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DISINTEGRABILITY CHARACTERISTICS OF THREE SELECTED TABLET EXCIPIENTS

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ABSTRACT

Three relatively new tablet excipients which included a water-insoluble, anionic, polymer derived from cellulose[1] (D_1), a carboxymethyl substituted starch[2] (D_2), and a complex of aminoacetic acid and sodium carbonate[3] (D_3) were compared with each other and against Starch USP (D_4) as to their ability to effect the disintegration of compressed tablets.

In this study, tablets were made by direct compaction from both a soluble and insoluble matrix containing a pharmacologically active drug substance. The drug substances were either a water-soluble, weak acid (A_1), a water-insoluble, weak acid (A_2), a water-soluble

[1]CLD, Buckeye Cellulose Corp., Memphis, Tennessee
[2]Primojel, Edward Mendell Co., Inc., R.D. #5, Carmel, New York 10512
[3]Sodium Glycine Carbonate, Edward Mendell Co., Inc.

salt derived from an insoluble, weak base (A_3), and a water-insoluble, weak base (A_4).

In addition to the initial (I) measurement, the disintegration times were measured after six (M) and fourteen months (F) of storage at 30°C.

The experimental results were statistically analyzed. The averages as well as the variabilities (uniformity) associated with the performance of the disintegrants were compared and these results are presented.

In terms of ability to effect disintegration, the experimental results clearly indicated the following rank order: $D_1 > D_2 > D_4 > D_3$.

INTRODUCTION

Both corn and potato starch have enjoyed justified, worldwide popularity as disintegrants in tablet formulations. In fact, they frequently serve as standards in evaluations of other disintegrating agents (1-11). When one or both fail to produce disintegration, alginic acid or guar gum have been considered effective substitutes. Although the latter have proven useful, they have never attained the popularity nor the general acceptance of the starches. This may be due to variations in quality. It could, on the other hand, be that they lose some effectiveness with time. Experience in these laboratories has shown the latter to be true.

Certain ion exchange resins have recently been used as disintegrants. Synthetically produced, their quality has proven more consistent than natural products. Their ability to form chemical complexes has been recognized, however, and this potential probably limits some use. Recognizing a continuing need, the search for new and more efficient disintegrants continues.

In this study, a selected number of disintegrants were chosen and compared with each other with respect to the averages and variabilities associated with their performance. The effects of active drug substances, excipient matrices, and length of storage period on disintegration time have been considered. The primary objective of the study was to select one or more disintegrants which effected the most rapid disintegration rate with no loss of effectiveness with time. It should be noted that, though highly desirable, no consideration was given in this study to the mechanisms involved in tablet disintegration.

Two formulations, both known to compress directly into tablets, were chosen. Each, however, differed in terms of its water solubility characteristics. One formulation was considered essentially water soluble as it was made up primarily of lactose. The other was considered water insoluble, and it consisted mainly of dibasic calcium phosphate. Because active drugs influence disintegration, four types (also classed according to their water solubility) were chosen for incorporation into each formulation. They were identified earlier in this paper.

EXPERIMENTAL

Batch sizes to yield 1,000 finished tablets were prepared. The compositions of the formulations used in the study were:

Ingredient	Formulation I (in % w/w)	Formulation II (in % w/w)
1. Active Drug	10.0	10.0
2. Lactose USP	79.25	-
3. Diabasic Calcium Phosphate Hydrous NF	-	79.25
4. Purified Wood Cellulose	5.0	5.0
5. Disintegrant	5.0	5.0
6. Magnesium Stearate USP	0.75	0.75

The mixtures for compressing into tablets were made as follows: the active drug, the main diluent, either lactose or dibasic calcium phosphate, and the purified wood cellulose were mixed in a planetary type mixer[4] for five minutes, passed through a #30 bolting cloth, and remixed for five minutes in the same mixer. The disintegrant was then passed through a #60 bolting cloth, added to the mixture, and blended for five minutes, using a twin shell "V" type blender.[5] The magnesium stearate was passed through a #60 bolting cloth, added to the powder mixture, and blended for three minutes using the twin shell "V" type blender. The blends were then compressed into tablets on a single station press[6] equipped with a round, flat faced, beveled-edged punch .3125" in diameter, operated at a rate of 60 tablets per minute according to the following specifications:

Weight: 250 mg. ± 3.5%

Hardness: 7.0 kg. ± 1.5 kg.

Thickness: Sufficient to obtain above hardness, but ± 0.13 mm. once target was established.

Approximately ten thousand tablets were compressed for the study. All possible combinations of four ingredients, four disintegrants, and two excipient matrices totaling 32 distinct formulations were made. One thousand nine hundred twenty tablets (32 formulations x 60 tablets per formulation) were used in initial tests and three hundred eighty-four tablets (32 formulations x 6 tablets per formulation x 2 storage periods) were stored and subsequently tested. The remaining tablets were used in determining hard-

[4]Hobart Mixer, Model 80N, Hobart Mfg. Co., Troy, Ohio
[5]Patterson Kelly Co., Inc., East Stroudsburg, Pennsylvania
[6]Model "E", Stokes Compacting Div. Pennwalt Corp., Warminster, Pennsylvania

nesses, thicknesses, and friabilities of the formulations considered for the study for laboratory quality control purposes.

The tablets were stationed at 30°C during the two storage periods of six and fourteen months.

The statistical analysis was accomplished after a rankit transformation (12,13) of the data. This transformation is appropriate for the comparison of treatments involving data that are expressed as "greater than a given limiting value" and not as their actual measured response. It may be noted that much of the data associated with insoluble matrices went beyond the limit point of 60 minutes and are recorded as "greater than 60 minutes". Another advantage of such a transformation is that it makes the data meet some of the most important assumptions implicit in the analysis of variance procedure.

RESULTS

In making the comparisons and in assessing the effectiveness of each disintegrant, criteria of somewhat limited scope were applied. In this study it was desired to determine only that disintegrant producing disintegration in the shortest time; that disintegrant which accomplished this result most uniformly; and that disintegrant exhibiting the least change in effectiveness with time.

Judging performance with these constraints promotes a tendency to overlook what otherwise might be considered efficient excipients. For example, a disintegrant effecting disintegration in one minute would be considered, by any standard, an excellent performer. If in the comparison, however, another disintegrant produced more rapid results then that would have to be considered the better disintegrant. Such was the case in this study. We point this out primarily because

TABLE I

Comparison of Averages[α] of Four Disintegrants for Tablets with Water Soluble Matrix and Water Insoluble Matrix

		Statistical Intercomparison[β,γ]							
		Water Soluble Matrix				Water Insoluble Matrix			
Storage Period	Active Ingredient	D_1	D_2	D_3	D_4	D_1	D_2	D_3	D_4
I	A_1	0.49^a	1.18^b	8.76^d	4.01^c	0.25^a	0.25^a	60.00^c	0.56^b
I	A_2	0.78^a	5.54^b	8.44^c	5.71^b	0.25^a	0.50^b	60.00^d	5.42^c
I	A_3	2.57^a	5.94^b	5.89^b	5.90^b	0.50^a	3.50^b	60.00^d	17.54^c
I	A_4	0.61^a	2.68^b	12.79^d	4.66^c	0.25^a	0.25^a	60.00^b	0.25^a
M	A_1	0.83^a	3.56^b	8.66^c	4.08^b	0.08^a	0.16^b	60.00^d	0.41^c
M	A_2	1.79^a	5.76^b	9.13^d	8.18^c	0.17^a	0.33^b	60.00^d	0.58^c
M	A_3	2.46^a	5.97^c	4.87^b	5.79^c	0.37^a	4.58^b	60.00^d	23.70^c
M	A_4	0.64^a	3.24^b	13.83^c	3.77^b	0.08^a	0.22^b	60.00^c	0.21^b

F	A_1	0.84^a	3.17^b	8.84^c	2.91^b	0.08^a	0.28^b	60.00^d	0.41^c
F	A_2	1.11^a	6.46^b	8.81^c	6.07^b	0.17^a	0.58^b	60.00^c	0.54^b
F	A_3	2.19^a	6.27^c	5.65^b	5.99^b	0.46^a	4.37^b	60.00^d	26.36^c
F	A_4	0.59^a	4.06^b	15.46^c	3.33^b	0.08^a	0.24^c	60.00^d	0.18^b

α The values are the anti-rankit averages in minutes
β Two disintegrant averages are not statistically different (at P = 0.05) if they have at least one superscript in common (in each row for each matrix)
γ Two disintegrant averages are statistically different ($P \leq 0.05$) if they have different superscripts (in each row for each matrix)

the data indicate that three of the four disintegrants studied effected rapid disintegration. One, however, was significantly superior to all.

Both the ANOVA procedure and Duncan's multiple range test (14) were used to find the disintegrant producing the shortest significant disintegration time (Table I) and exhibiting the least change in effectiveness after storage (Table III). The Levene test (15) of homogeneity of average absolute mean deviations associated with the raw data was employed for determining the disintegrant performing most uniformly (Table II and IV).

Table I shows that in a water soluble matrix, disintegrant D_1 produced the most rapid disintegration rates and performed in this manner irrespective of the active ingredient included in the formulation. This superiority was maintained after six and fourteen months of storage at 30°C. In the water insoluble matrix, D_1 was equalled in performance by D_2 in only two of the twenty-four comparisons made at the first stage of testing. After six and again after fourteen months of storage, however, D_1 showed itself to be the best disintegrant.

Table II shows the comparison of the variabilities associated with the performance of the disintegrants. In the water soluble matrix, there were no significant differences among the disintegrants in 19 of the 24 comparisons at the initial stage of testing, 15 out of 24 comparisons at six month storage and 21 out of 24 comparisons at the final stage of testing. It may be noted that D_1 maintained a significantly lower variability irrespective of active ingredients and times of storage. In the water insoluble matrix and during the initial observation only D_4 was significantly more variable in the results it produced compared to the other three disintegrants; the other three being equivalent. After six months storage only D_1 and

D_3 were equivalent in uniformity in all cases. D_4 always produced more variable results compared to D_1 and D_3 and more variable results than D_2 in three of the four comparisons. At the end of fourteen months of storage, D_1 and D_3 continued to be equivalent in variability and were more uniform than D_4 in all comparisons. D_2 was equivalent to D_1 in two of the four comparisons and equivalent to D_4 in one of the four comparisons.

Table III shows the comparison of the average disintegration times of the four disintegrants initially and again at the six and fourteen month time periods. Examination of these data reveals that in the water soluble matrix the formulations containing D_1 showed no significant change in the average time of disintegration over the elapsed time. In the water insoluble matrix the average disintegration time over the three storage periods was significantly different in seven of the twelve comparisons associated with D_1 and D_2, and nine of twelve associated with D_4. With regard to D_3, no signficant changes in average were observed over the three storage periods.

Table IV shows the comparison of variability among the three storage periods for the disintegrants used in both the water-soluble and water-insoluble matrices. For the water soluble matrix, the results of the comparisons among the three storage times showed that 4 out of 12, 1 out of 12, 2 out of 12 and 2 out of 12 were significantly different for D_1, D_2, D_3 and D_4 respectively. For the water insoluble matrix, a comparison among the storage times showed that 3 out of 3, 4 out of 9 and 4 out of 12 were significantly different for D_1, D_2 and D_4 respectively. There were no statistical tests possible for the comparisons associated with D_3.

TABLE II

Comparison of Variabilities[α] Among Four Disintegrants for Tablets with Water Soluble Matrix and Water Insoluble Matrix

		Statistical Intercomparison[β,γ]							
		Water Soluble Matrix				Water Insoluble Matrix			
Storage Period	Active Ingredient	D_1	D_2	D_3	D_4	D_1	D_2	D_3^{Δ}	D_4
I	A_1	0.20^{a}	0.33^{a}	0.32^{a}	0.39^{a}	0.00^{a}	0.00^{a}	0.00^{a}	0.09^{b}
I	A_2	0.29^{a}	0.81^{b}	0.44^{a}	$0.58^{a,b}$	0.00^{a}	0.00^{a}	0.00^{a}	2.42^{b}
I	A_3	0.28^{a}	0.27^{a}	0.30^{a}	0.11^{a}	0.00^{a}	0.41^{a}	0.00^{a}	1.67^{b}
I	A_4	0.05^{a}	0.48^{b}	0.85^{b}	0.57^{b}	0.00^{a}	0.00^{a}	0.00^{a}	0.00^{a}
M	A_1	0.11^{a}	$0.83^{b,c}$	$0.33^{a,b}$	1.03^{c}	0.00^{a}	0.03^{b}	0.00^{a}	0.08^{c}
M	A_2	$0.50^{a,b}$	$0.50^{a,b}$	0.17^{a}	1.00^{b}	0.00^{a}	0.00^{a}	0.00^{a}	0.11^{b}
M	A_3	$0.28^{a,b}$	0.14^{a}	0.37^{b}	0.17^{a}	0.12^{a}	0.33^{a}	0.00^{a}	1.08^{b}
M	A_4	0.25^{a}	1.00^{b}	1.17^{b}	1.12^{b}	0.00^{a}	0.04^{b}	0.00^{a}	0.04^{b}

F	A_1	0.17^{a}	1.42^{b}	0.25^{a}	0.67^{a}	0.00^{a}	0.04^{b}	0.00^{a}	0.08^{c}
F	A_2	0.29^{a}	0.83^{a}	0.22^{a}	0.87^{a}	0.00^{a}	0.08^{b}	0.00^{a}	0.18^{c}
F	A_3	0.31^{a}	0.17^{a}	0.31^{a}	0.39^{a}	0.07^{a}	0.21^{a}	0.00^{a}	1.58^{b}
F	A_4	0.17^{a}	0.97^{a}	1.00^{a}	0.94^{a}	0.00^{a}	$0.02^{a,b}$	0.00^{a}	0.05^{b}

α The values are the average absolute mean deviations

β Two disintegrant average absolute deviations are not statistically different (at P = 0.05) if they have at least one superscript in common (in each row for each matrix)

γ Two disintegrant average absolute deviations are statistically different ($P \leq 0.05$) if they have different superscripts (in each row for each matrix)

Δ Since all results were above the limiting value of 60 minutes and were recorded as 60 minutes, the variability value becomes zero.

TABLE III

Comparison of Averages[α] of Three Storage Periods for Tablets with Water Soluble Matrix and Water Insoluble Matrix

		Statistical Intercomparison[β,γ]					
		Water Soluble Matrix			Water Insoluble Matrix		
Disintegrants	Active Ingredient	I	M	F	I	M	F
D_1	A_1	0.49[a]	0.83[a]	0.84[a]	0.25[b]	0.08[a]	0.08[a]
D_1	A_2	0.78[a]	1.79[b]	1.11[a]	0.25[b]	0.17[a]	0.17[a]
D_1	A_3	2.57[a]	2.46[a]	2.19[a]	0.50[b]	0.37[a]	0.46[a,b]
D_1	A_4	0.61[a]	0.64[a]	0.59[a]	0.25[b]	0.08[a]	0.08[a]
D_2	A_1	1.18[a]	3.56[a]	3.17[a]	0.25[b]	0.16[a]	0.28[b]
D_2	A_2	5.54[a]	5.76[a]	6.46[b]	0.50[b]	0.33[a]	0.58[c]
D_2	A_3	5.94[a]	5.97[a,b]	6.27[b]	3.50[a]	4.58[b]	4.37[b]
D_2	A_4	2.68[a]	3.24[a,b]	4.06[b]	0.25[a]	0.22[a]	0.24[a]

D_3	A_1	8.76^a	8.66^a	8.84^a	60.0^a	60.0^a	60.0^a
D_3	A_2	8.44^a	9.13^b	8.81^b	60.0^a	60.0^a	60.0^a
D_3	A_3	5.89^b	4.87^a	5.65^b	60.0^a	60.0^a	60.0^a
D_3	A_4	12.79^a	13.83^a	15.46^b	60.0^a	60.0^a	60.0^a
D_4	A_1	$4.01^{a,b}$	4.08^b	2.91^a	0.56^b	0.41^a	0.41^a
D_4	A_2	5.71^a	8.18^b	6.07^a	5.42^b	0.58^a	0.54^a
D_4	A_3	5.90^a	5.79^a	5.99^a	17.54^a	23.70^b	26.36^c
D_4	A_4	4.66^a	3.77^a	3.33^a	0.25^b	0.21^a	0.18^a

α The values are the anti-rankit averages in minutes
β Two storage period averages are not statistically different (at P = 0.05) if they have at least one superscript in common (in each row for each matrix)
γ Two storage period averages are statistically different ($P \leq 0.05$) if they have different superscripts (in each row for each matrix)

TABLE IV

Comparison of Variability[α] (Uniformity) Among Three Storage Periods for Tablets with Water Soluble Matrix and Water Insoluble Matrix

		Statistical Intercomparison[β,γ]					
		Water Soluble Matrix			Water Insoluble Matrix		
Disintegrants	Active Ingredient	I	M	F	I	M	F
D_1	A_1	0.20[b]	0.11[a]	0.17[a,b]	0.00[a]	0.00[a]	0.00[a]
D_1	A_2	0.29[a]	0.50[b]	0.29[a]	0.00[a]	0.00[a]	0.00[a]
D_1	A_3	0.28[a]	0.28[a]	0.31[a]	0.00[a]	0.12[c]	0.07[b]
D_1	A_4	0.05[a]	0.25[b]	0.17[a,b]	0.00[a]	0.00[a]	0.00[a]
D_2	A_1	0.33[a]	0.83[a,b]	1.42[b]	0.00[a]	0.03[b]	0.04[b]
D_2	A_2	0.81[a]	0.50[a]	0.83[a]	0.00[a]	0.00[a]	0.08[a]
D_2	A_3	0.27[a]	0.14[a]	0.17[a]	0.41[a]	0.33[a]	0.21[a]
D_2	A_4	0.48[a]	1.00[a]	0.97[a]	0.00[a]	0.04[b]	0.02[b]

D_3	A_1	0.32^{α}	0.33^{α}	0.25^{α}	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$
D_3	A_2	0.44^{b}	0.17^{α}	$0.22^{\alpha,b}$	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$
D_3	A_3	0.30^{α}	0.37^{α}	0.31^{α}	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$
D_3	A_4	0.85^{α}	1.17^{α}	1.00^{α}	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$	$0.00^{\alpha\Delta}$
D_4	A_1	0.39^{α}	1.03^{b}	$0.67^{\alpha,b}$	0.09^{α}	0.08^{α}	0.08^{α}
D_4	A_2	0.58^{α}	1.00^{α}	0.87^{α}	2.42^{b}	0.11^{α}	0.18^{α}
D_4	A_3	0.11^{α}	$0.17^{\alpha,b}$	0.39^{b}	1.67^{α}	1.08^{α}	1.58^{α}
D_4	A_4	0.57^{α}	1.12^{α}	0.94^{α}	0.00^{α}	0.04^{b}	0.05^{b}

α The values are the average absolute mean deviations

β Two storage period average absolute mean deviations are not statistically different (at P = 0.05) if they have at least one superscript in common (in each row for each matrix)

γ Two storage period average absolute mean deviations are statistically different ($P \leq 0.05$) if they have different superscripts (in each row for each matrix)

Δ Since all results were above the limiting value of 60 minutes and were recorded as 60 minutes, the variability value becomes zero

CONCLUSIONS

Judged on the basis of some rather limited constraints, the water-insoluble anionic, polymer derived from cellulose, performed remarkably well. It effected disintegration rapidly in both water insoluble and water soluble tablet matrices and performed well irrespective of the characteristics of the active compound incorporated into the formulation. This disintegrant when compared to the others was not as consistent with regard to variability of performance over the time period studied. However, its variability values, at any one time period, was generally lower than that of the other disintegrants. The carboxymethyl-substituted starch also performed well in these tests and deserves consideration as an effective disintegrant. Other favorable reports associated with this compound have appeared elsewhere in the literature (11,16).

The complex of aminoacetic acid and sodium carbonate performed poorly in these tests. It should be pointed out, however, that this material is not promoted to the Pharmaceutical Industry as a disintegrant, but rather as an excipient for consideration in effervescent type formulations. It was included in this study primarily to determine if it could induce disintegration in a formulation containing an acid type drug substance.

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