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# DEGRADATION KINETICS OF THIAMINE HYDROCHLORIDE IN DIRECTLY COMPRESSED TABLETS I:

## EFFECT OF AGEING UNDER VARYING TEMPERATURE AND RELATIVE HUMIDITY CONDITIONS

O.K. Udeala and S.A.S. Aly
Department of Pharm. Technology and Industrial Pharmacy, Faculty of Pharm. Sciences, University of Nigeria, Nsukka, Nigeria.

ABSTRACT

The degradation kinetics of thiamine hydrochloride in tablets directly compressed with either single or binary vehicles was studied. The presult shows that, tabletted vitamin stored at varying temperature conditions degraded by first order mechanism. The magnitude of the rate constant K, was dependent on the type and concentration of the vehicle used. The decomposition of vitamin $B_1$ at varying temperatures was amenable to Arrhenius treatment. The degradation pattern of the vitamin in Avicel or binary blend of Avicel with another vehicle, stored at varying relative humidity conditions deviated from a first order mechanism. There was indication that equilibrium phenomenon is involved in the degradation of the vitamin contained in these vehicles. A log-linear relationship was seen to exist between K, and moisture content of the tablet.

## INTRODUCTION

The development of direct compression excipients for tabletting during the last 25 years enables the formulator to conveniently produce stable tablet formulations of thermolabile and moisture sensitive drugs. The important feature is that the active ingredients are not subjected to the application of binder solution or/and heat for the purpose of drying. Drug decomposition or/and migration (1) may occur during drying. Richman et al (2) and Goodhart et al (3) prepared stable glyceryl trinitrate tablets by direct compression using Avicel PH 101 and Avicel PH 102 respectively.

The stability of vitamins has been the subject of extensive investigations. Campbell and McLeod (4) studied the effect of shelf storage on the potency of some vitamins. The use of expiration date based on actual stability of multivitamin preparations was suggested by these investigators as an adequate control on the potency of the preparations. Initially, the assessment of the stability of vitamin in pharmaceutical dosage forms was entirely dependent on the prolonged study of the labelled content at room temperature. This is time consuming, costly and not adaptable to modern method of predicting stability. Thus accelerated storage tests were introduced (5). Prindel (6) used the accelerated storage test and found that the loss of vitamin A was mainly related to the complexity of the formula. The thermodegradation characteristics of liquid vitamin preparations was investigated by Garett (5) who established the fundamental basis of stability studies. This investigator was, on the basis of log-linear relationship between reaction rate constant K, and reciprocal of temperature, able to predict the decomposition rate constant of vitamins stored at low temperatures. A simplified graphical method for predicting the decomposition rate constant of vitamins was introduced by Campbell et al (7). A similar technique was used by Tardif (8) in the study of the decomposition of vitamin tablets. The latter showed that accelerated stability tests are reliable for the purpose of predicting the decomposition rate constant of vitamins A, $B_1$ and C contained in different tablet matrices and stored at room temperature. Tardif (8) however, pointed out that the magnitude of the decomposition rate constant of a vitamin is greatly affected by the composition of the vehicle used in compressing the tablets.

Synthetic thiamine hydrochloride ($B_1$) has been reported to be an unstable drug (9). Stone (10) had earlier shown that thiamine nitrate has a better stability than the hydrochloride salt. Kassem et al (11) reported that thiamine disulphide is the most stable salt of thiamine. Lhoest et al (12) using paper chromatography not only studied the effect of pH on the degradation of thiamine but also detected the degradation products. A comprehensive study of the kinetics of thiamine hydrolysis was carried out by Windheuser and Higuchi (13). These investigators pointed out the dependence of thiamine hydrolysis on the pH of the liquid vehicle. It is however, generally agreed that thiamine hydrochloride contained in solid dosage forms degrades by a first order mechanism. An investigation carried out with thiamine hydrochloride tablets directly compressed with Emcompress showed that this vehicle is unsuitable for manufacturing the tablets (14). Carstensen et al (15) demonstrated that thiamine hydrochloride in tablets compressed with Avicel and stored at varying humidity conditions degraded by a pattern whereby an equilibrium is established.

The objective of the present investigation was to study the degradation kinetics of thiamine hydrochloride in tablets compressed with different single and binary blend of vehicles The effect of the proportion of tabletting base in the vitamin tablets on decomposition rate constant of thiamine hydrochloride was also examined.

## EXPERIMENTAL

### Materials:

Four direct compression vehicles namely Avicel[1], Anhydrous lactose[2], Celutab[3] and Emcompress[3] were used in compressing thiamine hydrochloride[4] into tablets. Magnesium stearate[5] was incorporated in the formulations as a lubricant. Potassium dihydrogen phosphate[6], chloroform[6] bromothymol blue[6] and sodium hydroxide[6] used for analysis were of analytical grade.

### Methods

Evaluation of powdered drug and vehicles

The various methods for evaluating the physical characteristics of the powdered drug and vehicles have been fully reported in previous publication (16). Similar techniques were adopted for determining the mean particle size, true density, bulk density, packing fraction, moisture content and angle of repose.

Formulation and Compression of Tablets

The work was designed to elucidate the effect of varying concentrations of a given vehicle/blend on some physical properties of the vitamin tablets.

A 0.250 g weight vitamin tablets were compressed on a Manesty single punch tablet machine[I] fitted with a 3/8 inch flat faced punches. An optimum concentration of a given vehicle/blend was used in compressing tablets of highest possible hardness and acceptable friability. The setting of the tablet machine was kept constant for a given vehicle or blend of vehicles and was adjusted when a new or a different vehicle/blend was introduced.

Evaluation of Tablets

The physical standard of the vitamin tablets compressed with either single or binary vehicles were evaluated using methods similar to those described by Sakr et al (17). The effect of the storage temperature and the amount of moisture absorbed on the decomposition rate constant of vitamin $B_1$ in a given formulation was determined. The effect of these conditions on the physical properties of the tablets was also evaluated.

Assay of Thiamine Hydrochloride

A sensitive colorimetric method used by Gupta and Cadwallder (18) was adapted for the analysis of thiamine hydrochloride. The method is based on the reaction of the vitamin and bromothymol blue to form a red complex. The absorbance of the thiamine-bromothymol salt was measured in chloroform at 420 nm. using an SP6-450 spectrophotometer. A calibration curve was constructed with the absorbances of varying concentrations of vitamin $B_1$ contained in solution. Subsequently, the concentration of the vitamin present in any sample was calculated by feference to the calibration curve.

Thermo degradation Study

Each of the tablet batches was divided into four samples A,B,C and D. A chosen sample was stored under a defined temperature which were 28 $\pm$ 2$^{o}$, (ambient temperature), 40, 60 or 70°C. The degradation of vitamin $B_1$ in the directly compressed tablets was monitored by analysing the tablets for thiamine hydrochloride content after a fixed time intervals. In order to elucidate the relationship between the degradation rate constant of the vitamin and the amount of vehicle contained in the tablet formulation, thiamine hydrochloride tablets were compressed with varying concentrations of a given vehicle and stored at 70°C. The thiamine hydrochloride content of the tablets was determined periodically.

Humidity and Degradation of Vitamin $B_1$

Since moisture plays a vital role in the instability of drugs, it was necessary to determine the moisture uptake - time profiles and hence the adsorption isotherms for the drug - vehicle tablet systems. For this purpose, the technique used by Wai et al (19) and Sangekar et al (20) was adopted. The tablet batches of thiamine hydrochloride tablets compressed with single or binary blend of vehicles were divided into three samples, A, B, and C. These were respectively stored at defined temperature and humidity conditions which were ambient temperature and 100 % RH; 35°C, 80% RH and 50°C, 47% RH. The thiamine hydrochloride content of the batches was determined periodically. Thus, the effect of ageing under different relative humidity conditions on the physical properties of the tablets was also evaluated.

## RESULTS AND DISCUSSION

Direct compression is the technique of choice for manufacturing tablets of unstable drugs. In the present investigation therefore the direct compression technique was used for the manufacture of thiamine hydrochloride tablets. The physical

Table 1: Some Physical Characteristics of Powdered Thiamine Hydrochloride and Direct Compression Excipients used to Manufacture the Tablets.

| Material | Part Size range (u) | Density g/cc | | Packing fraction Pf | Repose Angle | Moist Cont. % w/w |
|---|---|---|---|---|---|---|
| | | True[-a] | Bulk | | | |
| Thiamine HCl | 180.48 | 1.546 | 0.67 | 0.4366 | 64.0 | 4.76 |
| Avicel | 82.99 | 1.502 | 0.355 | 0.236 | 40.0 | 2.50 |
| AHL USP | 185.07 | 1.683 | 0.559 | 0.332 | 40.0 | 0.35 |
| Celutab | 342.58 | 1.720 | 0.683 | 0.397 | 31.58 | 9.75 |
| Emcompress | 280.75 | 2.215 | 0.903 | 0.4076 | 35.36 | 4.3 |

a. Mean of 5 determinations

standards of the powdered drug and vehicles which may affect the physical standards of the tablets were investigated. The results are presented in Table 1. The repose angles obtained for either the powdered drug or vehicles used indicate that the drug alone has very poor flow properties. A preliminary investigation also showed that the drug is not compressible. A combination of the drug and vehicles in ratios stated in the formula yielded a compressible powder mix. The tablets obtained showed uniformity of weight and thickness, high level of hardness, lower level of friability and good disintegration. The physical characteristics of the vitamin tablets compressed with 90.46% w/w of either single or binary blend of vehicles are presented in Table 2.

It is well known that the decomposition rate of drugs is affected by the storage temperature. This factor is particularly important for thermolabile drugs such as thiamine hydrochloride. Figs. 1 (a-b) show that thiamine hydrochloride compressed into tablets with different vehicles degraded by a first order mechanism. This is in agreement with the results obtained by Wai et al (19) and Tardif (8) who found that thiamine hydrochloride contained in different tablet matrices decomposed by a first order mechanism. The highest degradation rate constant of the vitamin was obtained at a storage temperature of 70°C. There was also the indication that the magnitude of the rate constant obtained was influenced by the nature of the direct compression vehicle used. Wai et al (19) and Tardif (8) investigated the effect of binary blend of different tablet matrices on the value of the degradation rate constant. These workers found that the value of the decomposition rate constant of thiamine hydrochloride in a given tablet matrix is mainly dependent on the moisture bound to the vehicle. It follows therefore that a vehicle with a high percentage of bound moisture will generate a high degradation rate constant for thiamine hydrochloride. Figs. 1 (a-b) show that the degradation rate constant of thiamine hydrochloride is low in tablets compressed with Avicel and Anhydrous lactose USP respectively. This confirms that the amount of water bound to these vehicles is low (Table 1). Richman et al (2) and Goodhart et al (3) respectively investigated the stability of glyceryl trinitrate in tablets directly compressed with Avicel PH 101, Avicel PH 102 and Anhydrous lactose respectively. Although the low water content of these vehicles

Table 2: Some Physical Characteristics of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of Named Vehicles

| Vehicle | Weight (g) Mean ± (SD) | Thickness (mm) Mean ± (SD) | Hard. Friab. Ratio HFR | Comp. Ratio $gmm^{-1}$ | Packing Fraction PF | Disint. Time (min) Mean ± SD |
|---|---|---|---|---|---|---|
| Avicel | 0.2550(0.063) | 2.96(0.021) | 44.85 | 0.861 | 0.809 | 1.2(0.58) |
| AHL USP | 0.256 (0.0082) | 2.72(0.036) | 16.08 | 0.941 | 0.791 | 10.2(0.296) |
| Celutab | 0.24888(0.006) | 2.768(0.036 | 32.17 | 0.899 | 0.747 | 5.48(0.61) |
| Emcompress | 0.2478(0.008) | 2.00 (0.047) | 12.34 | 1.24 | 0.820 | 45.30(4.3) |
| **1:1 Binary Blends** | | | | | | |
| Avicel/AHL | 0.269(0.014) | 2.91(0.056) | 15.05 | 0.92 | 0.854 | 23.75(1.28) |
| Avicel/ Celutab | 0.259(0.013) | 2.95(0.035) | 151.5 | 0.8779 | 0.795 | 23.58(1.8) |
| Avicel/ Emcompress | 0.258(0.0106) | 2.6 (0.039) | 100.65 | 0.99 | 0.794 | 6.388(0.45) |

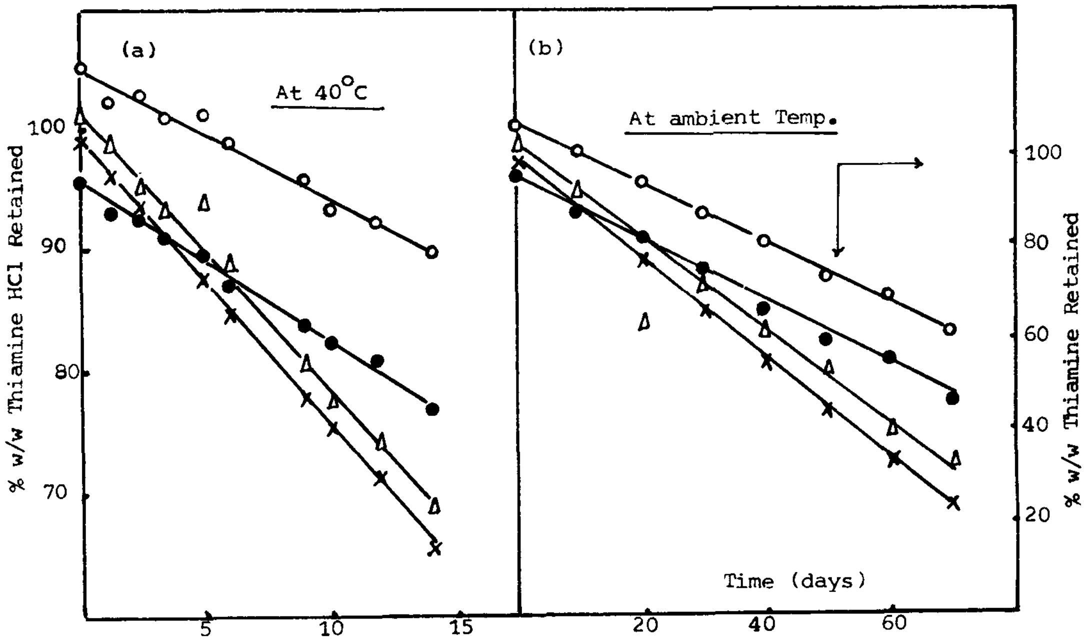



Fig. 1: Decomposition Pattern of Thiamine Hydrochloride in Tablets compressed with 90.46% w/w O Avicel, ● AHL, Δ Celutab and X Emcompress.

could have been responsible for the stability of the drug, these investigators attributed the stability achieved with these vehicles to hydrogen bonding between vehicle and drug. The result obtained in the present investigation show that thiamine hydrochloride is unstable in tablet compressed with either Celutab or Emcompress. The former vehicle has a high moisture content and this can obviously account for the high degradation rate constant of the vitamin. The latter vehicle, Emcompress in contrast does not have a high moisture content. However, its alkanity would have been responsible for the higher degradation rate constant obtained for thiamine hydrochloride tablets compressed with it. The fact that thiamine hydrochloride is unstable in the pH range of 6 - 7 (13) and that Emcompress in the presence of moisture can attain this pH would give rise to the instability of the vitamin in this vehicle. There would therefore be a rapid degradation of thiamine hydrochloride in tablets compressed with Emcompress. The stability parameters of shelf stored thiamine hydrochloride compressed with different direct compression bases are presented in Table 3. There is an exponential relationship between the degradation rate constant of thiamine hydrochloride and the storage temperature. This can be expressed as

$$K = A \exp(-\Delta E/RT) \qquad \text{Eq. 1}$$

where K is the degradation rate constant; $\Delta E$, the activation energy; A, the frequency factor; R, the gas constant and T the absolute temperature. Table 4 shows the values of $\Delta E$ and A calculated from the curve shown in Fig. 2. It can be seen that the highest value of E was obtained for the vitamin formulated with Avicel. This is followed by the $\Delta E$ obtained for the drug in Anhydrous lactose vehicle. The vitamin tablets formulated with Celutab and Emcompress respectively yielded low $\Delta E$ thus indicating the ease with which the drug degraded in these tablet matrices. The effect of varying concentration of a given tablet vehicle on the degradation rate constant of thiamine hydrochloride when the tablets were stored at 70°C is shown in Figs. 3(a-c). It can be seen that the reaction rate constant K, is dependent on the concentration C, of the vehicle in the formulation. A linear relationship exists between log K and log C. Carstensen (21) had pointed out that a linear relationship exists between log K of tabletted drugs and the moisture content of the tablet. Since the vehicles used

Table 3: Some Stability Parameters of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of Single Vehicles and Shelf Stored* for 70 Days

| Vehicle | Initial Drug Cont. $N_0$ % w/w | Final Drug Cont. $N_t$ % w/w | Decomp. Rate Const. $K \times 10^{-4}$ $h^{-1}$ | $t_{½}$ (h) | $t_{10\%}$ (h) | $t_{90\%}$ (h) | Change in Colour |
|---|---|---|---|---|---|---|---|
| Avicel | 105.81 | 63.21 | 3.070 | 2247.6 | 342.02 | 7501.6 | White |
| AHL | 95.83 | 50.81 | 3.87 | 1782.95 | 271.32 | 5950.9 | " |
| Celutab | 101.33 | 33.00 | 6.669 | 737 .18 | 112.18 | 2460.5 | Faint brown |
| Emcompress | 99.55 | 29.5 | 7.342 | 940.05 | 143.05 | 3137.6 | Faint Yellowish |

Table 4: Experimental Values of Freq. Factor A, and Activation Energy Δ E, for Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of a Named Vehicle.

| Vehicle | A $X10^{-3}$ | E K. Cal $Mol^{-1}$ $degree^{-1}$ |
|---|---|---|
| Avicel | 3.981 | 16.336 |
| AHL | 6.310 | 12.286 |
| Celutab | 63.095 | 08.008 |
| Emcompress | 16.405 | 11.44 |

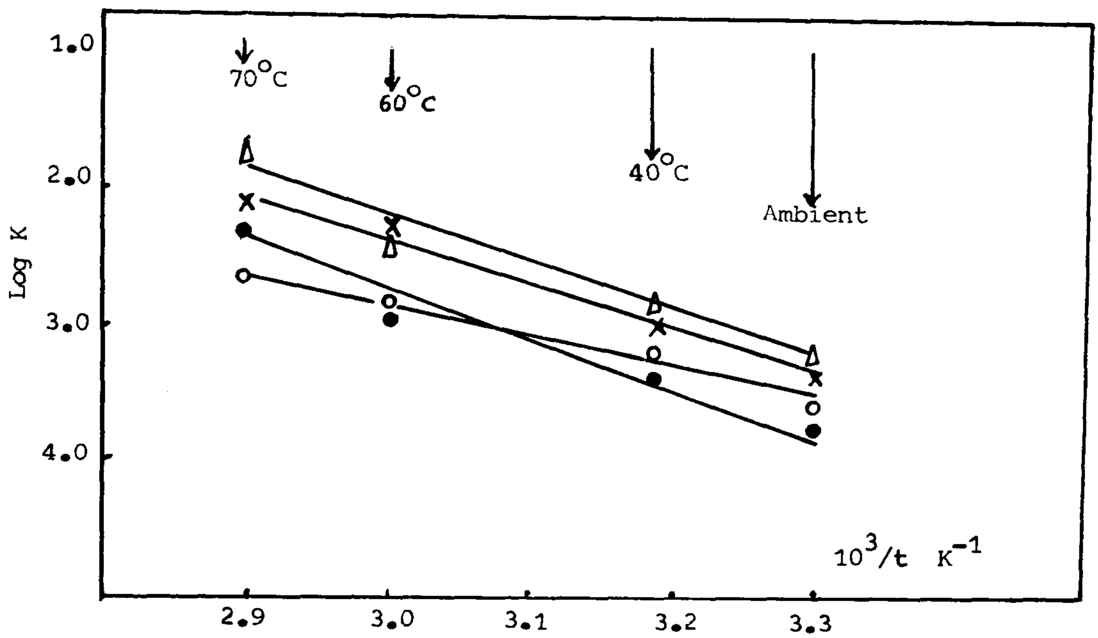



Fig. 2: Arrhenius Pot for Decomposition of Thiamine HCl in Tablets Compressed with 90.46% w/w single Vehicles.

Key as in Fig. 1.

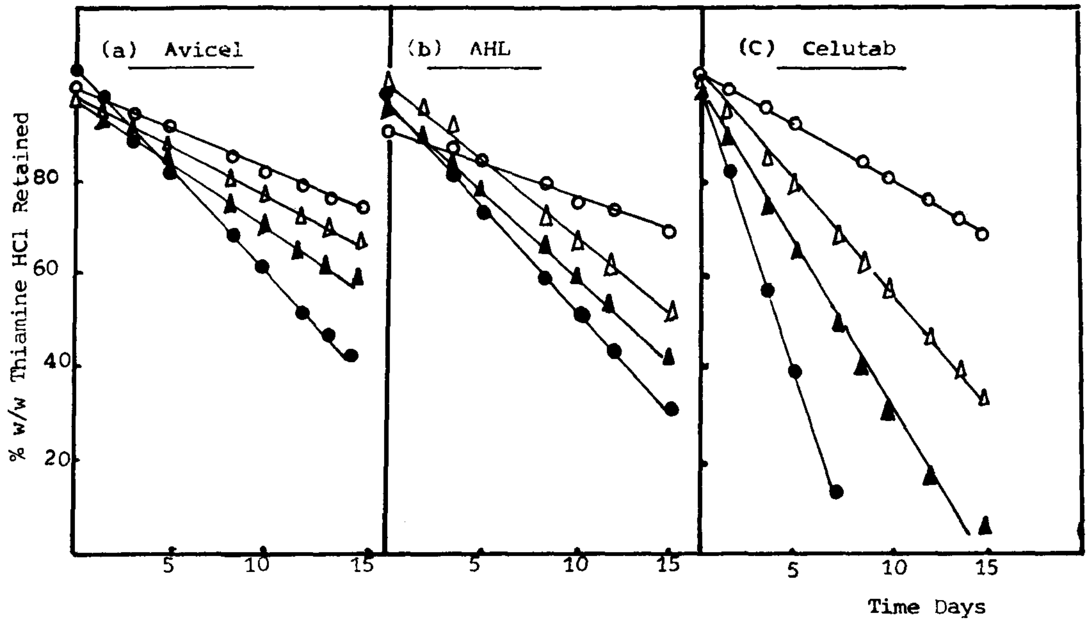



Fig. 3: Effect of varying concentrations of Different, Vehicles on Decomposition of Thiamine HCl in Tablets compressed with O 79.6, Δ 85.29, ▲ 88.29 and ● 90.46% w/w of Named Vehicles.

in the formulation of tablets may contain a certain amount of moisture in the form of "free" or "bound" water, it may be reasoned therefore that the linearity established between log C and log K. In Fig. 4 is really a reflection of the relationship between moisture content and the degradation rate constant, K.

Figs 5(a,b) show that thiamine hydrochloride tablets compressed with a blend of either Avicel or Anhydrous lactose, USP with either Celutab or Emcompress were more stable than those compressed with either Celutab or Emcompress alone. A combination of Avicel and Celutab would yield a binary blend of how moisture content and thus provides a millieu in which thiamine hydrochloride remains

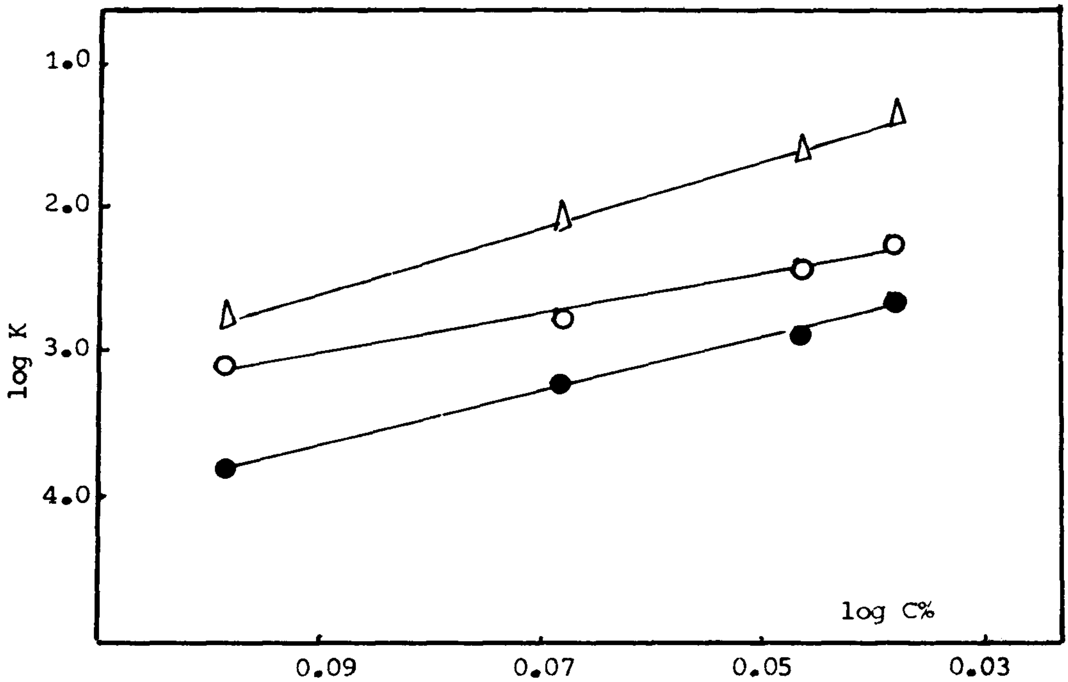



Fig. 4: log K vs log C% for Decomposition of Thiamine HCl in Tablets compressed varying concentrations of Δ Celutab, o AHL and ● Avicel.

stable. The replacement of Emcompres with Avicel or/and Anhydrous lactose would also constitute a vehicle within which the vitamin would be stable. Thus, Avicel and Anhydrous lactose have some stabilising effect arising from their low moisture content. On the other hand, the reduction or elimination of Emcompress in the blend would of course decrease the alkalinity of the system which is the major cause of instability of thiamine hydrochloride. Emcompress should therefore not be used or if used, the amount should be limited in the formulation of thiamine hydrochloride tablets. Table 5 contains some stability parameters for thiamine hydrochloride tablets compressed with binary blend

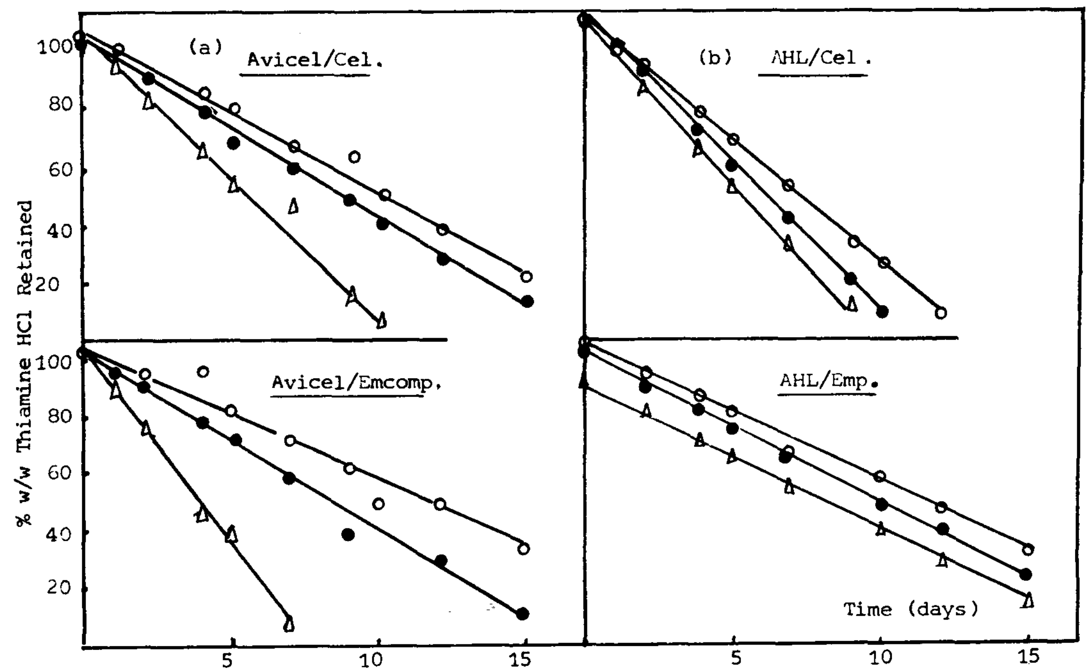



Fig. 5: Decomposition Pattern of Thiamine HCl in Tablets compressed with 90.46% w/w of vehicles and stored at 70°C. Key o 3:1, ● 1:1 and Δ 1:3

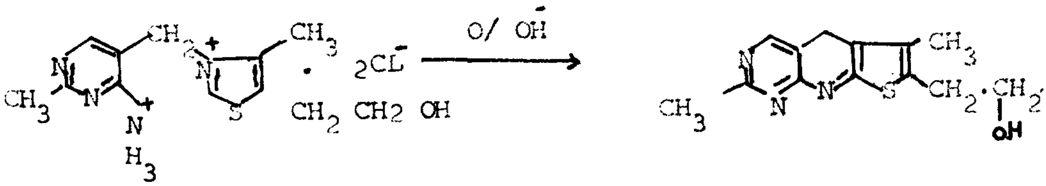
of vehicles and subjected to a temperature of 70°C. The incorporation of Avicel or Anhydrous lactose in the blends generally reduced the value of K.

The physical appearance of tablets stored at different temperatures is in agreement with the results discussed so far. The colour of tablets compressed with Avicel or Anhydrous lactose, USP remained unchanged. On the other hand, tablets formulated with either Emcompress or Celutab changed from white to yellow or white to brown. The degree of colour change varied with the storage condition. The colour change on tablets compressed with Emcompress was

Table 5: Some Stability Parameters for Thiamine Hydrochloride Tablets Compressed with 90.46% w/w Binary Blend of Vehicles and stored at 70°C for Varying Length of Time.

| Complementary Vehicle | Ratio | $KX10^{-4}$ $h^{-1}$ | % Change in K $100\,(1-\frac{KB}{KS})$* | $t_{1/2}$ (h) |
|---|---|---|---|---|
| | | | Avicel Blends | |
| | 1:1 | 22.83 | -21.70 | 302.23 |
| AHL | 1:3 | 14.57 | -50.03 | 473.57 |
| | 3:1 | 23.86 | -18.12 | 289.18 |
| | 1:1 | 62.69 | -61.02 | 110.06 |
| Celutab | 1:3 | 93.90 | -41.61 | 73.48 |
| | 3:1 | 41.39 | -74.0 | 166.71 |
| | 1:1 | 61.144 | - 9.90 | 112.30 |
| Emcompress 9 | 1:3 | 104.41 | +53.70 | 66.08 |
| | 3:1 | 28.03 | -58.73 | 246.16 |
| | | | AHL Blends | |
| | 1:1 | 75.84 | 52.84 | 90.98 |
| Celutab | 1:3 | 137.55 | 14.466 | 50.16 |
| | 3:1 | 110.30 | 31.40 | 62.55 |
| | 1:1 | 36.36 | -53.52 | 189.77 |
| Emcompress | 1:3 | 45.80 | -32.57 | 150.66 |
| | 3:1 | 32.31 | -52.44 | 213.56 |

*$K_B$&Ks Stand for reaction rate constant of thiamine HCl in tablets compressed with binary blends of vehicles and single vehicles respectively.



Scheme I Alkaline oxidation of thiamine hydrochloride into thiochrome.

probably due to alkaline oxidation of thiamine hydrochloride to thiochrome (22). This is illustrated in Scheme I.

This oxidation product thiochrome, was diluted and isolated by a well established thin layer and paper chromatographic techniques (22). Tablets formulated with Celutab developed a brown colour after a short storage period at elevated temperature. This was probably due to interaction between the primary amine group of the thiamine hydrochloride and the dextrose in Celutab. A similar result was reported by Castello and Mattocks (23) who investigated the reaction between amphetamine sulphate and lactose. The end product of such browning reactions is usually 5-methyl hydroxyfuraldehyde, (5-MHF).

The physical properties of the directly compressed tablets stored on the shelf were monitored during a period of one year. Table 6 shows that there was a general increase in tablet weight, thickness and diameter resulting from moisture uptake during this period. There was a decrease in hardness and an increase in friability with hardly any significant change in the disintegration times of these tablets. This suggests that their disintegration depended on the vehicle rather than the hardness of the tablets.

Table 6: The Effect of Shelf Storage* on the Physical Characteristics of vitamin Tablets Compressed with 90.46% w/w of vehicles

| Vehicle | Weight (g) Mean ± (SD) | Thickness (mm) Mean ± (SD) | Hardness $MNm^{-2}$ Mean ±(SD) | Disint. Time (min) Mean ± (SD) | Physical Appearance |
|---|---|---|---|---|---|
| Avicel (A) | 0.26015(0.015) | 3.21(0.211) | 12.64(2.5) | 1.51(0.3) | White |
| AHL (B) | 0.26011(0.031) | 2.75(0.29) | 6.58(1.6) | 10.0(1.2) | " |
| Celutab (C) | 0.2605(0.057) | 2.79(0.16) | 7.15(2.7) | 3.5(1.8) | Faint Brown |
| Emcompress(D) | 0.2511(0.055) | 2.015(0.17) | 12.16(3.11) | 38.61(8.11) | White |

* For one year

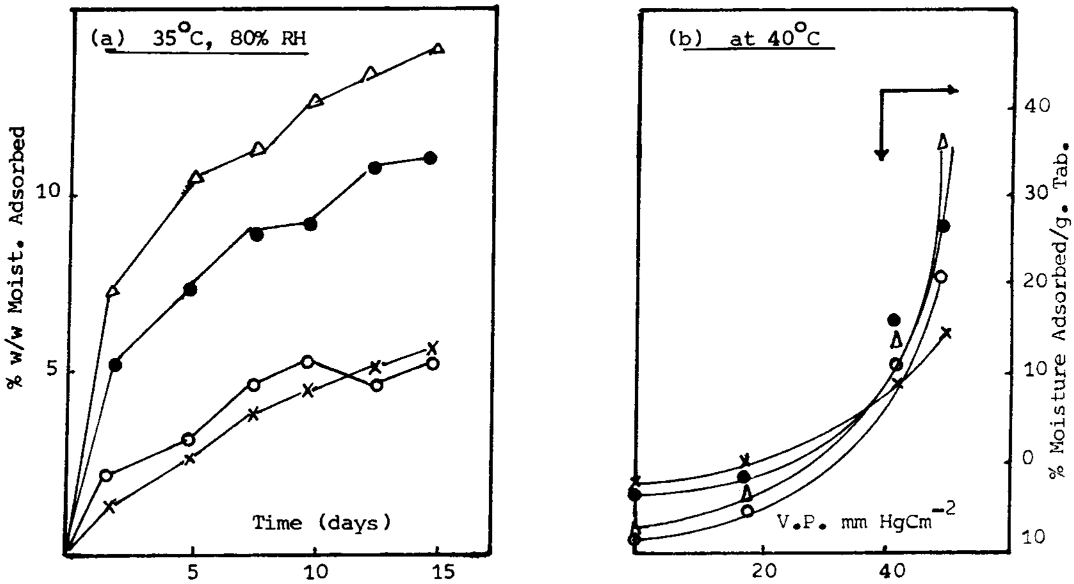



Fig. 6: Moisture Uptake-Time Profile (a) and Moisture Adsorption Isotherm (b) for Thiamine HCl Tablet Systems. Key Δ Celutab, ● AHL, O Avicel and X Emcompress.



The moisture adsorption isotherm and moisture uptake - time profiles of thiamine hydrochloride tablets are shown in Fig. 6. Under varying humidity conditions, the decomposition of the vitamin contained in tablets formulated with either Avicel or a blend of Avicel with another vehicle deviated from first order mechanism. The decomposition followed an equilibrium degradation phenomenon. This (Fig 7) pattern of degradation by thiamine hydrochloride tabletted with microcrystalline cellulose has been reported by Carstensen et al (15). These authors showed that a linearity exists between the amount of intact thiamine (A) and the time t, only if the equilibrium constant ($A_\infty$), of thiamine is taken into account. Thus

$$\log (A - A_\infty) = - kt \qquad \text{Eq. } 2$$

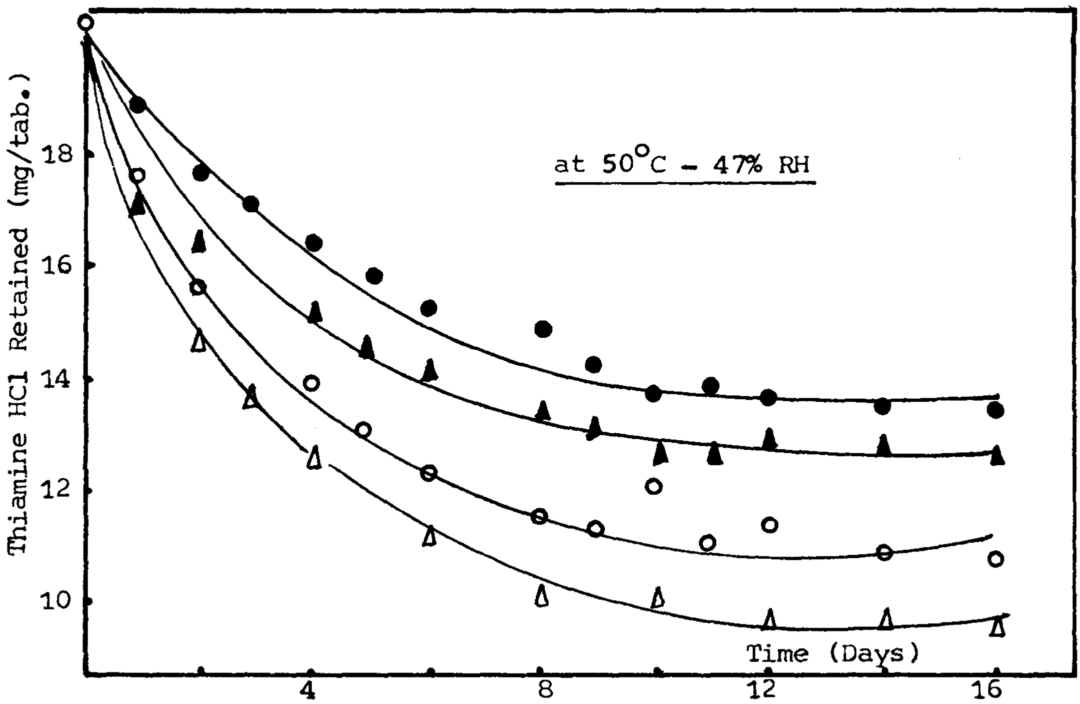



Fig. 7: Decomposition Pattern of Thiamine HCl in Tablets Compressed with 90.46% w/w of ● Avicel, 1:1 Avicel Blends with ▲ AHL, O Celutab and Δ Emcompress.

where K is the decomposition rate constant. This expression was applied to the degradation data of thiamine hydrochloride contained in a binary vehicle constituted with Avicel and any of the other direct compression vehicles. The values of k obtained are shown in Table 7. A plot of per cent thiamine hydrochloride remaining vs per cent moisture absorbed is shown in Fig. 8. It can be seen that the maximum instability of thiamine hydrochloride was at a point when the tablets adsorbed 4.6% of their weight of moisture. This agrees with the result obtained by Carstensen et al (15) who observed that more than 5% moisture content increased

Table 7: Decomposition Rate Constant K, for Thiamine Hydrochloride in Tablets Compressed with Avicel Binary Blends and Stored at Confined Conditions.

| | $KX10^{-3}$ $h^{-1}$ For Batches Stored at | |
|---|---|---|
| | 35°C, 80% RH | 50°C 47% RH |
| Avicel | 2.90 | 4.50 |
| Avicel/AHL | | |
| 1:1 | 4.40 | 6.6 |
| 1:3 | 4.90 | 9.40 |
| 3:1 | 3.30 | 5.80 |
| Avicel/Celutab | | |
| 1:1 | 3.90 | 3.0 |
| 1:3 | 4.20 | 4.70 |
| 3:1 | 3.60 | 2.70 |
| Avicel/Emcompress | | |
| 1:1 | 3.8 | 3.90 |
| 1:3 | 4.50 | 4.80 |
| 3:1 | 3.10 | 3.30 |

the stability of thiamine hydrochloride tablets formulated with microcrystalline cellulose. This is also reflected in Fig. 8 which shows that the stability of the tablets increased when more than 4.6% moisture was taken up by the tablets. The amount of moisture taken up by a tablet may depend on the nature of the vehicle. It would seem that a vehicle that retains 5% w/w moisture would promote the stability of thiamine hydrochloride. Where a single vehicle cannot retain this amount of moisture, a particular combina-

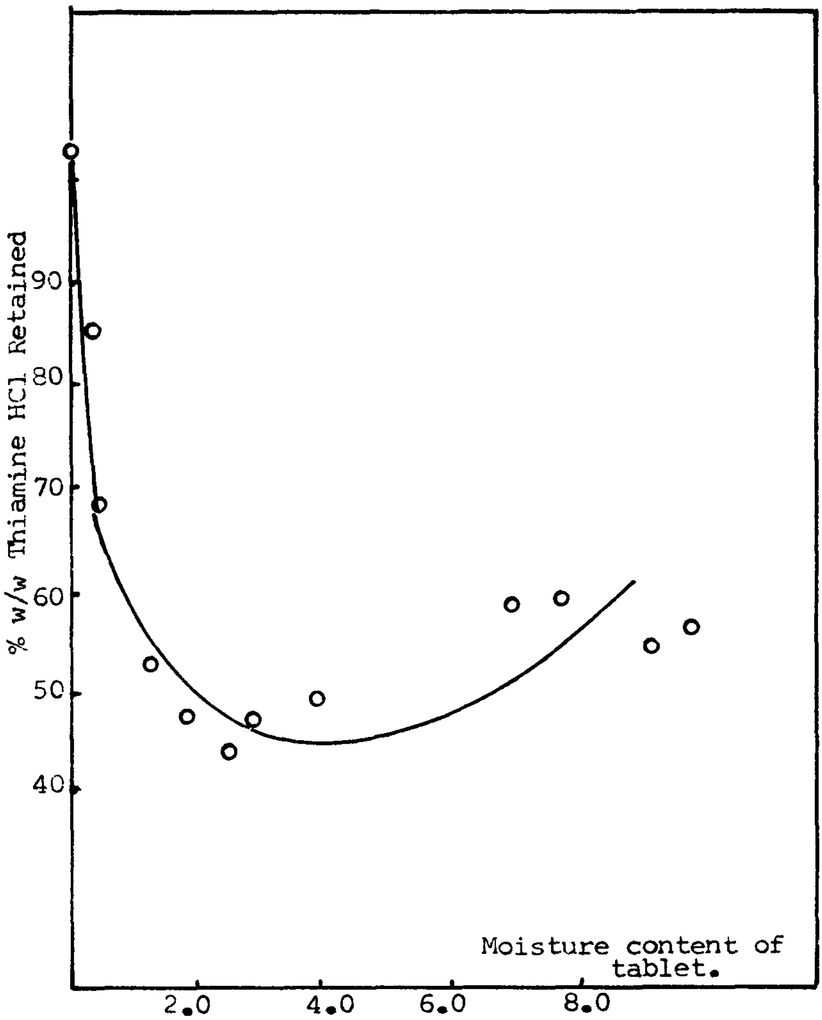



Fig. 8: Thiamine Hydrochloride (%) Retained as a Function of Moisture Content of Tablets.

tion of vehicles such as Celutab and Avicel may retain the requisite amount of moisture that increases the stability of thiamine hydrochloride tablets. Fig. 9 shows that a 3:1 combination of Avicel and Celutab provides such a vehicle. Fig. 9 also shows that a vehicle of low moisture absorption capacity such as Anhydrous lactose when blended with Avicel,

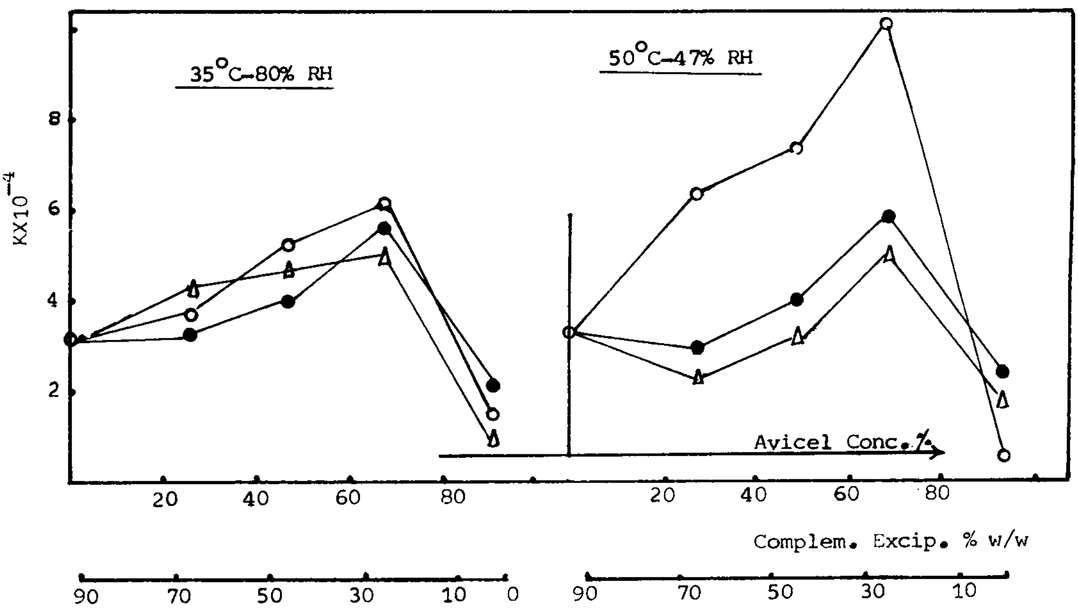



Fig. 9: Reaction Rate Coastant K, as a Function of Vehicle Concentration For Thiamine Hydrochloride batches compressed with 90.46% w/w of Avicel Binary Blends with O Emcompress, ● AHL and Δ Celutab.



yields a suitable tablet base for the formulation of thiamine hydrochloride. It is shown in Fig. 10 that thiamine hydrochloride tablets compressed with AHL, Celutab, Emcompress and binary blends of these vehicles degraded by a first order mechanism. Carstensen et al (15) suggested that the degradation of this drug in such tablet bases should attain equilibrium but recognised that it is rather difficult to detect the equilibrium phenomenon in such soluble systems such as AHL and Celutab. It would seem that for the equilibrium phenomenon to occur, the vehicle must have affinity for adsorbing the drug. The soluble vehicles will now contribute to form a solid-liqued interface where the drug can be adsorbed. The equilibrium phenomenon may well be obvious if

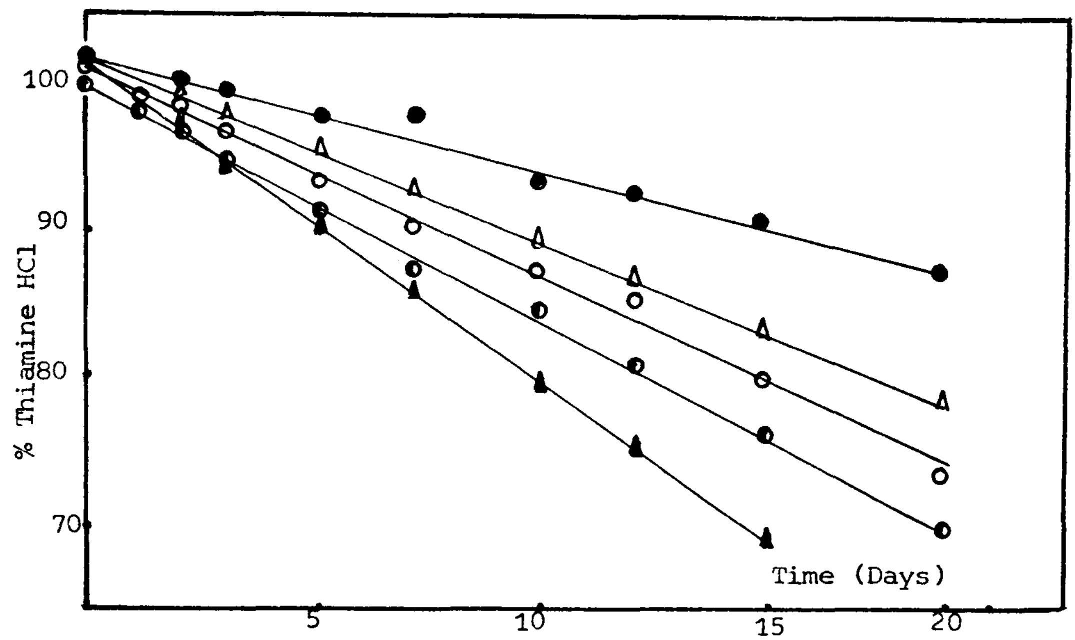



Fig. 10: Decomposition Pattern of Thiamine Hydrochloride in Tablets Compressed with 90.46% w/w of ● AHL, Δ AHL/Celutab 1:1 Binary Blend ○ Celutab, ◐ Emcompress and ▲ AHL/Emcompress 1:1 Binary Blend.

the soluble vehicle and the drug were involved in some other physical interaction. The degradation of thiamine hydrochloride therefore followed a first order mechanism since none of the vehicles interacted physically with the drug. The variation of the degradation rate constant k, with the amount of moisture adsorbed is shown in Fig 11. The stability parameters presented in Table 8. lend further support to the fact that k depends on the amount of moisture adsorbed by the vehicle. There is a log-linear relationship between the decomposition rate constant k and the moisture content of the tablet.

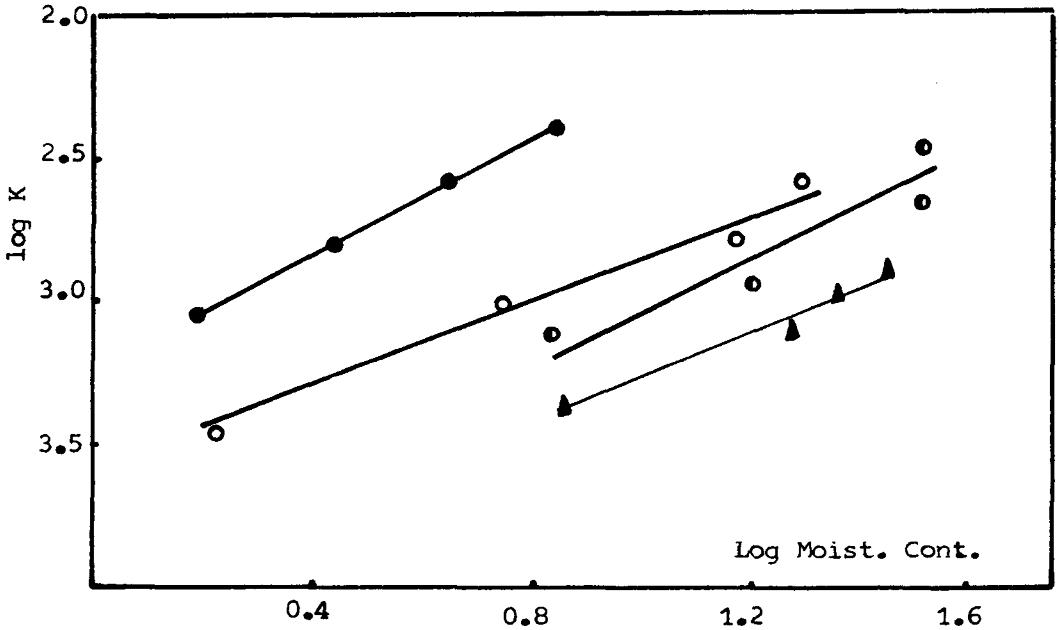



Fig. 11: log Reaction Rate Constant K, as a Function of log Moisture Content of Thiamine Hydrochloride Tablets compressed with 90.46% of ● AHL, o Avicel, ◐ Celutab and ▲ Avicel/Celutab 1:1 Binary blend.

## CONCLUSION

The results obtained in this investigation show that thiamine hydrochloride in different direct compression tablet vehicles when stored at elevated temperature, decomposed by a first order mechanism. The degradation was amenable to treatment with Arhenius equation. Thiamine hydrochloride in tablets compressed with Avicel or a blend of Avicel with another vehicle showed an equilibrium phenomenon during degradation. This was not observed with the other vehicles irrespective of whether they are soluble or insoluble. The phenomenon may depend on adsorptivity of the

Table 8: Some Stability Parameter of Thiamine HCl in Tablets Compressed with 90.46% w/w of Single and Binary Blends of Vehicles and stored at Confined Conditions.

| Vehicle | 28°C 100% RH | | | 50°C, 47% RH | | |
|---|---|---|---|---|---|---|
| | Moisture Content % w/w | Decomp. Rate Const. $KX10^{-4}h^{-1}$ | $t_{1/2}$ Days | Moisture Content % w/w | Decomp. Rate Const. $KX10^{-4}h^{-1}$ | $t_{1/2}$ Days |
| AHL | 6.51 | 7.31 | 39.33 | 11.58 | 12.50 | 22.82 |
| Celutab | 10.89 | 5.12 | 56.15 | 21.66 | 13.89 | 21.93 |
| Emcompress | 3.88 | 11.69 | 24.60 | 6.81 | 28.10 | 10.229 |
| AHL Blends | | | | | | |
| Celutab | | | | | | |
| 1:1 | 6.61 | 7.41 | 38.77 | 18.76 | 5.82 | 49.2 |
| 1:3 | 12.52 | 8.98 | 32.01 | 16.88 | 3.41 | 84.09 |
| 3:1 | 7.85 | 11.30 | 39.66 | 10.11 | 6.20 | 46.37 |
| Emcompress | | | | | | |
| 1:1 | 6.299 | 12.899 | 22.28 | 6.91 | 14.41 | 19.95 |
| 1:3 | 2.96 | 17.57 | 16.36 | 4.77 | 16.51 | 17.45 |
| 3:1 | 6.20 | 14.44 | 19.90 | 11.3 | 17.09 | 16.82 |

vehicle for the drug and not on its solubility. It was found that thiamine hydrochloride was most unstable when the moisture content was 4 - 6% of the tablet weight. This agrees with results obtained by Carstensen (21). The reaction rate constant depends on the amount of moisture absorbed. The physical properties of the tablets obviously changed due to water absorption. The general conclusion from this investigation is that either Avicel alone or a 3:1 blend of Avicel and Celutab constitutes a vehicle which is suitable for the manufacture of thiamine hydrochloride tablets.



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## FOOTNOTES

1. FMC Corporation, Avicel Dept. Pennsylvania USA
2. Shiffield Union, N.L., 07083 USA.
3. E. Mendell Co. Inc., USA
4. Hoffman La-Roch, Basle, Switzerland.
5. E. Merk N.J. USA.
6. BDH Chemicals Ltd., Poole U.K.
7. Manesty Machine Ltd., Liverpool, U.K.

## REFERENCES

1. J.W. Warren and J.C., Price, J.Pharm. Sci., 66, 1409-12 (1977)

2. M.D. Richman, C.D. Fox and R.F. Shangraw, ibid, 54, 447 (1965).

3. F.W. Goodhart, H. Gucluyildiz, R.E. Daly, L. Chafetz and F.C. Ninger., ibid, 65, 1466 (1976).

4. J.A. Campbell and H.A. McLeod, J.Amer. Pharm. Assoc. Sc. Ed., 44, 263 (1955).

5. E.R. Garrett, ibid, 45, 171 (1956).

6. R.F. Prindle, Proc. A.A.A.S., Dec. 1950.; through ref. 4.

7. A.H. McLeod, O. Pelletier and J.A. Campbell Can. Pharm. J. 3, 55 (1958).

8. R. Tradif, J.Pharm. Sci., 54, 281 (1965).

9. A. Taub, I. Katz and M. Katz, ibid 38, 119 (1949).

10. G.B. Stone, ibid, 39, 159 (1950).

11. A.A. Kassem, N.A. Rofaiel, S.W. Amin and E. Ghazy Drug Res. J., 1, 39 (1968).

12. W.J. Lhoest, L.W. Busse and C.A. Baumann, J.Amer. Pharm. Assoc., 47, 254 (1958).

13. J. T. Windheuser and T. Higuchi, J.Pharm. Sci, 51, 354 (1962).

14. W. D. Shah and A. Arambulo This Journal 6, 495 (1974-75).

15. J. T. Carstensen, M. Osadca and S.H. Rubin, J.Pharm. Sci, 58, 549 (1969).

16. A. M. Kassem, 1975 in a Thesis submitted for partial fulfilment of M.Pharm. to Faculty of Pharmacy, Cairo University Cairo Egypt.

17. A. M. Sakr, A.A. Kassem, A.A. Aziz and A.H. Shalaby, Canad. J. Pharm. Sci, 8, 6 (1973).

18. D. V. Gupta and D. E. Cadwallder, J. Pharm. Sci, 57, 2 (1968).

19. K. Wai, G.H. DeKay and G.S. Banker, ibid., 51, 1076 (1965).

20. S. A. Sangekar, M. Sarli, and P.R. Shelt, ibid, 61, 939 (1972).

21. J. T. Carstensen, ibid, 53, 839 (1964).

22. M. A. Hashim in "Assay of Vitamins in Pharmaceutical Preparations", (1979), John Wiley & Sons 3rd Ed. pp. 49.

23. R. A. Castello and A.M. Mattocks, J. Pharm. Sci., 51, 106 (1962).