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DEGRADATION KINETICS OF THIAMINE HYDROCHLORIDE IN DIRECTLY COMPRESSED TABLETS II: RELIABILITY OF ACCELERATED STABILITY TESTING FOR EVALUATING TABLET FORMULATIONS

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ABSTRACT

Directly compressed thiamine hydrochloride tablets formulated with single or binary blend of vehicles were used in this investigation. The change in the physical characteristics of vitamin tablets stored under different relative humidity conditions was statistically assessed and scored by relative ranking. Although Emcompress is known to accelerate drug decomposition (1,2) the results obtained with tablets formulated with this vehicle alone or in combination with other vehicles failed to show that the use of this vehicle may give rise to any discernible changes in the physical characteristics of the tablets. Although formulations containing Celutab as the vehicle are chemically stable (2) the tablets compressed with this vehicle showed a high

degree of change in physical characteristics. The results obtained in this study indicate that Avicel alone or a blend of Avicel with either Celutab or Anhydrous lactose are suitable vehicles for the manufacture of thiamine hydrochloride tablets of high stability characteristics.

INTRODUCTION

The basis and fundamental aspects of chemical stability of solid dosage forms is now well established (3-6). Garrett (3) introduced accelerated stability testing as a reliable mathod for predicting shelf life of pharmaceutical preparations. Carstensen (4) reviewed different theories and models that explain the mechanism of drug decomposition. Preformulation screening programms designed to detect drug decomposition or/and drug excipient interaction have also been reviewed in a number of publications (5-8). Highly sophisticated analytical tools have facilitated the study of chemical changes in drugs contained in dosage forms. So far, no simple relationship has been designed for extrapolating the effect of ageing under stress conditions to the change in physical characteristics of the stored form. Available published results only record the changes which

occur in the dosage forms as a result of ageing. Sangekar et al (9) made use of such changes in their application of relative ranking method as a statistical tool in assessing different direct compression formulation. Horhota et al (10) pointed out that there is no simple relationship between the change in dissolution efficiency DE, of a given formulation and the storage conditions. Chowhan (11) also observed and reported similar results.

The aim of this work was to use accelerated stability testing for evaluating different batches of direct compression tablet formulations containing thiamine hydrochloride. Due to the inherent instability of the drug (12) change in dissolution efficiency DE, was not used as one of the criteria.

EXPERIMENTAL

Materials: The direct compression vehicles used in this investigation were Avicel PH (101)[1], Anhydrous lactose USP[2], Celutab[3] and Emcompress[3]. Magnesium stearate[4] was incorporated in the formulation as lubricant.

METHODS

Formulation and Compression of Tablets:

Batches of powder mix containing 1 part of thiamine hydrochloride and 4-10 parts of a given single or binary blend of direct compression vehicle were blended in a laboratory drum mixer[I] for 15 mins. An F_3 single punch tabletting machine[II] fitted with flat punches of 3/8 inch diameter was used for compressing the tablets. Each blend was compressed into 0.25g vitamin tablets and the tablets were evaluated according to methods which have been reported previously (13, 14). The physical properties of the vehicles used and the tablets formulated with single or binary vehicles are given in Tables 1 and 2 respectively.

Moisture adsorption by Tablets:

The technique used by Wai et al (15) and Sangekar et al (9) respectively was adapted for the study of both the moisture adsorption isotherm and moisture adsorption time profiles of the tablets.

A given batch of tablets was divided into four samples out of which one was used as a control

Table 1: Some Physical Characteristics of Powdered Thiamine Hydrochloride and Direct Compression Excipients Used in Manufacture Vitamin Tablets

Material	Particle[-a] Size Range (u)	True[-b] Density g/cc	Pacting fraction (Pf)	Moist.[-b] Content % w/w
Thiamine HCl	180.48	1.546	0.4366	4.76
Avicel	82.99	1.502	0.236	2.47
AHL	185.07	1.683	0.332	0.35
Celutab.	342.58	1.72	0.397	9.75
Emcompress	194.61	2.215	0.407	4.25

a. Data obtained from Ref. 13

b. Mean of 5 determinations.

Table 2: Some Physical Characteristics of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of Named Vehicles and 1:1 Binary Blends

Vehicle	Weight (g)		Thickness (mm)		Hardness MNm^{-2}		Disint. Time		Packing Fraction Pf
	Mean	C.V.%	Mean	C.V.%	Mean	C.V.%	Mean	C.V.%	
Avicel (A)	0.2547	1.53	2.96	0.722	21.26	4.23	1.24	48.84	0.809
Anhydrous lactose USP (B)	0.2558	3.19	2.72	1.33	9.135	6.43	10.25	2.9	0.791
Celutab (C)	0.24888	2.32	2.768	1.336	11.26	10.83	5.48	11.12	0.747
Emcompress (D)	0.2478	3.5	2.00	2.368	12.33	11.23	45.3	9.48	0.820
1:1 Binary Blends									
A + B	0.2688	5.06	2.91	1.895	16.86	6.98	23.25	5.0	0.85
A + C	0.2586	5.06	2.95	1.159	16.07	7.733	23.58	7.7	0.795
A + D	0.258	4.05	2.59	1.54	17.01	9.80	6.88	6.9	0.794
B + C	0.2858	2.77	2.81	1.56	12.89	6.12	8.41	4.5	0.853
B + D	0.2461	2.89	2.47	2.202	8.38	6.53	8.46	7.4	0.768

under ambient temperature and humidity condition. The other three samples were stored under 100% RH at 28°C, 80% RH at 35°C and 47% RH at 50°C respectively.

Evaluation of Stored Tablets:

The stored tablet samples were periodically assessed for changes in physical characteristics resulting from water uptake. The physical characteristics investigated included hardness, disintegration time, tablet diameter, thickness and volume. The effect of moisture adsorption and the storage temperature on the absolute drug content of a given formulation was also assessed. The method used for the analysis of the drug, thiamine hydrochloride has been fully reported else where (2).

RESULTS AND DISCUSSION

It has been recognised that there are legal, moral economic and competitive reasons as well as those of safety and efficiency to monitor, predict and evaluate drug product stability (5). The use of direct compression technique in manufacturing tablets is expected to produce stable drug products of therm-

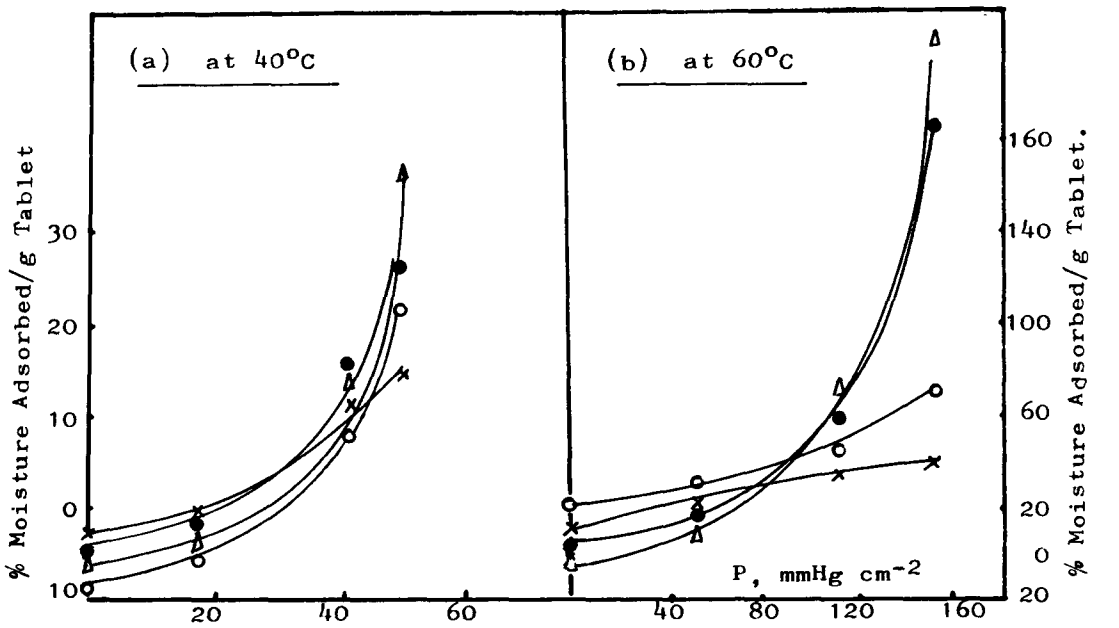


Fig. 1(a,b) Moisture Adsorption Isotherm of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w Δ Celutab ● AHL, ○ Avicel and × Emcompress

olabile and moisture sensitive drugs (13). The stability of drugs contained in direct compression compacts is dependent on the moisture content of the vehicles used in the formulation. Moisture adsorption capacity of the vehicle is an important factor which plays a vital role in stability characteristics of the compacts. The moisture adsorption isotherms obtained for drug/vehicle tablet system are shown in Fig. 1 (a,b). These figures show that the type of vehicle used in the formula-

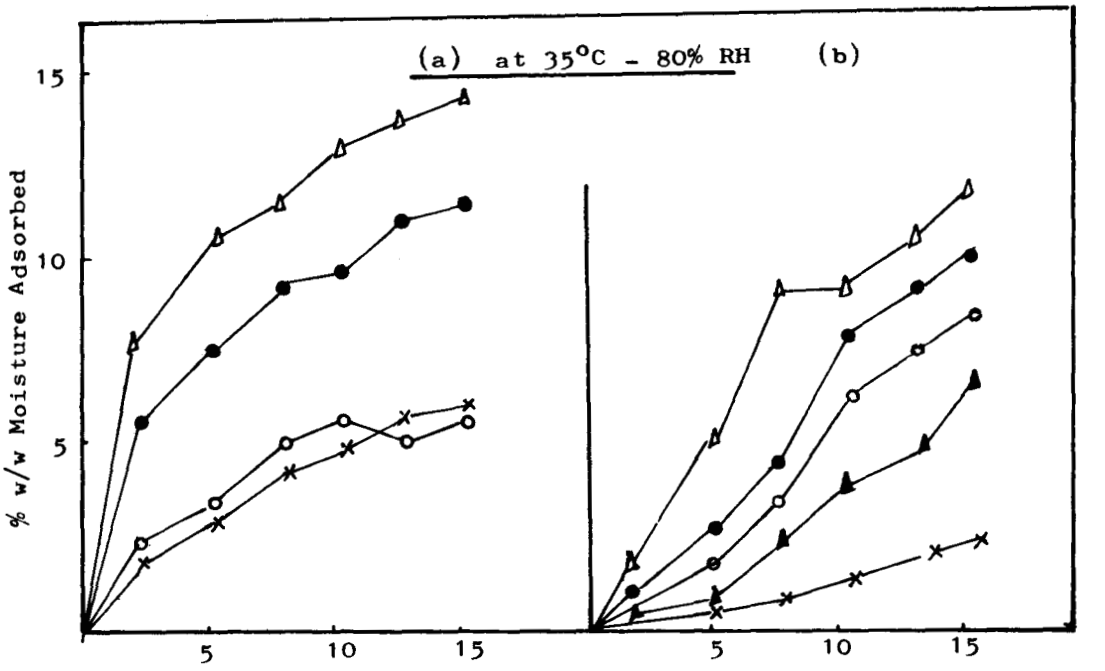


Fig. 2 (a,b) Moisture Adsorption-Time Profile of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of (a) Δ Celutab, ● AHL, ○ Avicel and × Emcompress and (b) 1:1 Binary Blends of Δ Celutab/Avicel, ● Celutab/AHL, ○ Celutab/Emcompress ▲ Avicel/AHL and × Avicel/Emcompress.

tion affected the degree of moisture adsorption. The van der Waal type moisture adsorption isotherm exhibited by each formulation was influenced by the vapour pressure. Fig. 2 shows moisture adsorption time profiles for the thiamine hydrochloride tablet batches investigated. The degree of moisture adsorption was influenced by the type and concentration of the complementary vehicles incorporated in each formulation. Both Fig. 2 and Table 3 show that

Table 3: Effect of Storage* at 28°C, 100% RH on Moisture Uptake M, Diameter D, Thickness h, and Disintegration Time Dt, for Thiamine Hydrochloride Tablets Compressed with 90.46% of Named Vehicles

Vehicle	M ± (SD) % w/w-a	D ± (SD) (mm)-b	h ± (SD) (mm)-b	Dt ± (SD) (min)-c
Avicel (A)	2.18(0.98)	9.93(1.3)	3.69(1.3)	3.3(1.35)
AHL (B)	3.98(1.3)	9.99(1.6)	3.00(0.12)	3.45(1.95)
Celutab (C)	6.18(0.78)	9.97(0.86)	2.97(0.68)	4.68(1.80)
Emcomp. (D)	1.69(0.81)	9.77(0.85)	2.15(0.86)	32.7 (5.68)
		1:1 Binary Blends		
A + B	4.69(1.68)	9.74(1.3)	3.1 (0.82)	8.11(3.26)
A + C	9.79(3.8)	9.97(0.72)	3.51(0.18)	14.5 (2.15)
A + D	1.65(0.21)	9.81(1.5)	2.88(1.5)	6.61(1.9)
B + C	4.3 (1.2)	9.8 (0.78)	2.9 (1.5)	2.78(1.15)
B + D	4.8 (2.2)	9.81(1.31)	2.5 (0.7)	5.6 (1.91)

* Samples were stored for 5 days
a. Mean of 5 determinations b. Mean of 10 determinations
c. Mean of 6 determinations.

of all the formulations investigated, tablet batches formulated with Emcompress showed the least adsorptive capacity while those formulated with Celutab alone or a blend of Celutab with another vehicle showed the highest adsorptive capacity. The same tablet also shows that tablets compressed with Emcompress/Anhydrous lactose combination showed the least tendency for moisture adsorption.

Moisture adsorption by tablets would generally affect their physical standards and absolute drug content for moisture sensitive drugs. Fig. 3 shows that the adsorption of moisture caused a decrease in the hardness of the tablets. The highest reduction in hardness were recorded to those tablets compressed with either Celutab alone or a blend of Celutab and Anhydrous lactose USP. After five days storage at $50^{o}C$ and 47% RH, the hardness of tablets compressed with 90.46 w/w of Celutab changed from 11.26 to 0.7 MNm^{-2}; also the tablets became soft and sticky. A change in tablet hardness resulting from moisture adsorption may be brought about by two possible mechanisms. Initially the moisture adsorbed may actually cause an increase in hardness due to the binding effect of water. Then further

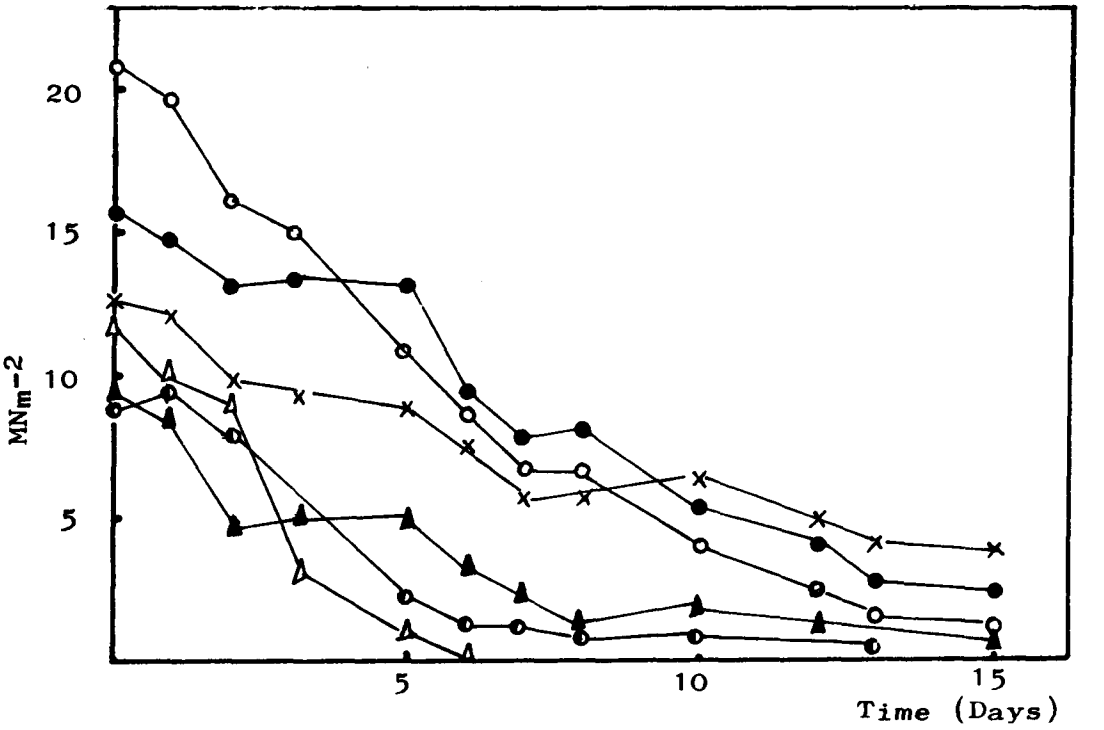


Fig. 3: Effect of Storage at 35°C, 80% RH on Hardness of Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of ○ Avicel, ● AHL, x Emcompress, Δ Celutab and 1:1 Avicel Binary Blends with Δ Celutab, ▲ AHL, ●

adsorption of moisture would bring about the enlargement of particles in the tablet matrix. This will generally increase the surface area and thereby weaken interparticular bonds. It is also, possible that a decrease in hardness was brought about by the solvent effect of the adsorbed moisture. The change in volume of the tablets under the specified storage conditions. The inspection of the data presented

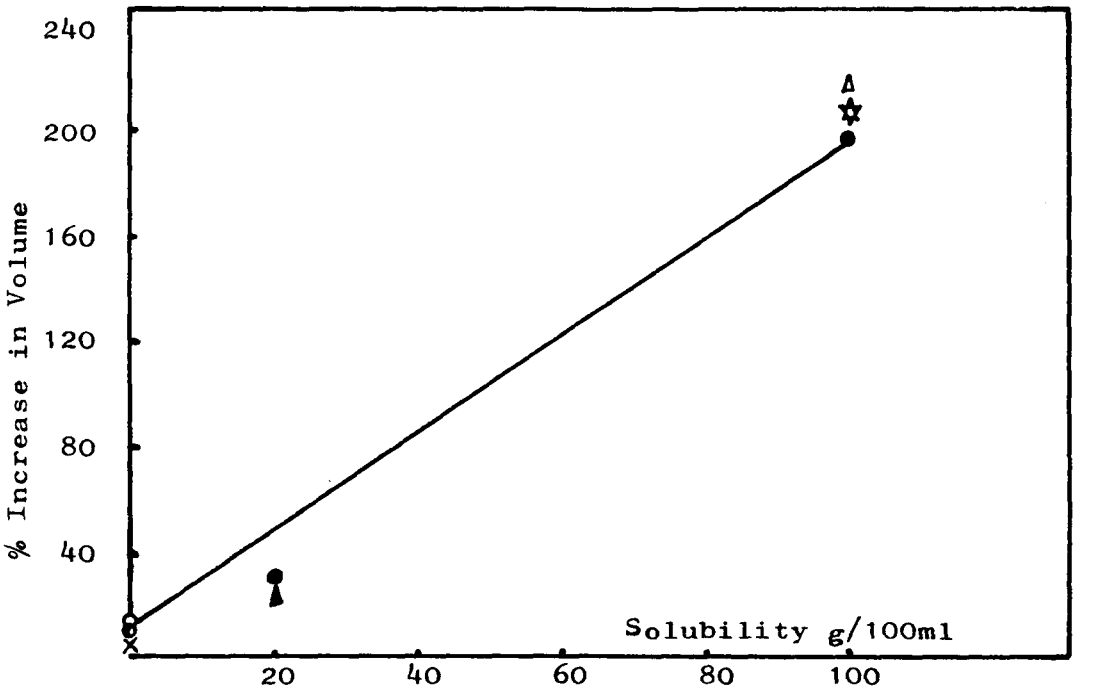


Fig. 4: Increase in Tablet Volume (%) as a Function of Vehicle Solubility for Different Thiamine Hydrochloride Tablet Formulations.

in Table 3 shows that a maximum increase in tablet thickness was recorded for the tablets formulated with Avicel. On the other hand, tablets formulated with Anhydrous lactose USP showed the highest increase in diameter. A plot of the increase in tablet volume against the solubility of vehicle used in formulation is shown in Fig. 4. This agrees with the results obtained by Sangekar et al (g) who pointed out that increase in tablet volume

Table 4: Summary of Ranking and Relative Scoring for Change in Physical Properties of Thiamine Hydrochloride Tablets Stored at 28°C; 100% RH, 35°C; 80% RH and 50°C; 47% RH.

Excipient	% w/w Moisture Adsorbed	Hardness MNm^{-2}	Disint. Time (min)	Change in volume (%)	Summ. of Ranking	Relative Scoring
Avicel (A)	6.0	4.0	2.0	12.0	24.0	4.0
AHL (B)	13.0	7.0	5.0	14.0	39.0	12.0
Celutab (C)	19.0	19.0	_a	_b	238.0	19.0
Emcomp. (D)	7.0	1.0	15.0	3.0	26.0	5.0
1:1 Binary Blends						
A + B	9.0	3.0	14.0	9.0	35.0	8.5
A + C	2.0	2.0	13.0	6.0	49.0	14.0
A + D	15.0	15.0	1.0	_b	231.0	15.0
B + C	8.0	14.0	3.0	2.0	27.0	6.0
1:3 Binary Blend						
A + D	1.0	6.0	12.0	1.0	20.0	1.0
B + D	4.0	5.0	9.0	4.0	22.0	2.5

a. Could not be determined b. Change in volume was considered 200%

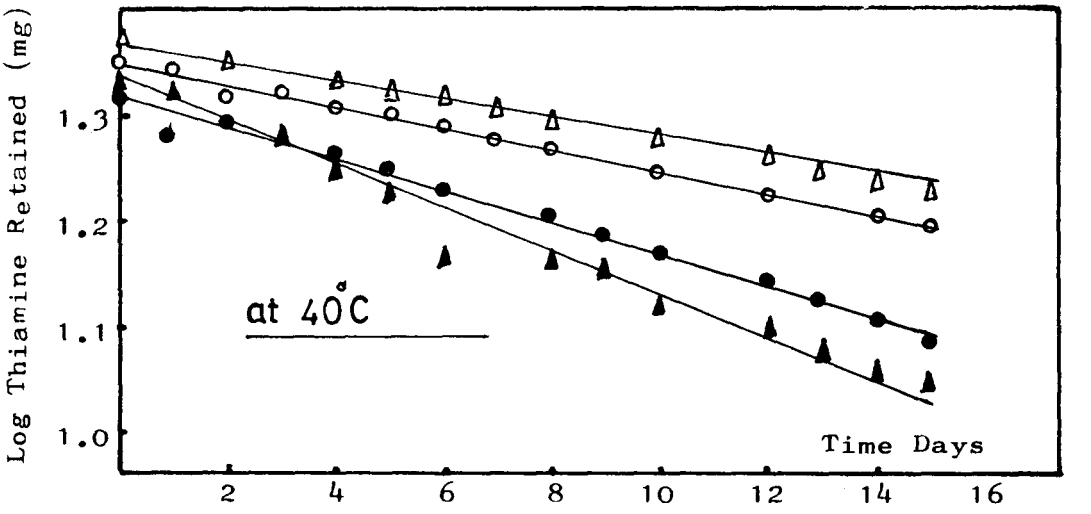


Fig. 5

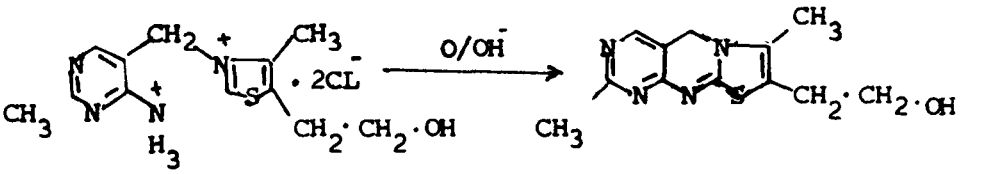
First order Mechanism of Thiamine Decomposition in Tablets Compressed with 90.46% w/w Δ AHL, o Emcomp/AHL 1:3 Binary Blend, ▲ Emcompress and ● AHL/Emcomp 3:1 Binary Blend.

is function of vehicle solubility. Table 4 shows that formulations prepared with Emcompress, a blend of Emcompress with Avicel or Anhydrous lactose scored the highest relative ranking for overall performance. However, these vehicles cannot be recommended for the formulation of vitamin B_1 tablets, due to the hydrolytic effect of Emcompress on the drug (1,2). Fig. 5 shows that Emcompress accelerated the decomposition of the drug by inducing alkaline oxidation of thiamine hydrochloride to thiochrome. This oxidation product was responsible

Table 5: Some Stability Parameters For Thiamine Hydrochloride Tablets Compressed with 90.46% w/w of Named Vehicles and Stored at Confined Conditions

Vehicle	28°C, 100% RH				50°C, 47% RH			
	K x 10^{-4} h^{-1}	Days			K x 10^{-4} h^{-1}	Days		
		$t_{1/2}$	t10%	t90%		$t_{1/2}$	t10%	t90%
Anhydrous lactose (A)	7.31	39.3	6.00	131.3	12.50	22.8	3.50	76.77
Emcomp. (B)	11.69	24.6	3.74	82.09	28.10	10.23	1.56	34.15
A + B								
1:1	12.899	22.3	3.39	77.4	14.41	19.95	3.04	66.67
1:3	17.57	16.36	2.5	54.65	16.51	17.45	2.65	58.12
3:1	14.44	19.9	3.03	66.45	17.09	16.82	2.55	56.15

for the faint yellowish colour acquired by tablets stored at varying relative humidity conditions. The reaction leading to the production of thiochrome is as follows:



Scheme 1 Alkaline oxidation of Thiamine Hydrochloride into Thiochrome.

A thin layer chromatographic technique fully reported in previous publication (16) was used in the identification of the degradation product. Table 5 shows that the decomposition rate constant of the vitamin contained in the tablet increased with increasing concentration of Emcompress. This is reflected in the values of $T_{\frac{1}{2}}$, $T_{10\%}$ and $T_{90\%}$ given in the same table.

CONCLUSION

The formulation factors affecting the stability of drugs in solid dosage forms are complicated and are not easily elucidated. Although adsorbed moisture is a major contributor to the instability of drugs, the results show that other formulation

factors such as the physico-chemical nature of excipients are important.

Formulations prepared with Emcompress when stored under varying conditions of relative humidity showed very little change in physical characteristics. This vehicle however has a hydrolytic effect on thiamine hydrochloride and therefore is not recommended for formulation. The study declared that, there is no simple way of relating physical changes or lack of it to possible chemical degradation of tablet formulation under varying storage conditions.

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FOOTNOTES

1. FMC Corporation, Avicel department, Pennsylvania, USA.
2. Shiffield Union, N.L. 07083 USA.

3. E. Medell Co. Inc. USA.

4. E. Merck Dramstadt W.Germany.

I Forster Equipment Co. Ltd., Leicester, England.

II Manesty Machines Ltd., Liverpool, England.

REFERENCES

1. Shah; D.H., and Arambulo; A., This Journal, 6, 495 (1974-75).

2. Udeala; O.K., and Aly, S.A.S., ibid in press.

3. Garrett; E.R., J.Pharm. Sci., 45, 17 (1958).

4. Carstensen; J.T., ibid, 63, 1 (1974).

5. Garrett; E.R., In "Advances in Pharmaceutical Sciences" Vol. 2 H.S. Bean, A.H. Backett and J.E. Carless, Eds. Academic New York, N.Y. (1967).

6. Van Dooren, A.A., Drug Devel. & Ind. Pharm. 9, 43 (1983).

7. Carstensen; J.T., Johnson, J., Valentine, W., and Vance, J., J.Pharm. Sci., 53, 1050 (1964).

8. Lach; J.L., and Bronstein; M., ibid, 54 173 (1965).

9. Sangekar; S.A., Sarli; M. and Sheth P.R., ibid, 61, 939 (1972).

10. Horheta; S.T., Burgio; J., Lonski; L., and Rhodes; C.T., ibid 56, 1746 (1976).

11. Chowhan; Z.T., J.Pharm. Pharmacol., 32, 10 (1980).

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

13. Aly; S.A.S. and Abu-Taleb, A.E;, Drug Devel. & Ind. Pharm., 11, 945 (1985).

14. Sakr; A.M., Kassem; A.A., Aziz, S.A.A. and Shalaby; A.H., Canad. J.Pharm. Sci., 8, 1, 6 (1973).

15. Wai, K., DEKay; G.H., and Banker; G.S., J.Pharm. Sci., 511, 1076 (1965).

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