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Dissolution of Directly Compressed Thiamine Hydrochloride Tablets

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ABSTRACT

Directly compressed thiamine hydrochloride tablets with varying concentrations of different vehicles as well as their binary blends, were prepared for this investigation. The results showed that, formulated tablets with avicel anhydrous lactose and celutab completely dissolved within short times. First order mechanism was reported for the tablets prepared with single vehicles. The dissolution rate constant "k", was a function of disintegration constant "D" of the tablets by the relation In K = a + n In D. In addition to that, it is proved that, "K" of produced tablets of short disintegration times was a function of the contributed vehicle concentration "C" by the relation, I/K = A exp. + NC.

On the other hand, (T 50%) of thiamine hydrochloride in a given batch was a function of its disintegration time.

INTRODUCTION

Disintegration time merely measures the time required for a tablet to break into granules smaller than given size, but it does not give information about how rapidly medicaments are released from these granules, a condition that is almost necessary for gastraintestinal absorption. Earlier, parrott et al (1) indicated the importance of dissolution kinetics

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in determining the drug availability to the body. Nelson and other workers (2 - 6) have pointed out that, dissolution rate does indeed control the rate of build up of certain drugs in blood stream. In another study Wurster and Taylor (7) have written an excellent review article discussing the theory of dissolution as well as the affecting factors.

In fact, many investigators have reported the formulation additives as an effective factor which to a great extend controls the dissolution rate of tabletted drugs (8,9).

Hixon and Crowell (10) have drived a general expression, the cube root law, that holds for dissolution of monodesperse and poly desperse powders (11).

Carstensen et al (12) have given a mathematical explanation to interpretate why directly compressed tablets have a sigmoid shape for their dissolution profiles when tested under sink conditions using usp dissolution test apparatus. Recently carstensen et al (13) proved that, the dissolution rate of dyphyllin from its tablets is a function of the hardness and the contributed polymer concentration in the formula.

Abu-Taleb and Aly (14) have found a correlation between the dissolution time (T50), disintegration times and urinary excretion of directly compressed oxytetracycline hydrochloride tablets.

Directly compressed thiamine hydrochloride with varying concentrations of either single or binary blended vehicles were prepared for this study. Apart from the physical properties of the tablets, the invitro availability was carried out to recommend a vehicle or blend of vehicles in order to achieving the best formulation, that is of highest release.

EXPERIMENTAL

Materials

The direct compression vehicles used were. Avicel[1], Anhydrous lactose usp[2], Celutab[3], STAR-x[4] and Emcompress[3].

Thiamine hydrochloride[5], the active ingredient was used as received from the manufacturer. Magnesium stearate and stearic acid[6] were used as lubricants.

Methods

The physical standards, the mean particle size, density bulk density, packing fraction and angle of repose of powdered drug and excipients were evaluated using the previously published methods (15), and results are shown in Table 1.

The reported methods by Aly and Abu-Taleb (16) were used to compress flat tablets each of an average weight of 0.25g and scored 9.75 + 0.01mm in diameter. With respect to the formulation, tablets should contain varying concentrations of a given vehicle or blend, that is ranging between 79.6 - 90.46% w/w. Furthermore, the tablets were lubricated with 0.5% w/w of either magnesium stearate or stearic acid (17).

Dissolution rate determination

Dissolution rate was determined using usp dissolution test apparatus[1]. The usp requirements were kept for the dissolution test. The stirer was adjusted to revolve 100 rpm. The dissolution medium used was 900ml of 0.1N Hcl. The mean of five determinations at each type and concentration of a given vehicle was calculated as percent of thiamine dissolved.

Assay for thiamine hydrochloride

A sensitive colourimetric method reported by Runtil (18) was used for determining thiamine hydrochloride in withdrawn samples. The method of assay is dependent on condensation reaction of thiamine hydrochloride with diazo-drivatives of amino compounds such as 2-(P. amino benzene sulphonamido) pyridine to form Pinkish colour. The colour obays Beer's law at 450nm. The dissolved thiamine hydrochloride is determined by reference to the calibration curve. Spectrophlometer[2] SP6-450 was used for measuring the absorbance.

Table 1: Some Physical Properties of Powdered Thiamine Hydrochloride and Direct Compression Vehicles

Material	Particle size range 'U'	Apparent density g/cc	Bulk density g/cc	Bulk fraction	Angle of repose
Thiamine hydro-chloride	180.48	1.548	0.675	0.4366	64 00
Avicel	82.99	1.502	0.355	0.236	40 00
Anhydrous lactose	185.07	1.683	0.559	0.332	40 00
Celutab	342.58	1.720	0.683	0.397	31 58
STAR-x 1500	113.21	1.544	0.668	0.4326	28 30
Emcompress	194.61	2.215	0.903	0.4076	35 36

RESULTS AND DISCUSSION

The produced thiamine hydrochloride tablets were evaluated for their physical standards using the reported methods (16). On the basis of HFR avicel, anhydrous lactose usp and celutab were the best single vehicles for the manufacturing. However, as it is shown in Table 2, the binary blends of these vehicles either with each other or with the rest produced good tablets of higher physical standards. These results were obtained earlier (16). The dissolution behaviour of directly compressed thiamine hydrochloride tablets is shown in Figs. (A - D). It is clearly shown in these figures that, the type as well as the concentration of used vehicle affected the dissolution of the tabletted thiamine hydrochloride. Figure A shows that the increase in avicel concentration in the formula increased the dissolution rate of thiamine hydrochloride. A compelet dissolution for thiamine hydrochloride tablets formulated with Avicel was obtained after 16 min.

Table 2: Physical standards of directly compressed thiamine hydrochloride tablets using single and binary blended vehicles

Vehicle Name	Conc.% w/w	Weight (g) Mean	Weight (g) C.V.%	Thickness (mm) Mean	Thickness (mm) S.D	Hardness "N" Mean	Hardness "N" C.V.%	Friability Mean	Friability C.V.%	Poro-sity E %	Disint. Time (min) Mean	Disint. Time (min) C.V.%
	0	-	-	-	-	-	-	-	-	-	-	-
Avicel	79.60	0.2428	4.86	3.08	1.203	12.757	9.366	2.26	5.59	26.8	8.1	17.16
	85.29	0.244	4.196	3.05	0.958	16.923	6.886	1.19	13.9	25.2	4.685	36.7
	88.46	0.24588	2.636	2.94	1.04	19.057	10.22	0.85	2.6	21.5	1.87	40.5
	90.46	0.25473	1.5286	2.957	0.7219	21.26	4.23	0.474	3.88	14.06	1.239	48.84
A.H.L	79.60	0.2358	6.116	2.67	3.85	3.089	38.2	16.31	9.66	25.04	2.50	8.50
	85.29	0.24531	5.266	2.78	1.92	5.63	1 .58	3.86	41.8	24.86	5.57	22.55
	88.46	0.24878	5.11	2.72	1.85	7.528	13.53	1.09	14.4	22.9	8.41	9.79
	90.46	0.2558	3.19	2.77	1.33	9.135	6.43	0.58	3.22	20.9	10.25	2.9
Celutab	79.60	0.2389	4.66	2.796	1.83	7.93	6.44	1.764	10.19	28.9	2.55	1.75
	85.29	0.2434	3.88	2.788	1.3	9.213	9.30	0.79	111.33	27.16	3.088	13.68
	88.46	0.245	4.82	2.733	1.46	10.63	10.30	0.60	21.96	25.92	4.29	4.66
	90.46	0.2488	2.32	2.768	1.336	11.26	10.83	0.35	128.2	25.29	5.48	11.12
Avicel/ A.H.L 1:1	90.46	0.2688	5.06	2.91	1.895	16.86	6.98	1.12	9.03	14.63	23.25	5.4
Avicel/ Celutab 1:1	90.46	0.2586	5.062	2.95	1.15	16.06	7.733	0.106	11.61	20.5	23.58	7.73
A.H.L/ Celutab 1:1	90.460	0.2458	2.77	2.81	1.5633	12.89	6.12	0.395	7.93	14.67	8.41	4.49

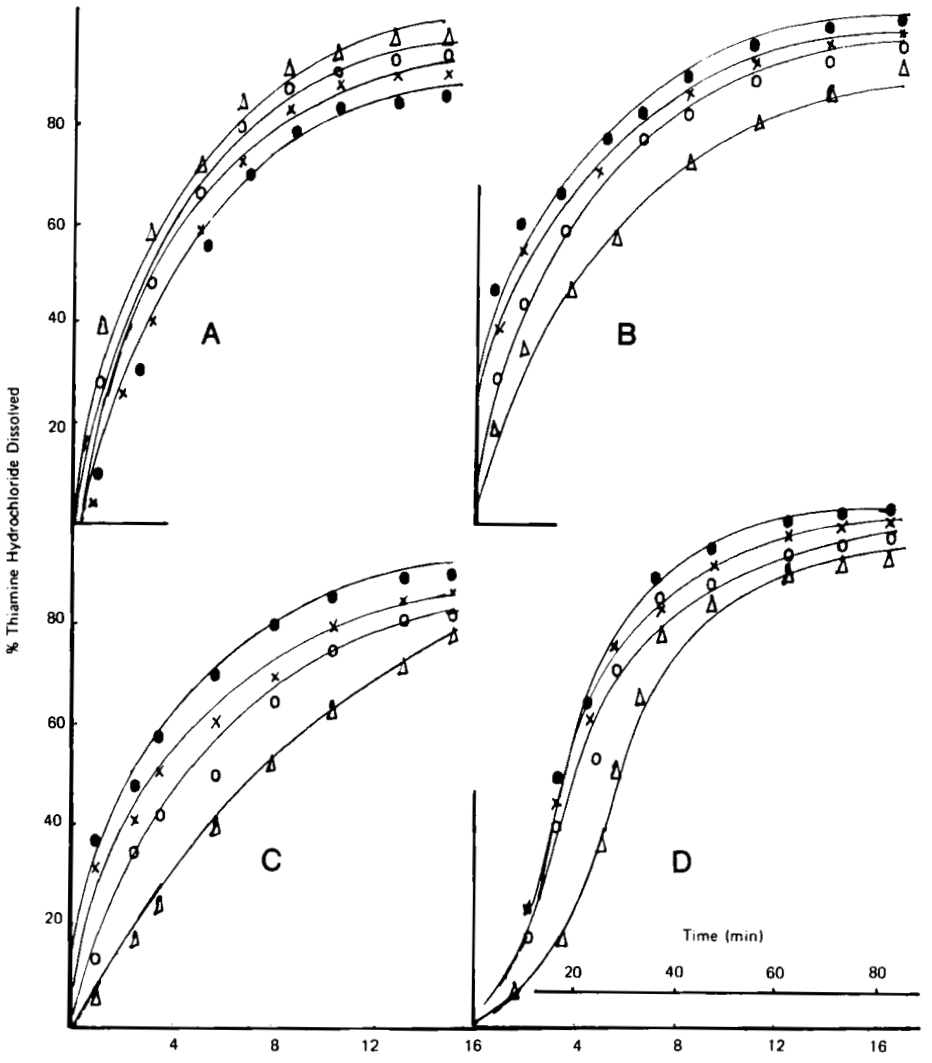

Fig. 1 Dissolution profiles thiamine hydrochloride tablets compressed from, A Avicel B Anhydrous lactose, C Celutab and D Emcompress 79.6 x 85.29, 88.46, 90.46% W/W

These expected results are due to the disintegrating effect of avicel. Earlier, khan and Rhodes (19) have stated that, the dissolution efficiency of the compressed tablets from avicel and lubricated with small percent of magnesium stearate was dependent on the compression force as well as

the contributed avicel concentration. In fact, due to the capillary action of its particles which helps to draw water into the tablet structure, avicel has a powerful disintegrating effect. Further more, Bremer et al (20) have supported the concept that fast disintegrated and hence dissoluted tablets could be compressed from avicel and water soluble drugs. In addition to that the use of small percent of magnesium stearate (0.5% w/w) as a lubricant did not offer the tablets hydrophobic protection against the dissolution medium. Therefore fast disintegrated and dissoluted tablets could be produced. The produced tablets from anhydrous lactose usp and celutab, dissolved completely within short times. But the dissolution rate decreased by increasing the concentration of the contributed vehicle. The same results were obtained for the compressed tablets with emcompress. As it was expected emcompress delayed the disintegration and hence the dissolution of the tablets. The dissolution profiles obtained for the tablets were sigmoid in shape (12). Fig. 2 shows that the contribution of either avicel or lactose to the formulation decreases the dissolution times. However, the concentration of the contributed vehicle merely affected the dissolution.

In fact, many studies have been done (7,12,13,21,22) to thraw the light on the mechanism by which a tabletted medicament would be released from their dosage forms. In this study the equation of Wagner (21) and that of Kitazawa et al (22) were employed to analyse the obtained results on the dissolution.

It is assumed in Wagner's equation that the surface area of the drug available for dissolution is initially zero, by the time it increases to a maximum as disintegration occurs. Progressively, the surface area decrease to zero when dissolution is complete. Wagner's equation can be written.

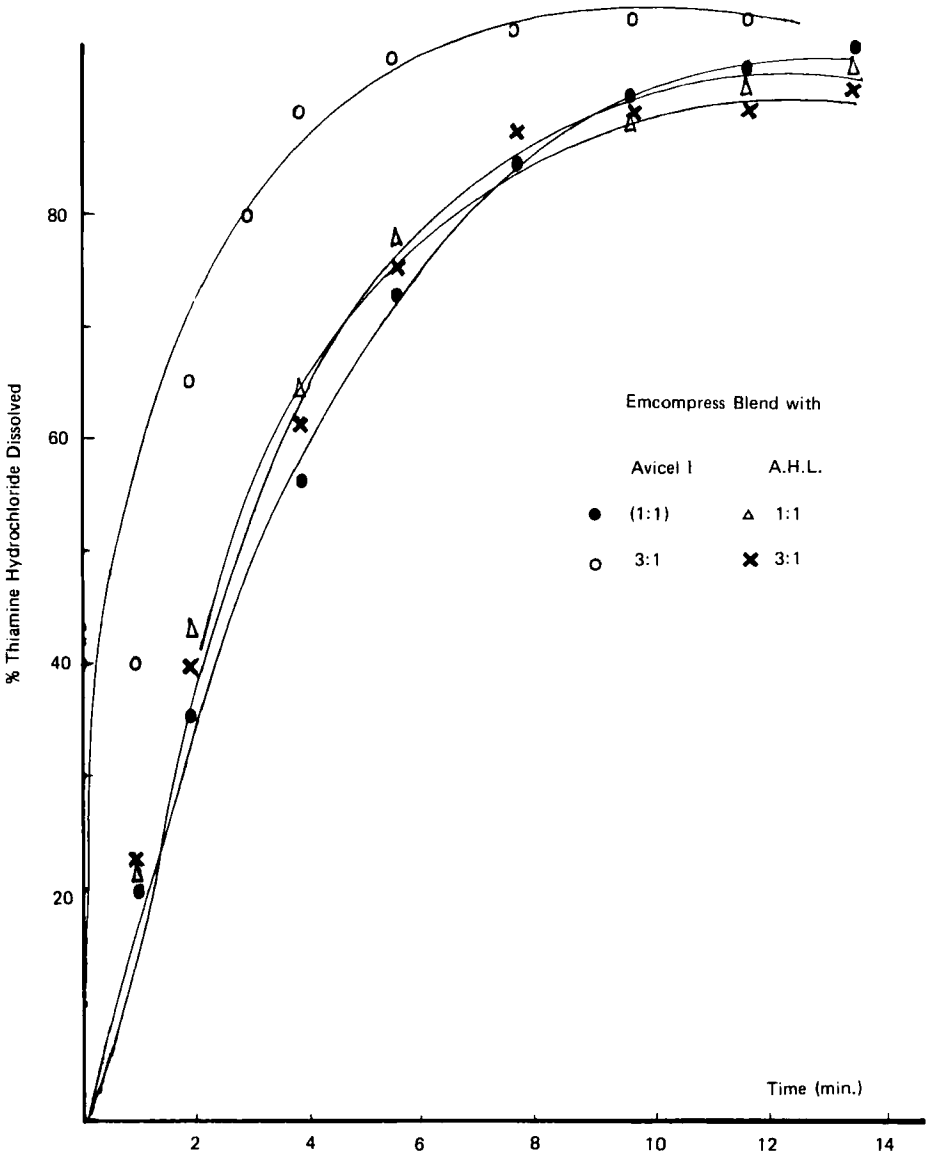

Fig. 2 Effect of contribution of Avicel and Anhydrous lactose on the dissolution of thiamine tablets compressed from Emcompress.

$$\% \text{ dissolved } t = \frac{\int_0^t S_t . dt}{\int_0^{\infty} S_t . dt} = W/W_{\infty} \times 100 \qquad \text{Eq. 1}$$

The term W/W_{∞} stands for the ratio of drug dissolved at times t and t ∞ respectively, which in turn equals to the percent of generated area. The obtained data on dissolution of directly compressed thiamine hydrochloride tablets formulated with 90.46% w/w of a given vehicle, were treated using equation 1. i.e. the cumulative amount of dissolved thiamine hydrochloride was plotted as a function of time on probability logarithmic scale as it is shown in fig.3. In this figure, two formulations compressed from avicel and anhydrous lactose did not conform to Wagner's plot while that formulated with celutab and emcompress conformed to the plot. This method of analysis was used by Esezobo and Pilpel (9) to describe dissolution behaviour of uncoated oxytetracycline tablets compressed to different packing fractions. However, Wagner's method of analysis, enables the dissolution to be described in terms of two parameters: the value of t 50% and the standard deviation. Obviously one can also obtain values of T10% and T90% from the plot. Esezobo and Pilpel (9) have pointed out that the dissolution data obtained for their prepared tablets with more than 5% w/w gelatin did not conform to Wagner's plot. This was accounted for the presence of apsirities on the particle which are responsible for strong bonding. Similarly, the neumrous sites of hydrogen bonding found on the molecules of avicel and anhydrous lactose may be accounted for the results obtained with the two vehicles. Table 3 shown T50 and standard deviation of the tested batches compressed from celutab and Emcompress.

On the other hand dissolution data on the tablets prepared from celutab and Emcompress conformed to the

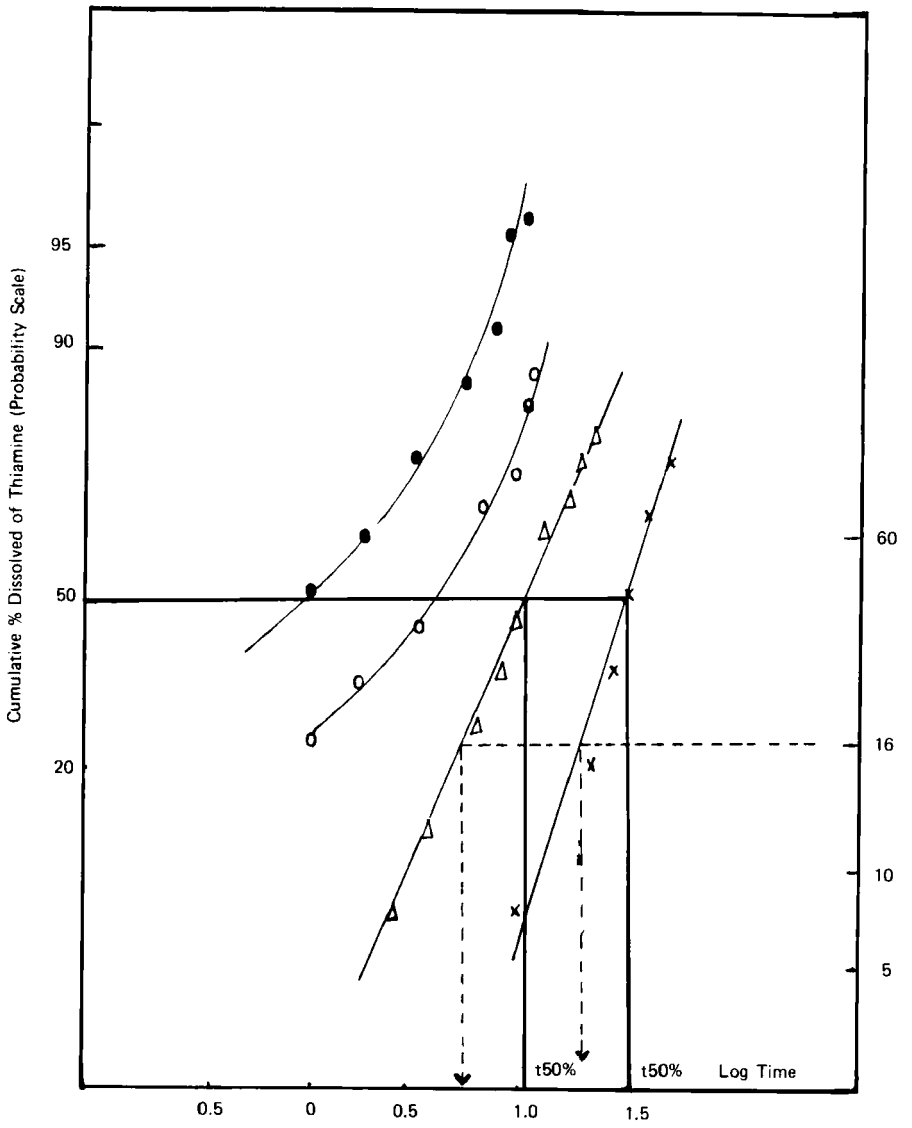

Fig. 3 Wagner's plot, cumulative % of dissolved thiamine (probability scale) as a function of log time for the tablets compressed from 90.46% w/w of Avicel, A.H.L Celutab and Emcompress

Table 3: T50% and standard deviation of dissolved thiamine hydrochloride from its tablets prepared with 90.46% w/w of single vehicles

Vehicle	T50% (min.)	SD (+)
Avicel	-	-
A.H.L	-	-
Celutab	10.10	2.23
Emcompress	30.199	1.318

wagner's. Although celutab is soluble vehicle (sugar), it seemed that it did not alter the dissolution of the drug i.e. it did not form a layer around drug particle so, drug is dissolved in a manner that obay Wagner's concept. The insolubility of Emcompress might assure this.

Fig. 4 shows that formulated tablets with 90.46% w/w of a given vehicle disolved completely following pseudo-first order decay, with two different values of "K" dissolution rate constant as shown in Table 4.

Figs. 5(A - C) shows the analysis of the obtained results on dissolution by using the equation of kitazawa et al. This equation can be written.

$$\ln Cs/Cs-Ct = Kt \qquad \text{Eq. 2}$$

where Cs and C stand for saturation concentration and concentration at time t respectively.

It is shown in fig. 5a that only one batch of avicel formulations (90.46% w/w) has K in Ks. The dissolution rate constant of the tablets changed from 0.69 to 0.31 min. at certain time 't'. This change in the dissolution rate constant ascribed to an increase in the surface area due to the break up of the tablets in large and small fragments at time t,(9).

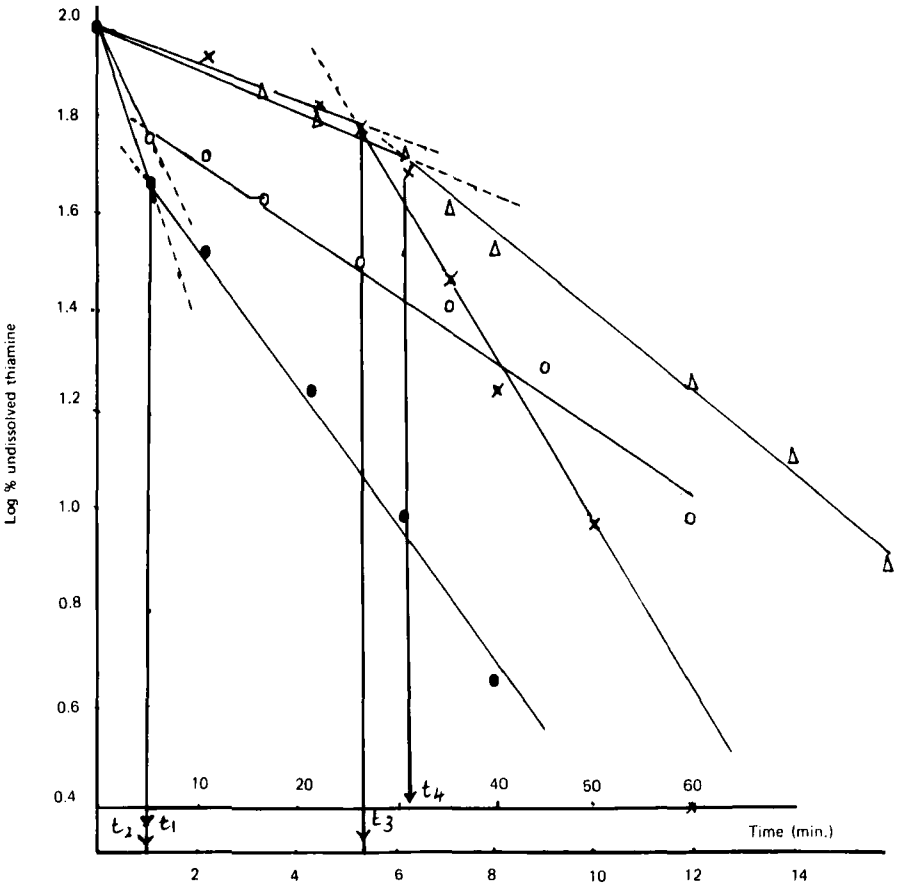

Fig. 4 Log % undissolved thiamine as a function of time "pseudo first order decay" for the tablets prepared from different vehicles, key see Fig. 3.

Table 4: Dissolution rate constants "K" in "Ks" min^{-1} of thiamine hydrochloride from directly compressed tablets with 90.46% w/w of single vehicles

Vehicle	K1 (Min^{-1})		Time (t) Min	K2 Min^{-1}	
	a	b		a	b
Avicel	0.806	0.69	1.00	0.335	0.31
A.H.L.	0.438	0.25	1.00	0.18	0.16
Celutab	0.567	0.08	6.00	0.184	0.172
Emcompress	0.018	-	25.00	0.46	-

a' Caculated from log% undissolved vs. time plot

b Calculated from the equation kitazawa et al it is show that a & b values "K2" are identical.

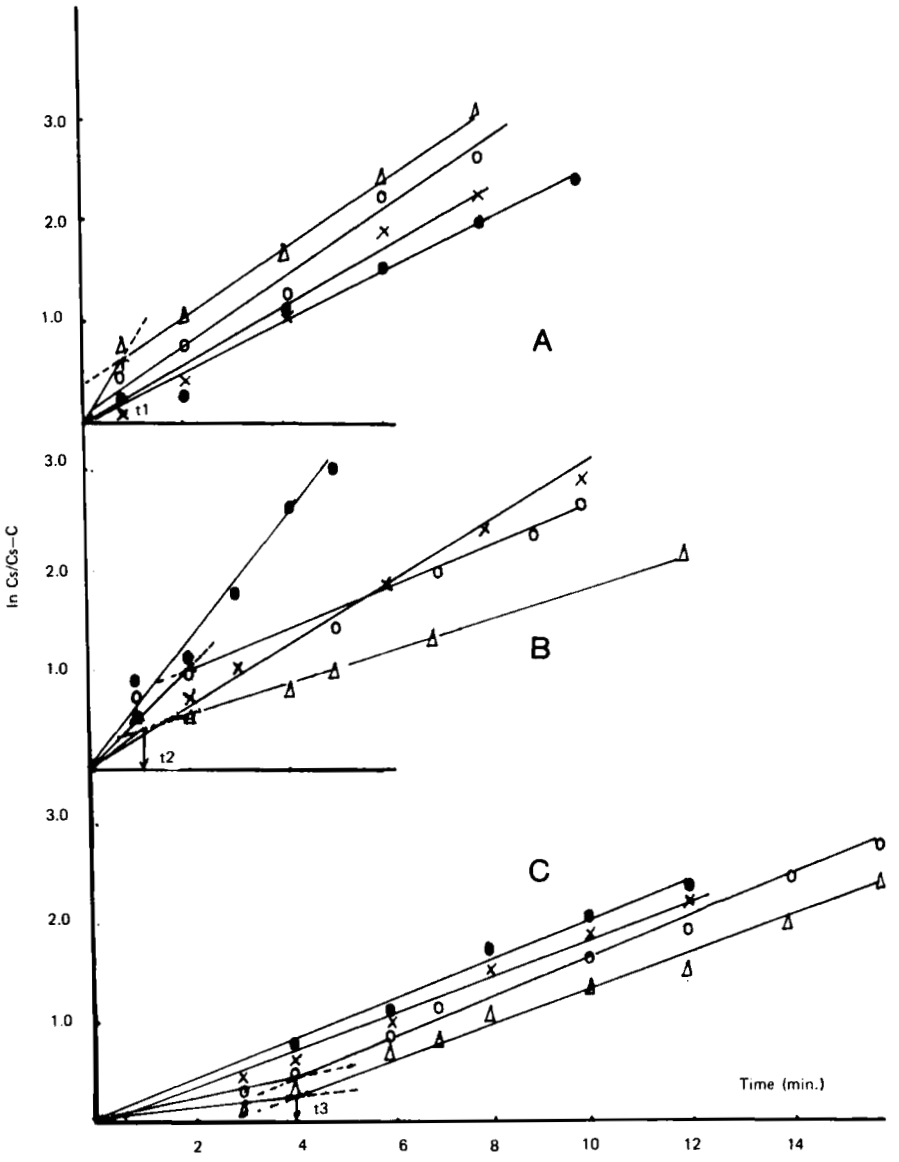

Fig. 5 In Cs/Cs-C as a function of time for thiamine tablets prepared from varying concentrations of different vehicles key, see Fig. 1.

Visual observations led to a conclusion that tablets formulated with avicel burst and then disintegrate into fragments of different sizes. The case is not the same with the tablet formulated with higher concentrations of anhydrous lactose or celutab. The corresponding tablets of these vehicles disintegrated by leaching. In other words, the dissolution rate constant K1 is describing the first dissolution of drug from the intact tablets while the second dissolution rate constant K_2, is describing the dissolution of drug from the produced fragments. However, the times corresponding to the K in Ks in Fig. 4 were indentical with that values obtained from Figs. 5(A-C) and more or less equals to the disintegration time. This might be supported by the concept that lage times observed in dissolution profiles are likely standing for disintegration, while the drug particles dissolve with respect to cube root law (12). Table 4 shows the dissolution parameters of the compressed tablets with single vehicles. In fact, the dissolution rate constant K_2(after time "t") was found to be a function of disintegration time of the compressed tablets by the relation (12).

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

The relationship is presented in Fig. 6a. On the other hand, Fig. 6b shows that the disintegration constant "D" was a function of the vehicle concentration contributed to the formula by the relation.

$$\text{Log } D = A - NC \qquad \text{Eq. 4}$$

By in serting Eq, 4 in to Eq. 3 and putting $a + nA = A'$ and $nN = N'$ one can write

$$\text{Log } K = A' - N'C$$ but A' and N' are negative values, so

$$\text{Log } 1/K = A' + N'C \qquad \text{Eq. 5}$$

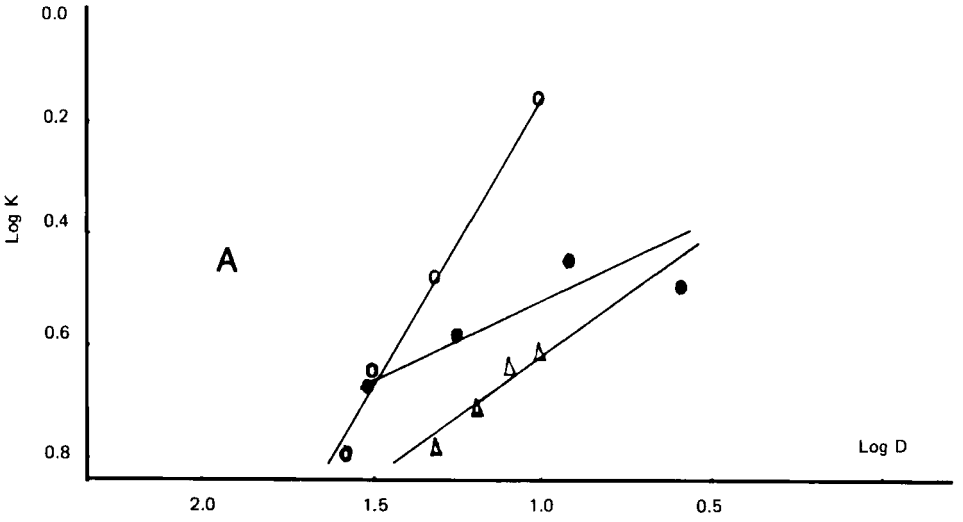

Fig.6 Log dissolution rate constant "K" as a function of Log disintegration constant "D" according to Eq. 3.

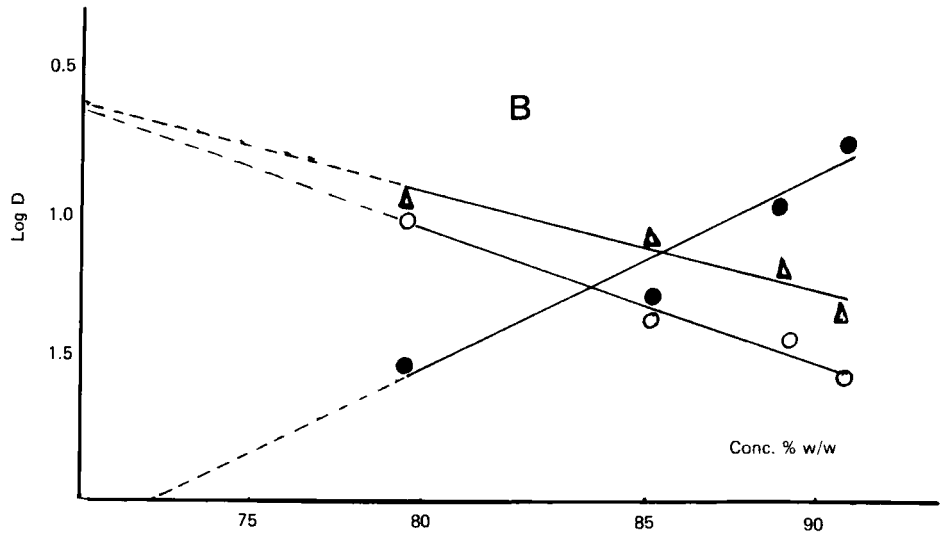

Fig. 6 Log dissolution constant "D" as a function of vehicle concentration "C" key, see Fig. 3.

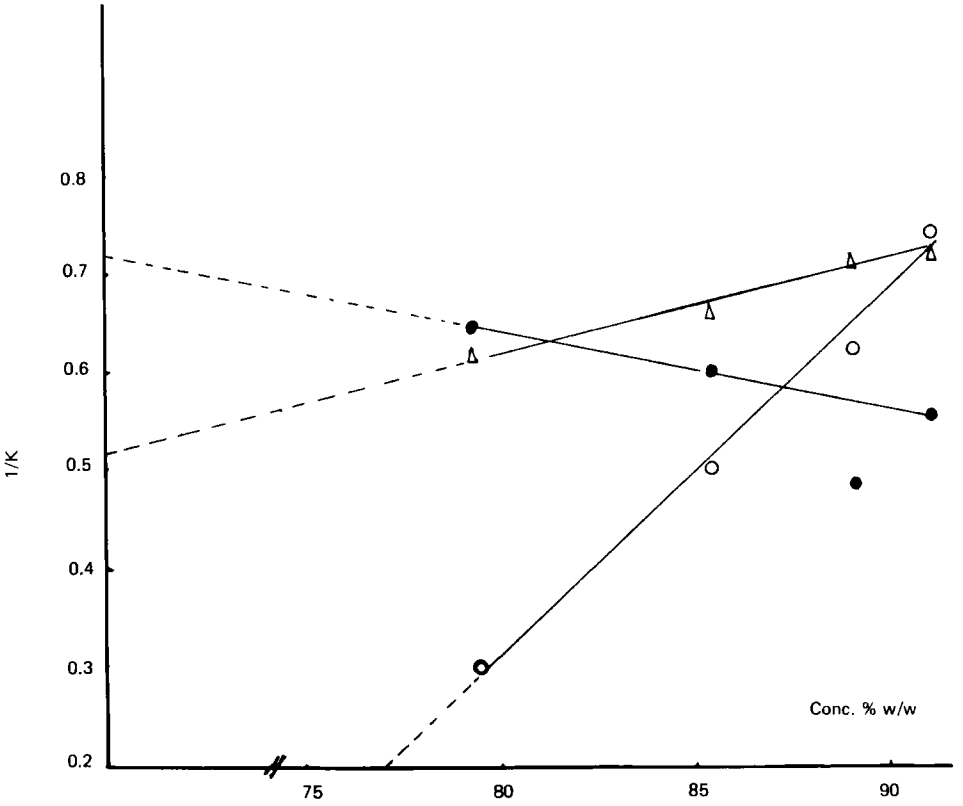

Fig.7 Log 1/K as a function of contributed vehicle concentration for thiamine tablets; key see Fig. 3.

Table 5: The estimated (N's) and found (N'f) values of the slope and correlation coefficient (r) for the equation 5

Vehicle	N	n	N's	N'F	(r)	(r*)
Avicel	0.58	0.92	0.533	0.54	1.01	0.985
A.H.L	0.85	0.58	0.49	0.44	0.98	0.85
Celutab	1.83	0.3	0.55	0.56	1.018	0.996

*Correlation coefficient for equation 6

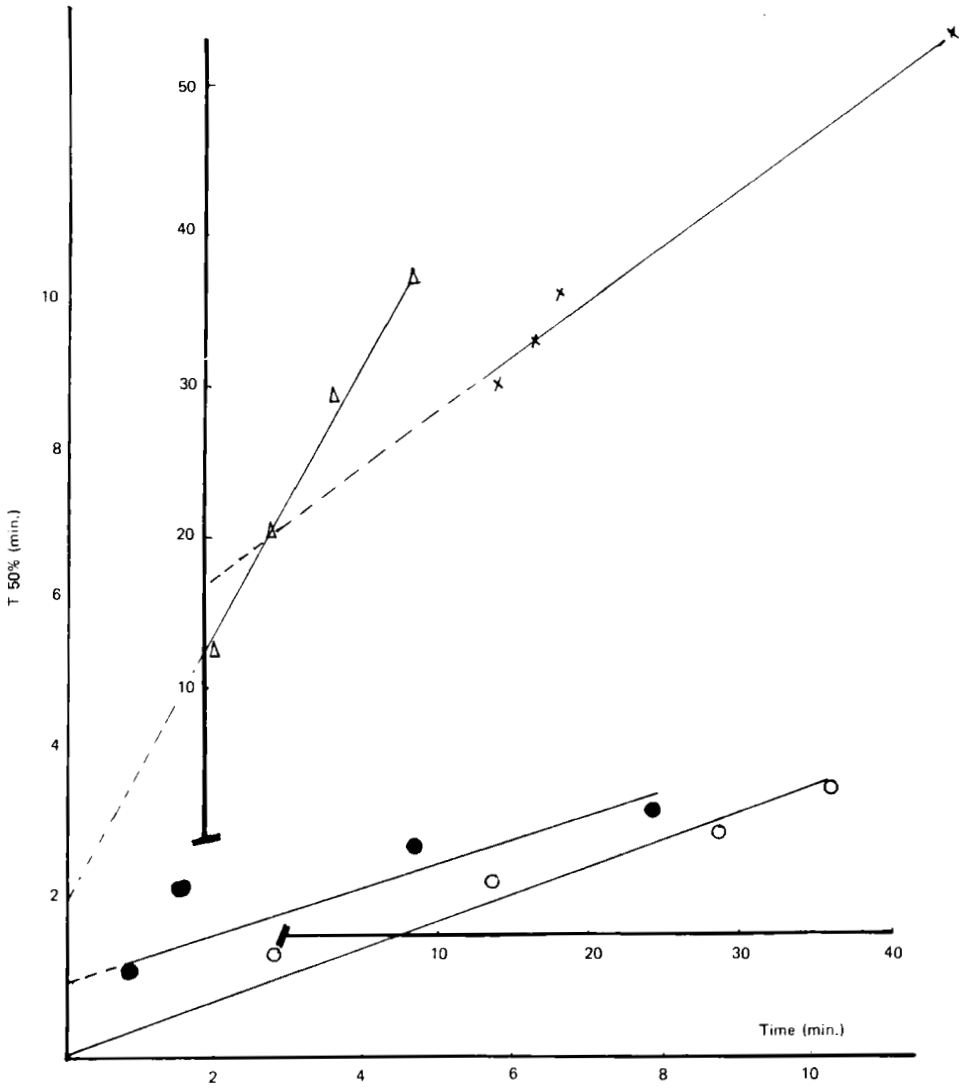

Fig. 8 T50% of directly compressed thiamine tablets as a function of their disintegration times, key see Fig. 3.

Fig. 7 shows the dissolution rate constant "K" was a function of contributed vehicle concentration, according to the equation 5. Table 5 shows the found and estimated values of slopes (N') and the correlation coefficient of the lines. It was found that, the calculated values of t 50% determined by using Wagner's plot or kitazawa et al equation were in correlation with disintegration times by the general relation.

$$t50\% = a + x\,Dt \qquad \text{Eq. 6}$$

where x and Dt stand for slope and disintegration time. However, statistically it was found that a = 1, 0 and 2.0 and x = 1.6, 0.47 and 1.45 for avicel, anhydrous lactose and celutab respectively. Table 5 shows the regression of the obtained straight lines shown in Fig. 8.

CONCLUSION

From this study it is concluded that thiamine hydrochloride tablets directly compressed from varying concentrations of single vehicles completely dissolved within short times. It was proved that Pseudo first order decay is the mechanism by which the dissolution takes place. The analysis of the results on dissolution using equation ofKitazawa et al has declared that the actual drug dissolution took place from the tablets having been disintegrated i.e. disintegration is the rate determining step. In general, the determined dissolution rate constant was a function of vehicle concentration in formula. A good correlation was obtained between the calculated t50 of the tabletted drug and the disintegration times of the corresponding tablets. As a result of this study, avicel and anhydrous lactose either singly or in binary combinations are recommended for the manufacturing of vitamin B_1 tablets by direct compression.

FOOT NOTES

1. F.M.C corporation Avicel Dept. Peunsylvania U.S.A.
2. Shiffield Union N.L. 07083 U.S.A.
3. E. Mendell Co. Inco., US.A.
4. Staley Mgf. Co. Ill. U.S.A.
5. Roch.(Nig.) Ltd., Lagos.
6. E. Merck N.J. U.S.A.

I. USP Dissolution test apparatus Erweka type - DT.D apparatebau W.Germany.

II. Pyunicum SP6 - 450, England.

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