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COMPARATIVE EVALUATION OF SEVERAL DIRECT COMPRESSION SUGARS

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ABSTRACT

Three new and two commercially available sugar matrices were comparatively evaluated for several fundamental properties of direct compression powder systems. These properties included: particle size distribution, powder flow (determined by a recording powder flow meter), bulk density and moisture content. The matrices studied were Dipac, Nutab, and California and Hawaiian (C & H) Products A, B, and C. These matrices were formulated into chewable ascorbic acid, multivitamin, and antacid tablets, and analyzed for: weight uniformity, thickness, diameter, hardness, disintegration, resistance to impact stress, friability, dissolution and effect due to aging.

The data obtained showed that the new products (C & H products) were comparable, and in some cases, even superior to the commercially available ones.

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INTRODUCTION

Sucrose-based tableting matrices, such as Dipac, Nutab and Sugartab, have been used quite successfully for some time (1). These matrices contain various levels of sucrose, ranging from 90 to 98%. The remaining portion may be one or more of the following: invert sugar, modified dextrins, cornstarch, and in some cases, magnesium stearate. These additives are present at various levels (2,3).

The utility of these diluent-binders is not limited to the formulation of chewable tablets. These matrices also find application in the direct compaction of conventional tablets. Mendes and co-workers have reported the use of Nutab as a chewable direct compression carrier for a variety of products (4). The flow properties of various mixtures using Dipac as the matrix have been evaluated by Bagster et al (5).

Because of the high sucrose content of these matrices, there may be a tendency to under go substantial moisture uptake. In addition, when formulated into chewable tablets, it is imperative that the matrices impart acceptable palatability and mouth-feel.

This study comparatively evaluated the potential utility of three new sucrose based matrices (California and Hawaiian Sugar Company (C & H, Products A, B, and C) and two commercially available products, Dipac and Nutab.

A preliminary investigation revealed that, of the three C & H products, A and B were most promising. Therefore, only the two products were fully investigated.

EXPERIMENTAL

Intrinsic Physical Properties - Matrices Moisture Content

The moisture content of each matrix was determined using a 10g sample on a Ohaus[1] moisture determination balance.

Particle Size Distribution

Particle size distribution was assessed by the use of a series of preweighed sieves on a Fisher[2] shaker. A 50g sample was shaken for two minutes, and amount collected on each sieve expressed as percent of initial 50 g weight.

Bulk Density

The bulk density of each matrix was determined by measuring the volume of a 50g sample (passed through sieve #20). The samples were poured into a 100 ml graduated cylinder from a height of 2.5 cm. at a rate of two seconds.

Flow Properties

'Flow grams' of the matrices, without any of the formulation additives, were obtained by the use of recording powder flowmeter[3] as reported by Jordan and Rhodes (6), and Rudnic and co-workers (7).

Three flow-grams were obtained for each matrix, and analyzed for linearity (based on the least squares correlation coefficient; (r^2) and mass flow (total weight recorded, grams, divided by total time taken for powder to flow, seconds).

Dilution Potential

The loading capacity of each of the matrices was determined using three levels of ascorbic acid (8). The effect of increase in percent active on flowability, hardness, friability, and disintegration was monitored.

Preparation of Tablets

Three chewable formulas were used to comparatively evaluate the matrices. These formulas are shown in Tables I-III.

The ascorbic acid formula used was similar to the one recommended by Roche (9) in the tableting of their Ro-coat vitamins. The antacid tablets were made from a formula suggested by Edward Mendel Company (10), while the multivitamin formula was one adpated in our laboratory. These formulas were kept simple in order to observe the compression characteristics of the matrices as much as possible.

TABLE I

VITAMIN C FORMULA

INGREDIENT	QUANTITY PER TABLET (MG)
Sodium Ascorbate[4]	199.00
FD & C Yellow #6 (Jet Milled)[5]	1.0
Syloid 74[6]	4.0
Ascorbic Acid 90%[7]	95.0
Orange Flavor[8]	7.4
Matrix	631.1
Avicel-pH-102[9]	20.0
Steavic Acid[10]	40.0
Magnesium Stearate[11]	2.5
	1000.0

TABLE II

MULTIVITAMIN FORMULA

INGREDIENT	QUANTITY PER TABLET (MG)
Riboflavin[12]	2.45
Pyridoxine[13]	3.50
Niacinamide[14]	24.50
FD & C Yellow #6 (Jet Milled)	2.10
Orange Flavor	3.50
Ascorbic Acid	70.00
Matrix	242.20
Magnesium Stearate	1.75
	350.00

TABLE III

ANTACID FORMULA

INGREDIENT	QUANTITY PER TABLET (MG)
F-MA 11[15]	400.0
Syloid 244[16]	50.0
Matrix	1100.0
Mint Flavor[17]	20.0
Magnesium Stearate	16.0
	1586.0

One kilogram batch of each formulation was compressed on a Stokes rotary press[18], at low, medium and high speed. The weight and hardness in both the ascorbic acid and multivitamin formulations were optimized using Dipac as the standard. These press settings were maintained throughout the compaction of all the batches. However, in the case of the antacid formula, Dipac did not produce satisfactory tablets. Therefore, the C & H products were compressed to their optimum weight and hardness levels.

Evaluation of Tablets

Tablets manufactured in this study, were analyzed for some fundamental physical properties. These properties included: weight uniformity, thickness, diameter, hardness, disintegration, resistance to impact stress, friability, and dissolution (ascorbic acid tablets).

Weight of twenty tablets from each batch were individually determined using a Mettler analytical balance. Both thickness and diameter measurements were obtained by the use of a micrometer.

Hardness values for twenty tablets were determined by an Erweka hardness tester[20]. Disintegration time for six tablets from

each batch was assessed using a USP disintegration apparatus[21] with discs. Resistance to impact stress was determined by dropping fifty tablets (of each batch) individually through a one meter glass tube placed on an aluminum plate.

Friability of twenty tablets from each batch was determined by a Roche friabulator[22]. The weight of twenty tablets (all together) was noted, and then subjected to the test for twenty minutes. The tablets were then separated from the powdered material, and reweighed.

Dissolution of the ascorbic acid tablets was performed suing 0.1 N HCl as the dissolution medium. The USP basket method was used (11). Six tablets from each batch were analyzed.

A 'mouth-feel' test was conducted on the ascorbic acid and multivitamin tablets after gaining approval from the University of Rhode Island's Institutional Review Board. Twelve subjects were provided with specially coded containers bearing the test tablets. Subjects were also provided with questionaires on which they were to rate the products on a scale of 1 to 5 based on specific criteria. These criteria included: tablet hardness, chewability, grittiness, degree of sweetness, and presence of after-taste. This data was analyzed using Chi-Square (χ^2) test (12).

A short term accelerated aging study, using moderate storage stress conditions, was conducted on the ascorbic acid tablets.

RESULTS AND DISCUSSION

Table IV shows the moisture content and the bulk density of the matrices. The moisture levels do not appear significantly different. However, the C & H products show slightly higher levels.

Particle size distribution of the matrices is shown in Table V. It is apparent from this data that C & H Product A has the largest percentage of the particles collecting on sieve #40 and the lowest bulk density (Table IV).

The intrinsic flow properties, as determined from flow-grams of matrices without tableting additives, are represented in

TABLE IV

MOISTURE CONTENT AND BULK DENSITY

MATRIX	MOISTURE CONTENT (%)	BULK DENSITY (GM/ML)
Dipac	0.4	0.68
Nutab	0.4	0.73
C & H Product A	0.6	0.53
C & H Product B	0.5	0.64

TABLE V

PARTICLE SIZE DISTRIBUTION

Matrix Sieve #	20	40	60	100	170	THRU 170
Dipac	0	4	52	32	10	2
Nutab	0	31	44	23	1	1
C&H Product A	0	48	38	10	2	2
C&H Product B	0	16	44	28	10	2

Table VI. C & H Product B shows the highest mean flow, $(r^2-0.8) \times 100$, where r^2 is the correlation coefficient derived from the points. Thus, the term FLOW has possible values of zero to twenty; twenty representing perfect linear flow whereas zero indicates the substantially poor flow rate.

Tables VII-IX show the effect of increasing levels of ascorbic acid (percent active) on the flow properties of Dipac and C & H Products A and B. It is evident that both flow and mass flow are significantly reduced as the level of active increases.

TABLE VI

INTRINSIC FLOW PROPERTIES

MATRIX	MASS FLOW* (GM/SEC)	LINEARITY* (r^2-0.8) x 100
Dipac	166.3	15.9
C&H Product A	180.8	19.9
C&H Product B	230.9	19.5

TABLE VII

MATRICES WITH 25% ASCORBIC ACID

MATRIX	MASS FLOW (GM/SEC)	LINEARITY (r^2-0.8) x 100
Dipac	79.8	17.8
C&H Product A	183.9	17.8
C&H Product B	160.1	17.1

TABLE VIII

MATRICES WITH 35% ASCORBIC ACID

MATRIX	MASS FLOW (GM/SEC)	LINEARITY (r^2-0.8) x 100
Dipac	71.7	10.4
C&H Product A	97.6	16.3
C&H Product B	96.4	16.2

*Mean values - n=3

TABLE IX

MATRICES WITH 4.5% ASCORBIC ACID

MATRIX	MASS FLOW (GM/SEC)	LINEARITY (r^2-0.8) x 100
Dipac	77.9	16.3
C&H Product A	61.7	16.9
C&H Product B	76.9	15.9

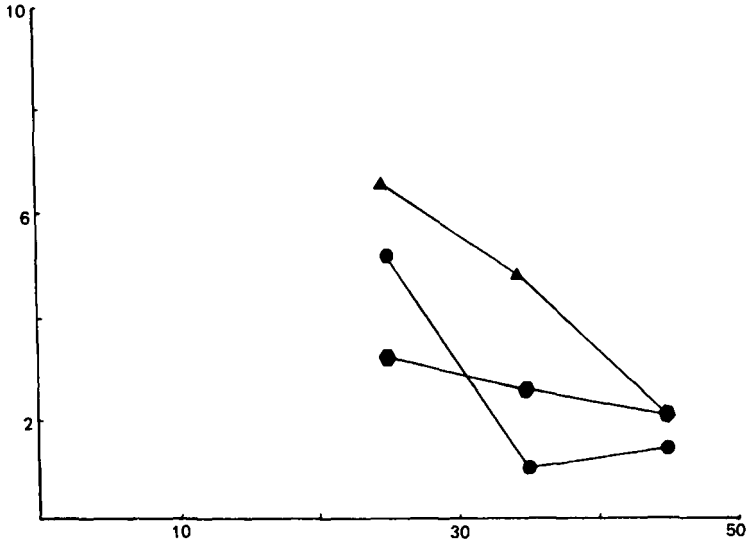

FIGURE 1

ORDINATE: HARDNESS (KILOGRAM)

ABSCISSA: PERCENT OF ASCORBIC ACID

KEY: ● DIPAC ▲ C & H PRODUCT A ● PRODUCT B

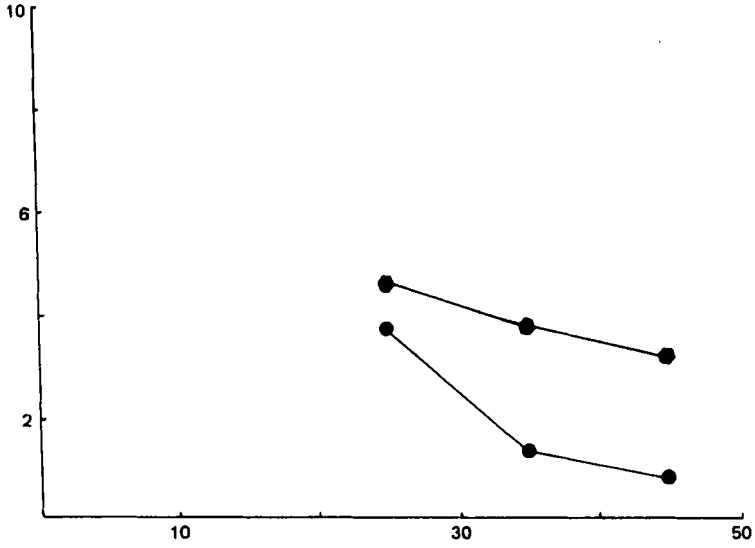

FIGURE 2

ORDINATE: DISINTEGRATION TIME (MINUTES)

ABSCISSA: PERCENT OF ASCORBIC ACID

KEY: ● DIPAC ▲ C & H PRODUCT A ● PRODUCT B

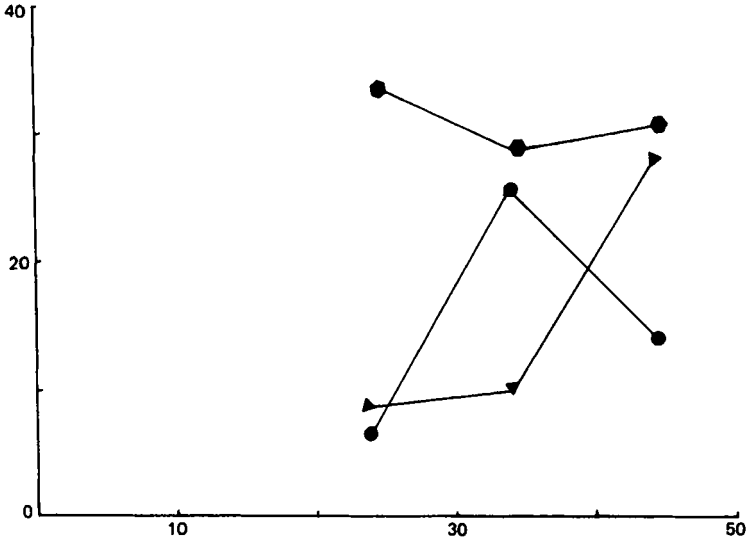

FIGURE 3

ORDINATE: PERCENT FRIABILITY

ABSCISSA: PERCENT OF ASCORBIC ACID

KEY: ⬢ DIPAC ▲ C & H PRODUCT A ● C & H PRODUCT B

TABLE X

PHYSICAL PROPERTIES - ASCROBIC ACID FORMULA

MATRIX	MEAN WEIGHT (MG)	MEAN HARDNESS (KG)	FRIABILITY (%)
Dipac	982.8	8.4	5.8
Nutab	1003.9	6.9	26.9
C&H Prodwct A	958.8	9.6	2.5
C&H Product B	975.8	9.7	5.2

*n = 20

TABLE XI

PHYSICAL PROPERTIES - MULTIVITAMIN FORMULA

MATRIX	MEAN WEIGHT (MG)*	MEAN HARDNESS (KG)	FRIABILITY (%)
Dipac	372.4	5.71	6.0
Nutab	385.0	5.47	4.5
C&H Product A	376.0	10.25	8.1
C&H Product B	377.1	6.78	22.7

TABLE XII

PHYSICAL PROPERTIES - ANTACID FORMULA

MATRIX	MEAN WEIGHT (GM)	MEAN HARDNESS (KG)	FRIABILITY (%)
Dipac[+]	-	-	
Nutab[+]	-	-	
C&H Product A	1.414	4.63	7.4
C&H Product B	1.690	8.56	4.6

*Mean Value - n=20

[+]Tablets were too soft to be

TABLE XIII

MOUTH - FEEL TEST, CHI SQUARE (X^2)

QUESTION	CALCULATED X^2*	
	ASCORBIC ACID	MULTIVITAMIN
1	13.2	4.3
2	6.7	2.0
3	5.2	8.7
4	7.3	8.4
5	10.8	8.6

*If greater than 18.3 (Critical value for 10 degress of freedom at 0.05 level) indicates significance.

Figure 1 shows the effect of increase in percent of ascorbic acid on the tablet hardness. A general trend of reduction in hardness with increase in ascorbic acid can be noted. A similar trend was observed in the disintegration time, Figure 2. This is expected since these matrices actually dissolve; thus the rate of dissolution would be a function of hardness.

Figure 3 illustrates the effect of increase in the levels of ascorbic acid on friability. Dipac and C & H Product B exhibit a decrease in friability with increase in ascorbic acid levels. However, C & H Product A shows an increase in friability with increase in percent ascorbic acid; perhaps as a result of alteration of a critical particle size distribution.

Tables X-XII represent the physical properties of ascorbic acid, multivitamin, and antacid tablets respectively. It may be noteworthy that the tablets were compressed at the same press settings. Therefore, variations in the weight are due to the inherent densities of the matrices, and perhaps to the flow properties.

In Table XII, it is evident that ascorbic acid tablets made from Nutab show high friability values. However, the mean hardness

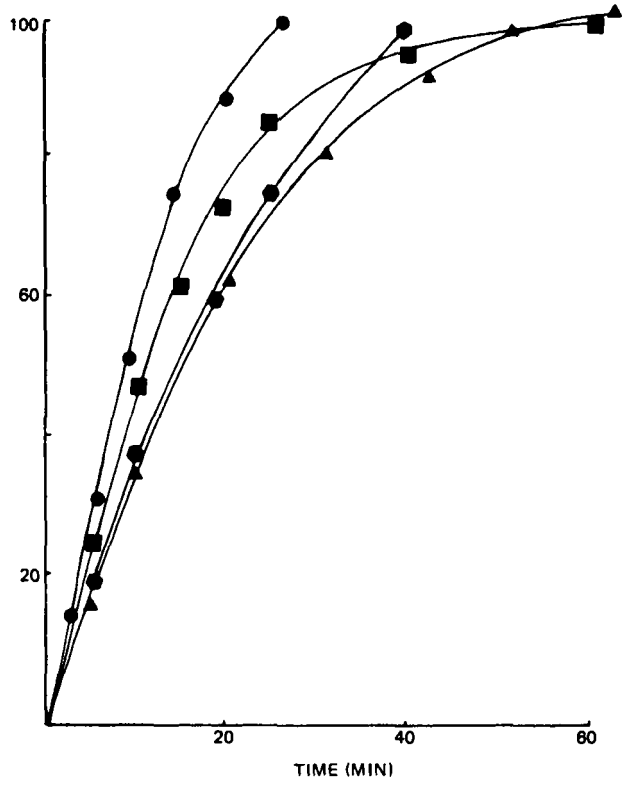

FIGURE 4

ORDINATE: PERCENT DISSOLVED

ABSCISSA: TIME (MINUTES)

KEY: ▲ DIPAC ● NUTAB ■ C & H PRODUCT A ⬣ C & H PRODUCT B

value was not substantially low compared to those of other formulations. This finding was also noted when C & H Product B was formulated into multivitamin tablets, Table XI.

Tablet XII shows the physical properties of antacid tablets. Only the C & H products were compressed into satisfactory tablets. Tablets obtained from Dipac and Nutab were too soft to be handled.

TABLE XIV

PHYSICAL PROPERTIES - AFTER AGING*

MATRIX	MEAN WEIGHT (MG)	MEAN HARDNESS (KG)
Dipac	981.6	5.49
Nutab	1038.4	4.66
C&H Product A	927.2	4.61
C&H Product B	978.9	4.90

*Ascorbic acid tablets used

Table XIII shows the results of a chi-square test on the mouth-feel data. As can be seen from calculated χ^2 values, all were less than the critical level, and no significant difference was detected in the samples tested.

Figure 4 illustrates the dissolution profiles of the ascorbic acid tablets obtained from the four matrices. Tablets compressed from Dipac and C & H Product A exhibit the slowest attainment of complete dissolution, while those made from Nutab and C & H Product B attain full dissolution in less than thirty minutes. This finding can be attributed to hardness levels of test tablets.

Table XIV illustrates the physical properties of ascorbic acid tablets following a short term aging study. A statistically significant, Student's t-test (13), reduction in hardness was observed.

CONCLUSION

The data presented in this paper indicates that the two C & H Products, A and B, have significant potential as direct compression excipients. Further, the data suggests that these matrices are quite comparable, and in some cases, even superior to some of the commercially available ones. However, it is felt

that additional work is necessary to show the versatility of these matrices.

FOOTNOTES

1. Model 6010
2. Fisher - Wheeler
3. Mettler PR 1200 and Mettler GA12
4. Hoffan La-Roche, Nutley, NJ
5. Warner Jenkinson, St. Louis, MO
6. Davison Chemical, Baltimore, MD
7. Hoffman La-Roche, Nutley, NJ
8. Warner Jenkinson, St. Louis, MO
9. FMC Corp., Newark, DE
10. Ruger Chemical Co., Irvington, NJ
11. Fisher Chemical Co.,
12. Hoffman La-Roche, Nutley, NJ
13. Hoffman La-Roche, Nutley, NJ
14. Hoffman La-Roche, Nutley, NJ
15. Reheis Chemical Co., Berkeley Heights, NJ
16. Davison Chemical, Baltimore, MD
17. Food Material Corp., Chicago, IL
18. Stokes Model 900-512-1, Pennwalt Corp., Warminister, PA
19. Mettler Instruments Corp., Hightstown, NJ
20. Erweka Apparatebau, Frankfurt, West Germany
21. United States Pharmacopeial Convention, Rockville, MD
22. Erweka G.M.B.H., Frankfurt, West Germany

REFERENCES

1. G.S. Banker, G.E. Peck and G. Baley, in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, H.A. Lieberman and L. Lackman, eds., Marcel Dekker Inc., New York, 1980, p. 61.

2. "DIPAC", Promotional Literature, Armstar Corporation.

3. "NU-TAB", Promotional Literature, Ingredient Technology Corporation.

4. Mendes et al, Drug Cosm. Ind., 42 (1974).

5. Bagster et al, Drug Devel. and Ind. Pharm., 3, 475 (1977).

6. R.P. Jordan and C.T. Rhodes, Drug Devel. and Ind. Pharm., 5, 151 (1975).

7. E.M. Rudnic, R. Chilamkurti and C.T. Rhodes, Drug Devel. and Ind. Pharm., 6, 279 (1980).

8. J.B. Daruwala, in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, H.A. Lieberman and L. Lachman, eds., Mercel Dekker, Inc., New York, 1980, p. 289.

9. "Ascorbic Acid 90%", Promotional Literature, Roche Chemical Division, Hoffman-LaRoche Inc., Nutley, NJ.

10. J.L. Kanig and C.T. Rhodes, Presentation at the "Symposium on Direct Compression Tablet Technology, Toronto, Canada, 1981.

11. "The United States Pharmacopeia", 20th rev., Mack Publishing Co., Easton, PA.

12. T.M. Little and F.J. Hill "Agricultural Experimentation", Wiley, New York, 1978, p.31.

13. "SAS User's Guide", SAS Institute, Cary, N.C., 1979, p. 121.