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A STUDY OF THE CHEMICAL AND PHYSICAL STABILITY OF ASCORBIC ACID, FOLIC ACID, AND THIAMINE HYDROCHLORIDE TABLETS FORMULATED WITH EMCOMPRESS STANDARD^{R}*

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Abstract: Tablets which were prepared from separate formulations of Emcompress Standard^{R}, a commercially available directly compressible granulation, with ascorbic acid, folic acid, and thiamine hydrochloride were subjected to accelerated aging conditions and studied for chemical stability and such physical parameters as hardness, friability, and disintegration time. Other physical factors which could affect the interpretation of the data, such as moisture content, particle size distribution, angle of repose, weight variation, and hardness were also studied using fresh samples.

Accelerated aging showed that the ascorbic acid formulation was chemically unstable; the tablets became

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soft, the frability increased markedly, and the disintegration time decreased. The folic acid formulation was chemically stable, but the tablets became soft, the friability increased, and disintegration time increased. The thiamine hydrochloride formulation was also chemically stable--the tablets became soft, the disintegration time decreased, and the friability increased.

For most pharmaceutical manufacturers the compressed tablet as a dosage form accounts for a major portion of the product line. The basis for this is the acceptability of this dosage form by both patients and physicians (1).

The traditional methods for preparing compressed tablets are by direct compression, wet granulation, and precompression. Owing to its simplicity and economy, direct compression is the method of choice. Materials which posses all the desirable attributes of a tablet granulation, including bulk, fluidity, binding ability, disintegrability, stability, absorbability, and lubricity, among others, lend themselves to direct compression (2). However, active ingredients rarely posses all of these attributes and, therefore, require processing by one of the other methods.

The availability of directly compressible formulations as Emcompress Standard^{R}, which are so constructed

that all that is presumably required is the dry mixing of the active component resulting in a mixture which may then be compressed into tablets, generates interest. From an industrial standpoint, the reduction in processing time and in the number of processing equipment makes this approach desirable.

Present Federal regulations require stability data (3). Ordinarily, these require time to develop. Procedure and validation of predictive methodology for chemical stability have become available (4). It is desirable to have predictive methodology for physical parameters of tablets, especially those which are presently official in the compendia.

This investigation deals with the study of the stability of ascorbic acid, folic acid, and thiamine hydrochloride in separate Emcompress Standard[R] mixtures. The factors studied were chemical stability, hardness, friability, and disintegration time. These factors were studied through accelerated aging methods. Factors which may affect the interpretation of the data such as moisture content, particle size distribution, angle of repose, weight variation, and hardness were also studied. These tests were performed on fresh samples only.

MATERIALS

The following formulations were studied:

A. Emcompress Standard^R which consists of dicalcium phosphate dihydrate, 89.0 parts; starch, U.S.P., 7.5 parts; magnesium stearate, 1.0 part; and microcrystalline cellulose, 2.5 parts.

B. Ascorbic acid (Merck Lot. No. 60042), 21.0 parts; Emcompress Standard^R (E. M. Mendell Lot No. 3168), 79.0 parts.

C. Folic acid (S.S.T. Corporation Lot No. 1263), 2.2 parts; Emcompress Standard^R, 97.8 parts.

D. Thiamine hydrochloride (Merck Lot No. V1-366-1), 21.0 parts; Emcompress Standard^R 79.0 parts.

METHODS

1. Moisture Content. These tests were carried out by placing about 1.5 Gm. of accurately weighed material in a shallow weighing bottle which has been dried to constant weight, exposing to 102 ± 0.5° C for 24 hours, cooling in a desiccator and weighing the sample until two successive weighings showed no significant change.

2. Particle Size Distribution. These tests were performed using nests of 6 successive sieves on a Cenco-Meinzer sieve shaker and operating the shaker for 25 minutes at slow speed.

3. Angle of Repose. These tests were performed using the fixed funnel method (5). A glass funnel with a stem bore of about 0.3 cm. with its stem tip 3.0 cm. above a quadrille paper was used. Powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel stem.

4. Weight Variation. Formulations were compressed in a Stokes D-3 rotary tablet press using 11/32" punches and dies. Five tablets were collected about every three minutes. The mean weights of each of the sample of five tablets were determined from which the grand mean and the standard error of the mean were calculated.

5. Hardness. The tablets collected as samples for the weight variation test were then utilized for determining the mean hardness using an Erweka hardness tester; the grand mean hardness per batch and finally the standard error of the mean were calculated.

6. Chemical Stability. a) Ascorbic acid was assayed using a titrimetric method with N-bromosuccinimide as reported by Barakat, et. al. (6). b) Folic acid was assayed by extracting with 0.1 N NaOH and taking the absorbance at $_{256}$ mu using a Beckman DBG spectrophotometer (7). c) Thiamine hydrochloride was assayed by extracting with absolute alcohol and taking the absorbance at 250 mu using Beckman DBG spectrophotmeter (8).

General Procedure: About 250 to 300 tablets each were placed in nine loosely capped 4-ounce amber-colored bottles. These samples were placed in three separate ovens which were calibrated at 40, 50, and 60°C. Samples at 60°C were collected at 24, 48, and 72 hours; samples at 50°C, 48, 96, and 144 hours; samples at 40°C at 96, 192, and 288 hours. Great care was employed to prevent the material from absorbing moisture from the room. Before removing the samples from the ovens, each bottle was tightly capped using a strip of aluminum foil as liner. The bottles were then allowed to cool to room temperature for about 30 minutes then stored in a refrigerator at 5° ± 1°C until ready for the assays.

7. Hardness After Aging. Tests were performed as in No. 5 above on samples which have been subjected to accelerated aging.

8. Friability After Aging. Tests were performed on samples which have been subjected to accelerated aging. An Erweka tablet abrasion tester was utilized. Ten tablets which were accurately weighed were used for the test. The drum was allowed to rotate at about 20 rpm for 5 minutes (about 100 revolutions). Friability was expressed as percent loss in weight.

9. Disintegration Time After Aging. Tests were performed on samples which have been subjected to accel-

erated aging. A U.S.P. XVIII basket rack apparatus with plastic disks was used.

RESULTS

The results of the test performed on fresh samples appear on Table I. The information on moisture content is believed to be significant. The fact that the Emcompress Standard[R] contains 4.18% of moisture may have affected the properties of the active compotents added to it, such as the relatively rapid decomposition of ascorbic acid.

The particle size distribution gave a clue as to the values of the angles of repose obtained. The increase in fines, i.e., particles which passed mesh 325, may have caused the increase in angles of repose as suggested by Nelson (9). No data were obtained for thiamine hydrochloride formulation which formed clumps that blinded the sieves.

The weight variation observed follows the trend shown by the angles of repose. The formulation with the greatest angle of repose, thiamine hydrochloride showed the greatest variation. The hardness variation followed the weight variation.

The results of test performed on aged samples are shown in Tables 2 and 3. The folic acid and thiamine

TABLE 1.

Results of Tests Performed on Fresh Samples

		FORMULATION			
		A	B	C	D
1.	Moisture content (%)	4.18	3.30	3.85	3.90
2.	Particle size distribution (%)				
	Retained on Mesh #35	0.05	0.04	0.05	-
	40	0.09	0.07	0.08	-
	45	0.11	0.09	0.11	-
	50	2.67	2.23	2.62	-
	60	8.89	7.18	8.71	-
	70	16.79	13.46	16.46	-
	80	12.87	10.16	12.61	-
	100	15.75	12.46	15.44	-
	120	2.11	1.65	2.07	-
	170	7.59	6.12	7.43	-
	200	4.38	3.47	4.29	-
	325	6.99	5.64	6.85	-
	Passed Mesh # 325	20.07	36.34	23.23	-
	Total	98.36	98.91	99.95	-
3.	Angle of Repose (°)	47°42'	51°28'	51°30'	58°21'
4.	Weight variation				
	Mean weight (mg.)	-	250.9	246.8	243.3
	Standard error mean N=5	-	4.4	4.0	13.6
5.	Hardness				
	Mean hardness (Kg.)	-	0.93	1.96	3.14
	Standard error mean N=5	-	0.22	0.16	1.42

TABLE 2.

Results of Tests Performed on Aged Samples

		FORMULATION		
		B	C	D
Chemical stability (% retained)				
40° C	96 hours	98.8	-	-
	192	93.6	-	-
	288	95.8	-	-
50° C	48	95.5	-	-
	96	91.4	-	-
	144	89.5	-	-
60° C	24	94.7	93.2	98.7
	48	90.0	90.9	101.0
	72	85.7	100.0	100.0

hydrochloride formulations were found to be stable as shown by the results of the assay after exposing the tablets at 60°C. The ascorbic acid formulations, on the other hand, degraded sharply probably due to the moisture content of the Emcompress Standard[R]. Control studies in dry powdered ascorbic acid did not show significant decomposition.

The hardness of ascorbic acid tablets, folic acid tablets, and thiamine hydrochloride tablets dropped as a result of aging.

The findings showed that friability increased with aging in all formulations. Data for ascorbic acid tablets at 60°C (formulation B) is not reported because

TABLE 3.

Results of Tests Performed Aged Samples

Physical Stability		FORMULATION B	C	D
a. Hardness (Kg.):				
Room Temp.	0 Hours	0.930	1.960	3.140
40° C	96	0.575	1.950	3.125
	192	⩽ 0.500	1.525	1.575
	288	,, 0.500	0.950	1.550
50° C	48	,, 0.500	1.375	1.250
	96	,, 0.500	1.275	0.700
	144	,, 0.500	1.250	0.675
60° C	24	,, 0.500	0.975	2.125
	48	,, 0.500	0.825	1.000
	72	,, 0.500	0.900	0.675
b. Friability (% loss)				
Room temp.	0 Hours	0.84	0.50	1.19
40° C	96	1.73	0.71	0.63
	192	2.66	0.70	0.69
	288	1.74	1.13	0.74
50° C	48	3.54	1.17	1.53
	96	4.45	1.23	0.90
	144	5.23	1.42	1.18
60° C	24	-	1.44	1.08
	48	-	1.42	1.03
	72	-	1.34	1.23
c. Disintegration Time (Minutes:seconds)				
Room temp.	0 Hours	1:00	2:00	10:20
40° C	96	1:30	1:30	12:20
	192	0:48	1:40	10:00
	288	2:00	4:45	9:40
50° C	48	1:07	5:22	11:30
	96	1:29	5:48	9:40
	144	0:54	6:41	5:00
60° C	24	0:30	5:19	4:04
	48	0:22	4:09	4:00
	72	0:28	1:06	0:52

more than one tablet was broken during the friability test.

The disintegration time decreased in ascorbic acid and thiamine hydrochloride tablets but increased in folic acid tablets with aging.

CONCLUSIONS

From the data it seems that ascorbic acid and thiamine hydrochloride formulations with Emcompress Standard[R] in the given proportions are not suitable. Folic acid formulation, however, shows very stable physical and chemical properties.

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