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CALORIMETRIC DISSOLUTION TESTING.

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ABSTRACT

It is frequently desirable to obtain dissolution information about a new drug in the pre-formulation stage. This is difficult for two reasons. One is that there usually is not much drug available at this particular point in time (and e.g. a rotation disk dissolution (Levich, l962) can hence, not be carried out). Another reason is that the assay methodology may not be completely worked out.

The article to follow deals with the possibility of using calorimetry for this purpose. With a sensitive calorimeter it may be possible to determine dissolution characteristics at the hydrodynamics prevalent in the calorimeter, and then to correlate them with what happens in a USP dissolution apparatus.

Sodium chloride has been used here as a hydrodynamic calibrator, and the system checked with ascorbic acid and propantheline bromide as

model drug substances, cornstarch and microcrystalline cellulose as model excipients and salicylic acid acetylsalicylic acid tablets as model tablets.

INTRODUCTION.

Dissolution is generally governed by the Noyes-Whitney equation (Noyes and Whitney, 1897):

$$dM/dt = - k^* A (S-C) \qquad \text{(Eq. 1)}$$

where M is mass dissolved, t is time, S is solubility C is concentration, A is surface area, and where k* (cm/sec) depends on the hydrodynamics. E.g. in plate dissolution it is given by the Levich equation (Levich, 1955), i.e.

$$k^* = 0.62\, D^{2/3}\pi^{1/2}\mu^{1/6}A \qquad \text{(Eq. 2)}$$

where D is diffusion coefficient, π is rotations per time unit, and μ is kinematic viscosity. For dissolution about a particle, π is unknown and the equation, stated in Eq. 1, is semi-empirical.

In pharmaceutical systems, dissolution from a particulate powder (or granule) is the parameter of importance. Based on Eq. 1, a powder will, in general, dissolve by a cube root equation (Hixson and Crowel, 1931, Carstensen and Musa, 1972, Brooke, 1972, Carstensen and Patel, 1975). However, from a dosage form it will dissolve by a sigma-minus plot (Carstensen et al., 1978a, 1978b):

$$\ln[M/M_o] = -k(t-t_i) = -kt + C \qquad \text{(Eq. 3)}$$

where

$$C = kt_i \qquad \text{(Eq. 4)}$$

M_o is the original amount of drug presented to the dissolution medium, k is a dissolution constant, t is time and t_i is a lag time depending on disintegration and dissolution.

If a given dosage form is placed in two different hydrodynamic situations (π_1 and π_2), then the ratio of the k values should simply be related to the π-values, and it should be possible to establish a one-to-one relationship.

If only a small amount of powder is available, then a mini-dissolution test could be conducted (a "minitest"). A known substance (freely available) could be used to conduct a comparison (a correlation) experiment, and it could then be assumed that this would hold under other circumstances as well.

As mentioned, assay is often a problem, initially, and in the following a calorimetric method will be investigated for this purpose.

EXPERIMENTAL

Sodium chloride (analytical reagent grade, Mallinckrodt, lot 7581), corn starch (Argo, lot 4NT4) and magnesium stearate (Fisher Scientific Co. lot 785150 commercial grade) were used. Water was obtained from a Barnstead PCS water purification system.

Tablets were made of sodium chloride (and of the drug substances as appropriate), by first crushing it in a mortar. A cylindrical drum with

inserts (and of 500 mL capacity) (Ertel and Carstensen, l987) was used and cornstarch and the magnesium stearate (0.25 to 1.5 w/w%) and 100 g of crushed sodium chloride were mixed for 30 minutes at 50 RPM. This type of tumbler provides a gentle agitation. Tablets were then compressed on a hydraulic press (F.Carver, Menomonee Falls, WI) either using a 8.0 mm or 9.5 mm diameter tablet dies and flat faced beveled punches. Tableting forces varied from 2,000 to 8,000 lb. force. These are converted from forces to pressures and are reported in units of MPa in the following.

When powders were used per se, they were used as received from supplier. To make possible comparison of heats of solution of compounded drug substances (containing cornstarch) and what the heats of solutions would have been without the cornstarch, the "heat of solution" of this latter was determined as well. This is, of course, not a heat of solution, but rather a heat of hydration. Subtracting this figure from the heats of solutions of compounded tablets, then gives the heat of solution of the drug substance itself.

The dissolution experiment in the calorimeter was carried out as follows: The tablet was allowed to dissolve in water in a micro-calorimeter (Parr Model 1451, Parr Instrument Co., 211 53rd St. Moline ILL, 61265). 100 mL of water were employed. A tablet was placed in the calorimeter at time zero and the decrease in temperature was monitored as a function of time. A typical calorimeter trace is shown in Fig. 1.

Dissolution of a single tablet was carried out in 1000mL of water, using the USP XX method II (paddle) at 20°C. The stirring speed was 150 rotations per minute. 3 mL samples were removed after 1, 2, 3, 5 10, 20, 30, 60 and 120 minutes, or until the sodium chloride (or drug substance as the case might be) had completely dissolved. The samples were removed and 3 mL of water were added. The sodium chloride samples were assayed

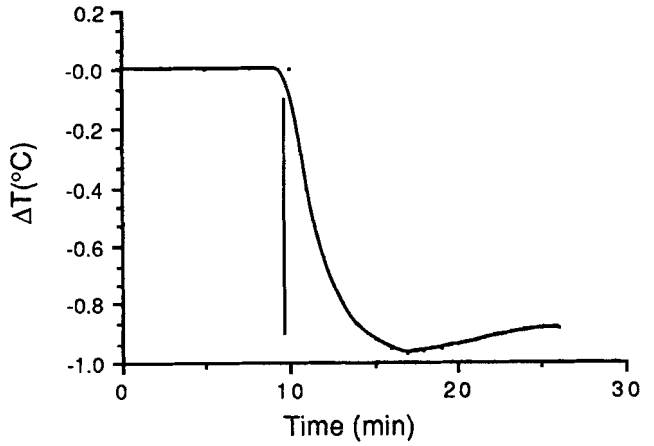

Fig. 1. Example of calorimetric temperature/time profile for sodium chloride.

by argentometrical titration with 0.01N silver nitrate using saturated silver chromate, potassium chromate test solution as an indicator. The drugs were assayed spectrophotometrically.

RESULTS AND DISCUSSION.

A typical trace of a temperature/time (i.e. heat/time) dissolution curve of sodium chloride in the calorimeter is shown in Fig. 1.

When a single substance is tested, then the experimental result represents the heat of solution for that substance.. Heats of solution for the various substances tested are shown in Table I.

For the tablets, the assumption is now made, that the asymptote represents dissolution, and the trace can, therefore, be converted to percent dissolved. This has been done for sodium chloride tablets in Fig. 2.

Table I. Heats of Solution*

Substance	ΔH (Kcal/g)	ΔH (cal/mole)
Sodium Chloride	19.2	1.12
Salicylic Acid	31.8	5.64
Acetylsalicylic Acid	20.5	3.69
Ascorbic Acid	32.4	5.71
Propantheline Bromide	14.7	6.59
Cornstarch¶	-8.7	
Avicel¶	-3.9	

*Adjusted for heats of solutions of excipients

¶Heats of hydration.

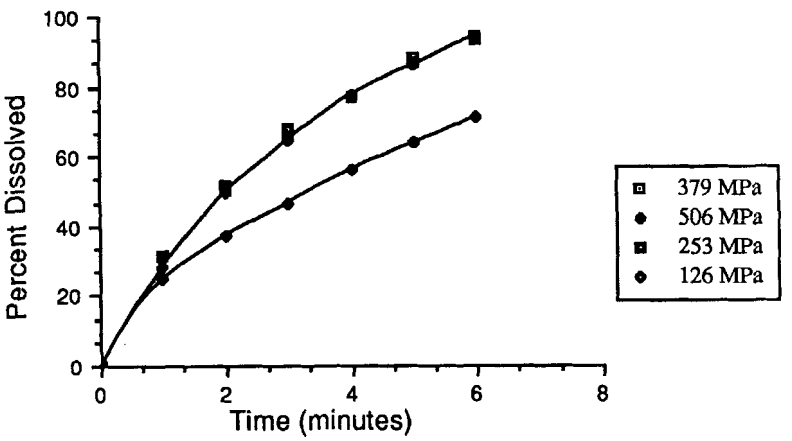

Fig. 2. NaCl tablets compressed at various pressures on a 9.5 mm FFB punch. Dissolution in calorimeter.

It is seen, as expected that at low pressure, the porosity is quite extensive and disintegration is impaired because the starch cannot exert the force from its swelling (Couvreur, 1971).

Fig. 3 shows the data obtained in the USP dissolution apparatus for the three *higher* pressures. It is seen that, again, there is no significant difference between the three curves. That there is a correlation between the two types of dissolution is obvious from Fig. 4, where % dissolved in the calorimeter at a given time is plotted versus the same parameter from the dissolution apparatus. The dissolution in the USP II apparatus *at 25°C* is, however, considerably slower. Fig. 4 would allow correlation calculations between percent dissolved in the calorimeter and up to 40% in the USP dissolution apparatus.

The data in the calorimeter are consistent with what is usually observed, in that, if no corn starch is added, then the tablet does not disintegrate, and dissolution is too slow to monitor. The dissolution patterns, are also of the correct type (i.e. Eq. 3). They are plotted in this fashion in Fig. 5 for sodium chloride determined calorimetrically. Fig. 6 is the companion graph, showing the sodium chloride dissolution in the USP apparatus.

The USP data show definite curvature for the first four points (concurrent dissolution and disintegration) and they have been removed in the construction of Fig. 6.

The effect of percent magnesium stearate on disintegration is plotted in Fig. 7. The figure demonstrates that the data adhere to the relation reported by Roblot et al. (1984), viz.

$$\ln[k-Q] = b - ax. \qquad \text{(Eq. 5)}$$

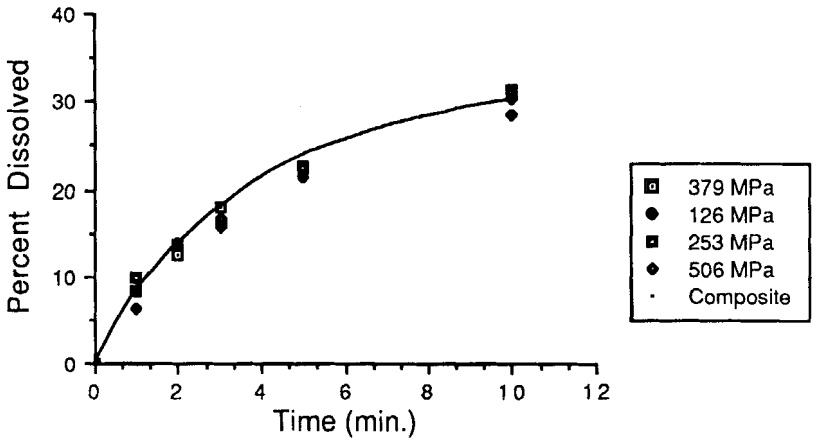

Fig. 3. Tablets from Fig. 2 subjected to USP dissolution method II at 150 RPM at 25°C.

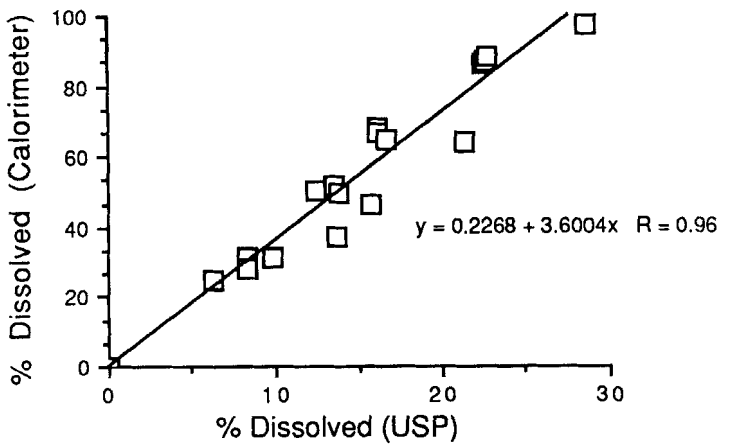

Fig. 4. Correlation between calorimeter and USP dissolution.

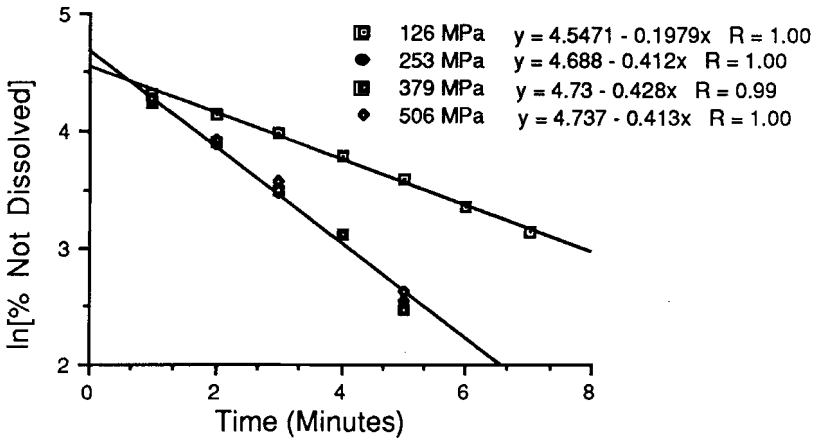

Fig. 5. Calorimeter data for sodium chloride according to Eq. 3. Only the fastest and slowest dissolution line are shown for graphical clarity.

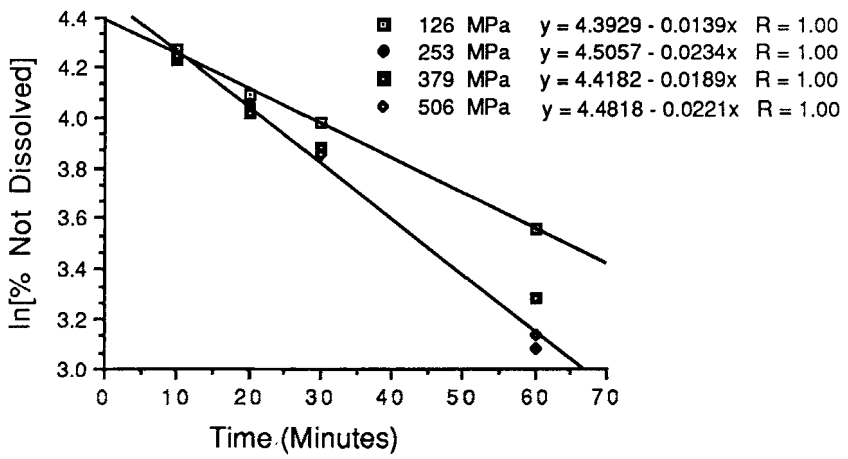

Fig. 6. USP method II data for sodium chloride according to Eq. 3. Only the fastest and slowest release line is shown for graphical clarity.

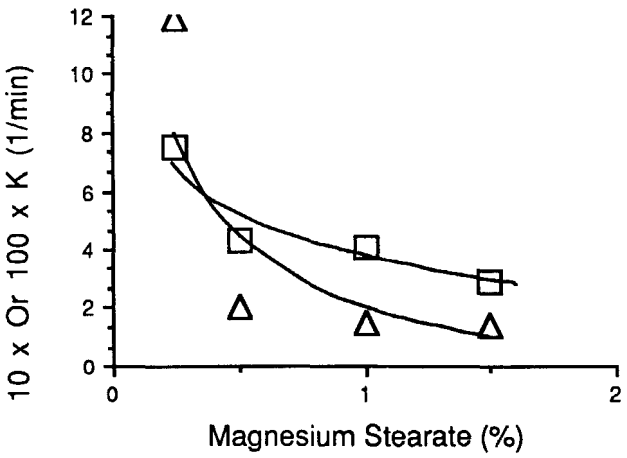

Fig. 7. Dissolution constant for NaCl as a function of magnesium stearate concentration. Δ = 100 x k for USP dissolution, Squares = 10 x k for calorimeter

where Q is a constant. For the calorimetric method it is 0.2, i.e. this is the lowest rate constant which can be expected (as far as magnesium stearate effect is concerned). The curves shown are the theoretical curves according to Eq. 5.

The data in Table II show, as expected, that with increasing concentrations of cornstarch, the disintegration time will decrease, so that the dissolution rate (k, min^{-1}) will increase. That there is a correlation between the two has been established by Cruaud et al. (l980). This is evident from the effect of pressure on the k-values. These are shown in Fig. 8. At low applied pressure (less than 250 MPa) the dissolution constant increases with increasing pressure, and then reaches a plateau. (At even higher pressures the dissintegration time will increase, and K will again decrease).

Table II Dissolution Rate of Sodium Chloride 700 mg Tablets Compressed on a 9.5 mm Punch.

	Formula			Calorimeter		USP	
	Starch	Mg-St	Force	Parameters in Eq. 3			
No.	(%)	(%)	(MPa)	k	C	k	C
1	2.0	0.5	126	0.198	4.55	0.0139	4.39
2	2.0	0.5	253	0.412	4.69	0.0234	4.51
3	2.0	0.5	379	0.428	4.73	0.0189	4.42
4	2.0	0.5	506	0.413	4.74	0.0221	4.48
5	0.5	0.5	379	0.403	4.74	0.0165	4.47
6	1.0	0.5	379	0.556	4.85	0.0173	4.45
7	4.0	0.5	379	0.582	4.88	0.0272	4.50
8	6.0	0.5	379	0.516	5.01	0.0157	4.46
9	2.0	0.25	379	0.750	4.96	0.1190	4.67
10	2.0	1.0	379	0.410	4.74	0.0150	4.48
11	2.0	1.5	379	0.294	4.74	0.0139	4.46

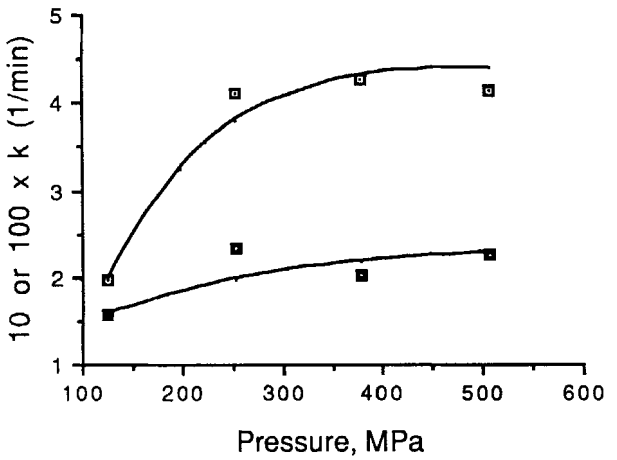

Fig. 8. Effect of pressure on dissolution constants. Light squares (upper curve) are 10 x k for calorometric dissolution and dark squares (lower curve) are 100 x k for USP dissolution.

Table III. Calorimetric K and C-Values for Some Drug Substances and Excipients.

Substance	Form (Strength,Punch,Pressure)	Calorimeter K_c min^{-1}	Calorimeter C_c	USP Apparatus K_u min^{-1}	USP Apparatus C_u
Salicylic Acid, 6% Starch	200 mg, 8.0 mm 535 MPa	0.448	4.55	0.069	4.59
Salicylic Acid, 10% Starch	200 mg, 8.0 mm 535 MPa	0.686	4.45	0.223	4.68
Propantheline Br. 0% Starch	400 mg, 9.5 mm 379 MPa	0.571	5.21	0.138	4.62
Propantheline Br. 2% Starch	400 mg, 9.5 mm 379 MPa	0.622	4.98	0.144	4.62
Aspirin, 2% Starch	200 mg, 8.0 mm 535 MPa	0.462	4.97		
Ascorbic Acid, 6% Starch, 10% Microcryst. Cellulose	500mg, 9.5 mm 379 MPa	0.630	4.96		

Dissolution parameters for the excipients and for the other drug substances are shown in Table III.

REFERENCES

Brooke, D.,l973, *J.Pharm.Sci.*, **62,** 795

Carstensen, J.T. and Musa, M.N., l972, *J.Pharm.Sci.*, **61**, 223

Carstensen, J.T. and Patel, M.H., l975, *J.Pharm.Sci.*, **64**, 1770

Carstensen, J.T., Wright, J.L., Blessel, K. and Sheridan, J., l978, *J.Pharm.Sci.*, **67**, 48

Carstensen, J.T., Wright, J.L., Blessel, K. and Sheridan, J., l978, *J.Pharm.Sci.*, **67**, 982

Couvreur, P. , l975. Thesis, Docteur en Sciences Pharmaceutiques, p. 87, Univ. Catholique de Louvain, Belgium

Cruaud, O, Dûchene, D., PUisieux, F. and Carstensen, J.T., l980, *J.Pharm. Sci.*, **69**, 607

Ertel, K.D. and Carstensen, J.T., l987, *Int. J.Pharmaceutics*, **42**, 1271

Hixson, A.W. and Crowell, J.H., l931, *Ind. Eng. Chem.*, **23**, 923

Levich, V.G., (l962), Physicochemical Hydrodyanmics, Prentice-Hall, Englewood Cliffs, N.J., p. 342

Nakamura, Y., Fukuoka, E., Terada, K., Makita, M., Yamamura, S. and Nakamura, Y. (l987), *J. Pharm. Sci.*, **76**, 284

Noyes, A. and Whitney, W., l897, *Z.PhysChem.*, **23**, 689

Roblot, L., Duchêne, D., and Carstensen, J.T., (l985), *J.Pharm.Sci.*, **74**, 697