DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(14), 1971-1989 (1988)

HANDLING OF NON-SINK CONDITIONS: IN-VITRO DISSOLUTION RATES OF SOME COMMON PHARMACEUTICAL CALCIUM SALTS.

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ABSTRACT

A model is developed for convenient treatment of data obtained from non-sink dissolution. To demonstrate its utility, the dissolution profiles of calcium sulfate, calcium carbonate and three calcium phosphates were determined by USP dissolution in pH 1.2 buffer. A model is developed taking into account both the decreasing size (surface area) and the changing concentration gradient during the dissolution process. All the salts adhere well to the proposed model.

INTRODUCTION

Most work in the field of dissolution has dealt with non-ionizable substances dissolving, under sink conditions, into their dissolution

media (1-3). Some work of importance (which shall be referred to later) has been carried out in the case of ionizable substances (4-5). Finally, some work has been published in the area of dissolution from defined surfaces under non-sink conditions (6).

In the case of ionizable substances, very complicated expressions result, and such results, hence, lack the desired utility by the practitioner. The article to follow proposes a fairly simple means of treating non-sink particulate dissolution.

To test this experimentally, systems have been chosen which are of pharmaceultical interest, viz. parmaceutically acceptable calcium salts. Sources of calcium have, in recent years, been of commercial interest as a nutritional supplement. The choice of salt used in such cases could be made based on (a) bioavailability and/or (b) the calcium content of the salt. Since large quantities of calcium are dosed, the compound with the largest calcium content will afford the smallest tablet or capsule, and hence is a logical choice, provided its absorption characteristics do not outweigh the content advantage. In-vitro dissolution tests have been conducted here (for the reasons stated above), and it should be pointed out that the absorption characteristics of the calcium salt can only be adequately gauged by in-vivo bioavailability studies.

MATERIALS AND METHODS

Monocalcium phosphate hydrate, dibasic calcium phosphate dihydrate, (Ditab™), and basic tricalcium phosphate (hydroxyapatite,

Tritab™) were obtained from Stauffer Chemical Co., Dobbs Ferry, N.Y. All materials were used as received from the manufacturer. The surface areas of each raw material were determined by nitrogen adsorption.

Dissolution studies were carried out using a U.S.P. dissolution apparatus II (paddle), operating at 50 rotations per minute. The dissolution medium was a pH 1.2 buffer. I0 mL aliquots were removed at the times indicated in the graphs, and these were assayed by titration with ethylenediamine tetraacetic acid, using hydroxynaphthol blue as indicator (9). For calcium carbonate the details of such an assay would be that the 10 mL sample was pipetted into a 250 mL Erlenmeyer flask. 30 ml of water and 6 mL of 1*N* sodium hydroxide and 300 mg of hydroxynaphthol blue were then added. The sample was then titrated with 0.005 molar ethylenediamine tetraacetate until a color violet to distinct blue was observed. An overtitrated reference solution was used as a comparative standard.

In the case of the phosphates, 125 mL of water were added to the sample, followed by 8 mL of HCl. 1 mL of 50% aqueous triethanolamine was then added, 300 mg of indicator added, and titration carried out as described above.

In the case of the calcium sulfate, 100 mL of water and 4 mL of 3*N* hydrochloric acid were added to the sample. 1 mL of 50% triethanolamine and 300 mg of indicator were added, and the titration carried out as above.

The apparent solubility, S, of each salt was determined by equilibrating an excess of the salt with 0.1 *N* HCl for 72 hours, and determining the calcium content in the supernatant. This is, of course, a situation dictated by solubility products, and although it cannot strictly be considered in the same vein as the solubility of a non-ionic compound, it is treated in this sense in the following. The amount of salt used for the dissolution experiment was, in each case an amount sufficient to produce a solution which, upon complete dissolution, had a concentration of calcium corresponding to S/2. It should be noted that the pH does not change by more than 0.1 pH unit during the dissolution process.

All studies were carried out at $37 \pm 0.5^{\circ}C$. Four dissolution experiments were carried out for each salt. The results reported are the averages of these. The standard errors of the means of most of the figures were 1-2%. The prime source of error is estimated to be the uncertainty in time, since the samples were drawn at fairly low times. The size of the symbols in the figures to follow exceed the standard errors of the mean.

RESULTS AND DISCUSSION

The apparent solubilities and the amounts of material used for each dissolution test are shown in Table I, and the results obtained are shown for the five compounds in Fig. 1 and Fig. 2. It should be pointed out here that the amounts tested are larger than what is usually

Table I. Amounts Used and Theoretical Values for the Various Calcium Salts Used.

Salt	S (mg) /900mL HCl	Amount Used mg Salt per 900 mL HCl	Formula	M.W.	% Ca Theo- retical	Act- ual	Equi- valent Weight
Carbo- nate	4700	2350	$CaCO_3$	100.09	40.04	39.2	50
Monocal- cium Phos- phate	9154	4577	$Ca(H_2PO_4)_2 \cdot H_2O$	252.09	15.9	16.4	126
Dicalcium Phosphate, DiTab	7740	3770	$CaHPO_4.2H_2O$	172.10	23.29	23.5	86
Hydroxy- apatite, TriTab	4492	2246	$3Ca_3(PO_4)_2.Ca(OH)_2$	1004.67	39.89	38	50
Calcium Sulfate	I6226	3113	$CaSO_4.2H_2O$	172.18	23.28	23.5	86

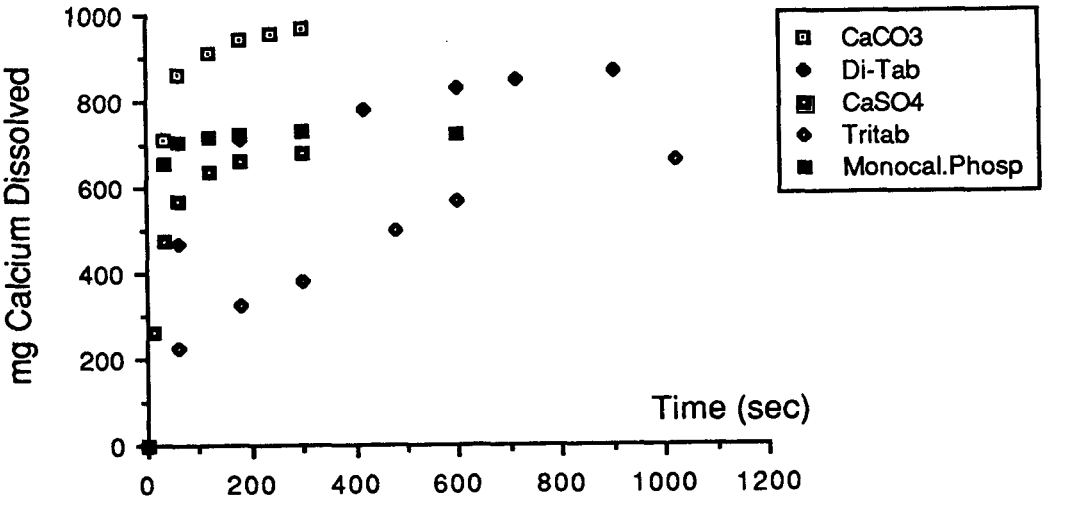

Fig. 1. Dissolution of the 5 Calcium Salts in 0.1 N HCl

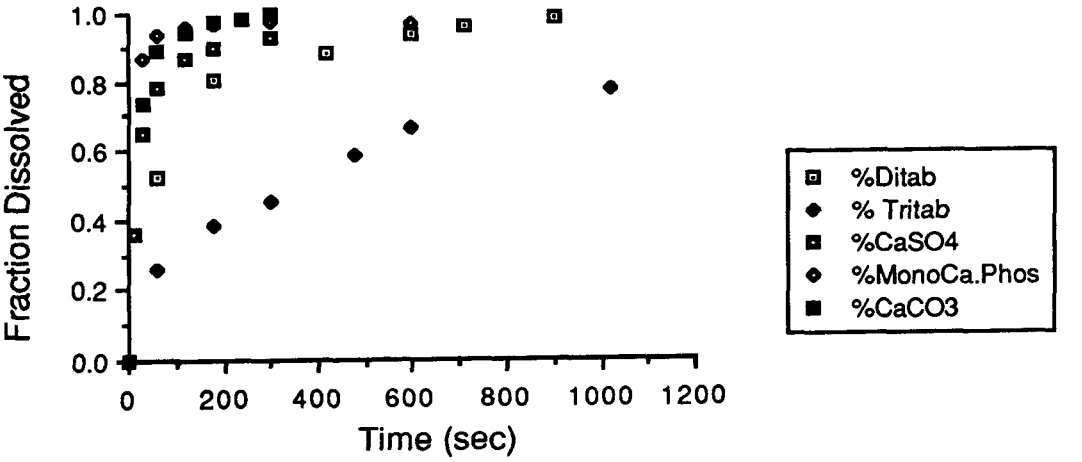

Fig. 2 Dissolution of 5 Calcium Salts

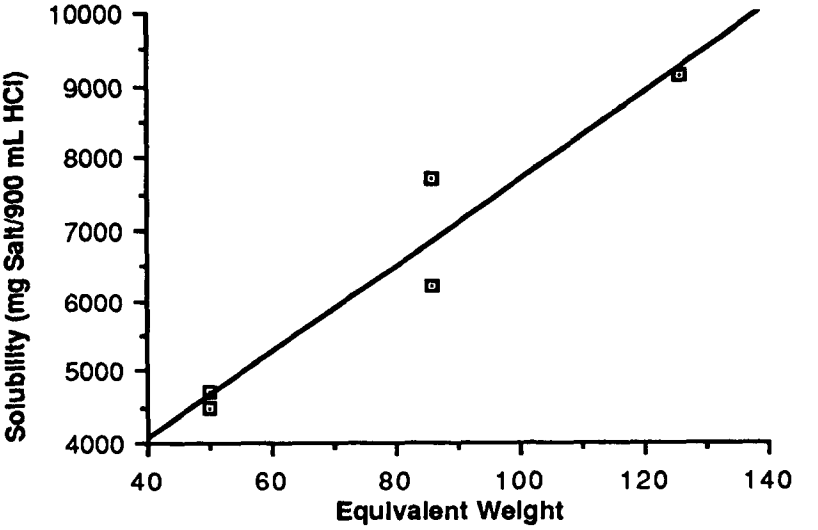

Fig. 3. Apparent Solubility as a Function of Equivalent Weight
$y = 1629.5233 + 60.6894x \quad R = 0.96$

present in a vitamin-mineral supplement solid dosage form, or in a calcium supplement solid dosage form.

Since each calcium salt has a different acid equivalent, it might be thought, on the surface, that this would affect dissolution. Acid equivalent weights are shown in Table I, as is the percent dissolved after five minutes. The table implies no such correlation between equivalent weight and percent dissolved after 5 minutes. However, examination of Table I shows that the apparent solubilities are in direct relation to the acid equivalent weight. This is shown graphically in Fig. 3.

It is obvious that the surface areas will affect the dissolution, and in this case it should be noted that the specific surface area of

TABLE 2

Surface Areas and C_{5min} Of The Various Calcium Salts

Salt	Specific Surface Area, m^2/g	Amount Used g	Total Surface Area, m^2	Percent Dissolved after 5 Min
Mono-phosphate	5.4	4.577	24.7	96
Sulfate	2.8	3.113	8.7	33
Tritab™	73.3	2.246	165	32
Ditab™	2.5	3.77	9.4	67
Carbonate	4.3	2.35	10.1	69

the hydroxyapatite (73 m^2/g) is considerably higher than that of the remaining substances (which have specific surface areas between 2 and 5 m^2/g). Since it is the dissolution *rates* that are inversely proportional to surface area (not the concentrations), a direct comparison of the figures cannot be made without further data treatment. Specific and total surface areas are shown in Table 2. More, in-depth treatment is therefore necessary.

For simplicity of model development (and this as shown in Appendix 2 in no way restricts the model) the amounts used were

selected to be one half the saturation concentration (S/2). These amounts, therefore, differ from salt to salt. Since the pH does not change markedly during the dissolution process, the apparent solubility (S) may be considered constant during the process. This statement is only partially true, because incongruent dissolution might change the value of S to some degree.

It is assumed that the mass transfer occurs via a Noyes Whitney type equation (10), and difference in transference numbers of the respective cations and anions (4-6) is not taken into consideration. The reduction in undissolved mass, *M*, with time *t*, is therefore given by:

$$dM/dt = -k' A [S-C] \quad \text{(Eq. 1)}$$

where *k'* is a mass transfer coefficient (dissolution constant) and *C* is the concentration at time *t* in the *V* cm^3 of dissolution medium. This is obviously given by

$$C = [M_o-M]/V \quad \text{(Eq. 2)}$$

where M_o is the initial amount of calcium salt which relates to half solubility, i.e.

$$S = 2M_o/V \quad \text{(Eq. 3)}$$

The initial surface area (A_o) of the sample, assuming the material to be isometric, is given by

$$A_o = \Gamma M_o^{2/3} \qquad \text{(Eq. 4)}$$

where Γ is the sample shape factor. An expression for this shape factor is obtained by the following consideration: If there are *N* particles in the sample, then the initial area is given by

$$A_o = N \gamma [M_o/(N\rho)]^{2/3} \qquad \text{(Eq. 5)}$$

where γ is the particulate shape factor (11). This latter is given by

$$a = \gamma v^{2/3} \qquad \text{(Eq. 6)}$$

where *a* and *v* are area and volume of the individual (average) particle.

Inserting Eq. 5 in Eq. 4 then gives

$$\Gamma = N^{-1/3} \gamma \rho^{-2/3} \qquad \text{(Eq. 7)}$$

so that in general the area (*A*) and volume (*V*) of the sample at any time is given by

$$A = \Gamma M^{2/3} \quad \text{(Eq. 8)}$$

i.e. Eq. 8 is valid as long as the particles are isometric.

Inserting Eqs. 2, 3 and 8 into Eq. 1 now gives:

$$dM/dt = - k M^{2/3}[M_o + M] \quad \text{(Eq. 9)}$$

where

$$k = k' \Gamma/V \quad \text{(Eq. 10).}$$

Inserting this into Eq. 7 then gives

$$k = k' A_o M_o^{-2/3} V^{-1} \quad \text{(Eq. 11)}$$

Eq. 9 cannot be integrated in closed form, and has been integrated graphically (Appendix 1) in the following. It is noted from Eq. 9, that if at time *t* there are *M* g of salt left undissolved, then *t* is given by:

$$kt = {}_o\int^t [M^{-2/3}\{M_o+M\}^{-1} dM \quad \text{(Eq. 12)}$$

Integrations of this type have been carried out for the five salts. The program and an example of the integration are shown in Appendix

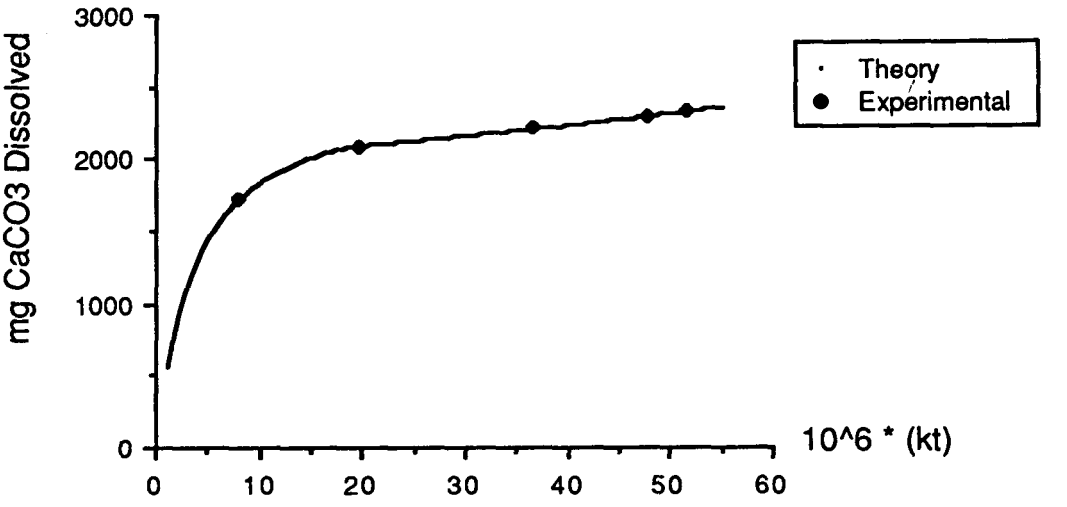

Fig. 4. Experimental Versus Theoretical Data for CaCO3

I. An example of such an integral is shown in Fig. 4 and Table III. Table III lists both the computer generated data and the actual data. The [kt]-values corresponding to experimental data are found by interpolation as demonstrated by the following example: the amount of calcium carbonate dissolved after 180 sec. is 2290 mg. This figure is between the generated 10^6kt-values of 43.68 (mg dissolved = 2256) and 55.15 (mg dissolved = 2350). Hence the10^6-kt value corresponding to 2290 is

$$43.68 + \{ [(2290-2256)/(21350-2256)] \times (55.15-43.68)\} =$$
$$43.68 + \{(34/94)\ 11.47] = 43.678+4.15 = 47.8 \qquad \text{(Eq. 13)}$$

These are the values shown in the last five row entries of the table and which are asterisked.

Table III -Generated and Real Time Values for Calcium Carbonate

10^6kt	mg $CaCO_3$ Dissolved		Real Time
	Generated	Experimental	
1.028	564		
1.523	752		
2.139	940		
2.924	1128		
3.960	1316		
5.388	1504		
7.495	1692		
10.95	1880		
17.93	2068		
43.68	2256		
55.15	2350		
7.9*		1720	30
19.7*		2990	60
36.6*		2220	120
47.8*		2290	180
51.5*		2320	240

* Interpolated values. See text.

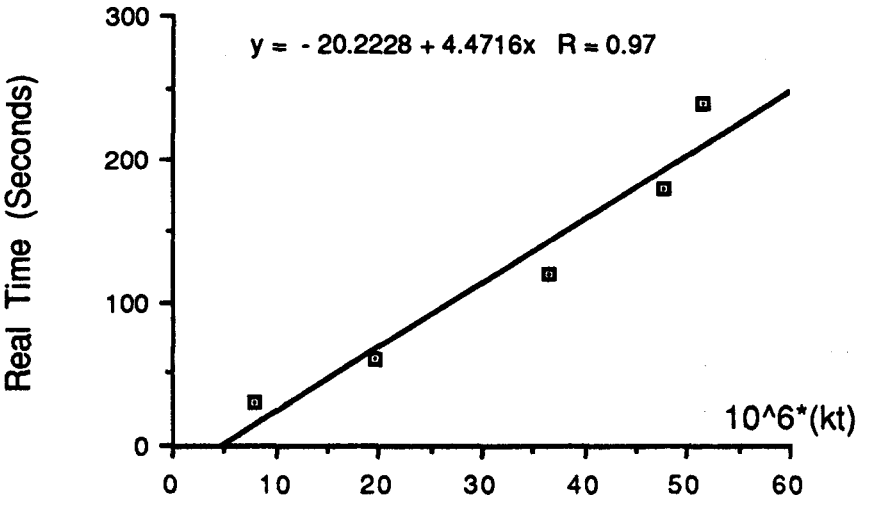

Fig. 5. Real Time Plotted versus kt for Calcium Carbonate

The data from Table III are plotted in Fig. 5. The equation for the line is

$$10^6 kt = q\,t \qquad \text{(Eq. 14)}$$

The slope, q, of this line is $10^6 k$. *k* can, hence, be found by least squares fitting of data in the manner shown in Table IV and Fig. 5. Least squares fit parameters for the five salts are shown in Table IV The k-values cannot be translated into dissolution rate constants, since the values of the shape factors are unknown. As an example if, for calcium sulfate the shape factor were six, then $k = 10^{-6} \times 0.089 \times 900/6 = 1.35 \times 10^{-5}$ cm/sec, which is of the correct order of magnitude. It is seen from Table III, that, except for the case of calcium monophosphate, the correlations are good.

Table IV: Least Squares Fit Parameters in Eq. 14

Salt	Slope $10^6 k$ $sec^{-1}cm^{-2}$	Inter-cept	R
Monocalcium Phosphate	0.086	21	0.81
Tritab™	0.0095	0.28	1.0
Ditab™	0.042	-0.55	0.98
Calcium Carbonate	2.12	4.28	0.97
Calcium Sulfate	0.089	2.11	0.99

CONCLUSIONS

It is obvious from the above that the five calcium salts tested exhibit different dissolution characteristics. The method developed for treating non-sink dissolution conditions gives fits that are good, and (using the program in the Appendix 1) provides a method for handling such situations when they arise. This type situation is one where the amount of drug is less than that required to saturate the system, but considerably more than the 15% of saturation which constitutes the upper limit for sink conditions.

One conclusion of the paper is, indeed, that *in vitro dissolution data of calcium salts are not good predictors for bioavailability*, because it has been reported in the past (15) that for the five salts, (all with varying dissolution characteristics as shown here), there would appear to be no significant difference between in-vivo performances. This statement holds only for the salts themselves, and not for dosage forms. It is perfectly possible that there are significant differences between two dosage forms both in-vivo and in in-vitro, but in such cases the differences must be assigned to formulation characteristics.

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APPENDIX 1

The BASIC program used for graphically integration of Eq. 12, is:

```
100     INPUT 'INITIAL MASS=";M1
110     INPUT "NO OF STEPS =";Z
120     Z1 = M1/Z
130     PRINT
140     PRINT "TIME";SPC(10);"MG DISSOLVED"
150     PRINT "----------------------------"
160     FOR M2 = Z1 TO M1 STEP Z1
170     B = B+1
180     M3 = M2^(2/3)
190     M4 = M1 + M2
200     M5 = (M3*M4)^(-1)
210     M6 = M5*Z1
220     FOR N = 1 TO 10
230     IF B = N*(INT(Z/10)) GOTO 260
240     NEXT N
250     IF B<>N*(INT(Z/10)) GOTO 270
260     PRINT M6; SPC(8);M1-M2
```

```
270     GOTO 280
280     NEXT M2
290     END
```

APPENDIX 2

The experimental set-up in the work described in this article was such that the final concentration in the dissolution vessel would be S/2. This is no limitation, since a more general treatment for a final concentration of αS would be as follows. (It should be noted that Niebergall and Goyan (14) have solved this in closed form for the case where the final concentration is *S*.).

In the case where the final concentration is a fraction α it follows that

$$\alpha S = M_o V$$

or $$S = M_o/(\alpha V) \qquad \text{(Eq. A-1)}$$

Inserting this and Eq. 2 in Eq. 1 gives

$$dM/dt = - k'A[(M_o/(\alpha V)) - (M_o-M)/V] =$$

$$-(k'A/V)\,[((1/\alpha)-1) + M] = -k'A/V)[\{(1/\alpha)-1\}M_o + M] \qquad \text{(Eq.A-2)}$$

which is equivalent to Eq. 9. The above is a variant of the method proposed by Patel and Carstensen (8)