1965; Mitchell & Saville, 1969). No inter-apparatus comparisons of agitation intensity have been previously reported largely because of the variations in the method of agitation, geometry and design of apparatus components and volume of solvent. The same kind of agitation (a rotating three-bladed propeller) was used in both the Levy beaker and resin kettle methods and an identical reciprocating motion of the same disintegration basket was used in both the F.D.D. and U.S.P. methods. In both pairs, only the volume of solvent and the volume and shape of the containing vessel were different. The increase in volume of solvent from 800 ml to 2 litres in the U.S.P. and F.D.D. apparatus results in a decrease in dissolution rate of about 50%. Similarly an increase in solvent volume from 450 ml to 900 ml in the Levy beaker and resin kettle apparatus results in a decrease of 14.4% in the dissolution rate.

For the rotating basket apparatus, rotation of the basket in the solvent medium resulted in a very small vertical component to the agitation. When dissolution of

⁶ The following argument was used to derive a range of expected values for the ratio of the root mean square ratio of the cube root and logarithmic data:

Let the difference between a measured point and the corresponding point on the theoretical curve be $\epsilon\%$ Undissolved, a small enough amount to justify first order approximation.

Then, if we ignore the fact that the fitted curve is different in the two cases, the difference in the cube root transformed data will be:

$$\frac{(y + \epsilon)^{1/3} - y}{\sim y^{1/3} (\epsilon/3y)} \quad \dots \dots \dots (1)$$

and in the logarithmically transformed data will be:

$$\frac{0.434 \ln (y + \epsilon) - \ln y}{\sim 0.434 \frac{\epsilon}{y}} \quad \dots \dots \dots (2)$$

The r.m.s. ratio, assuming only small random errors, would be the ratio of equation (1) to (2) which is $0.77y^{1/3}$. When $y = 20m$ the value is 2.1 and when $y = 100$, it is 3.6.

the cube commenced, the nearly saturated solution in the vicinity of the basket, remained near the bottom of the vessel owing to its relatively higher specific gravity. In subsequent determinations of dissolution rate the electrode was placed close to the upper surface of the solution but even this did not allow a true measurement of the intrinsic dissolution rate but rather monitored the sum of the dissolution rate of the cube and the rate of vertical mixing of the solution (or diffusion of solute molecules).

When the dissolution of a sodium chloride cube in the rotating basket apparatus was followed by a sampling technique in which three samples, one from near the bottom, one from the mid-point and one from near the surface of the solvent body, were abstracted simultaneously, the results depended on the depth of sampling (Fig. 5). Since most dissolution profiles for solid drug dosage forms are obtained by removing samples of the dissolution medium, spurious results could be obtained if its sampling depth is varied.

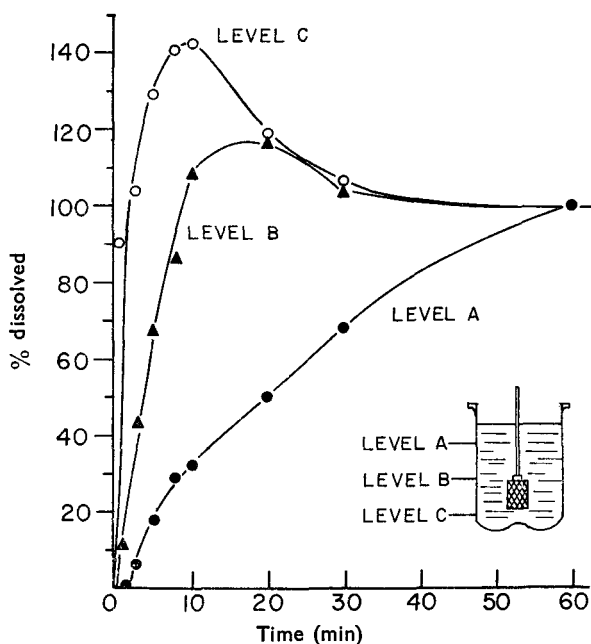


FIG. 5. Dissolution curves for a sodium chloride cube obtained by abstracting three samples simultaneously from the indicated levels.

CONCLUSIONS

It must be realized that few, if any, pharmaceutical dosage forms will behave like a sodium chloride cube in any of the apparatus since most preparations are formulated so that they disintegrate rapidly and the majority of drugs are probably not as soluble as sodium chloride. Although the U.S.P. and stationary basket apparatus allowed reproducible data to be obtained for the sodium chloride cube (and thus vindicated to some extent the use of the cube as a reference standard), the smaller particles of a disintegrated tablet would probably very rapidly become subject to less reproducible and more heterogeneous conditions after they had left their original

environment of a basket. In this respect, the tumbling cylinder may offer a more homogeneous and reproducible agitation of the dissolution medium. It should be mentioned that the dissolution rate was at least twice as fast in the tumbling cylinder as any other apparatus. This factor introduced some practical difficulties in assessing sampling times with sufficient precision since 80% of the dissolution had occurred in less than 2 min.

The Levy beaker and resin kettle apparatus, which have a close similarity, are probably more difficult to specify than any of the others in that the precise physical description of a three bladed impeller and its optimum rotation rate and geometry with respect to the containing vessel, preclude the reproduction of identical equipment. Sodium chloride cubes appeared (from visual observations) to dissolve, in the apparatus, in such a manner as to reduce the cube symmetry to that of a pyramid or cone.

The inherent liabilities of the rotating basket apparatus have been discussed in the light of the observation that, of the apparatus used in this study, the poorest reproducibility was obtained with this device.

Acknowledgements

It is a pleasure to acknowledge the collaboration of D. A. Lyon, M. Moulding and H. Yule of the Statistical Services Division, Food and Drug Directorate, in connection with the analysis of results and the construction of the necessary computer programs. I am also grateful for the services of Mr. L. Davies and his staff who constructed the tumbling cylinder apparatus.

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