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THE EFFECT OF AGING ON DISINTEGRANT EFFICIENCY IN DIRECT COMPRESSION TABLETS WITH VARIED SOLUBILITY AND HYGROSCOPICITY, IN TERMS OF DISSOLUTION

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ABSTRACT

The effect of tablet aging on the dissolution efficiency of three "super disintegrants", sodium starch glycolate, crospovidone, and croscarmellose sodium, was investigated utilizing directly compressed tablets. Lactose, dicalcium phosphate dihydrate, and sorbitol, alone or in combination, provided varying degrees of solubility and hygroscopicity to the direct compression tablet formulations. The results indicate that aging did not decrease the effectiveness of the super disintegrants in promoting in vitro dissolution. The composite solubility and hygroscopicity of the tablets did not adversely influence the aging characteristics of the super disintegrants. Super disintegrants that complied with the same compendial specifications but were obtained from different sources behaved similarly in promoting tablet dissolution after storage.

INTRODUCTION

Two consecutive processes are required for the absorption of orally administered tablets: the dissolution of the drug substance, ensued by movement of the drug substance across biological membranes into systemic circulation. For many solid dosage forms tablet disintegration preceeds drug dissolution. Many investigators have described the behavior of the "super disintegrants," sodium starch glycolate, croscarmellose sodium, and crospovidone, in tablet formulations. However, most of the studies dealing with super disintegrants have examined disintegration or dissolution immediately after the manufacture of the tablets.[1-11] In terms of designing effective tablet formulations, it is important to study and compare the effect of aging on tablet formulations containing different disintegrants. Two investigators have reported the effect of aging on the disintegration time of tablets containing super disintegrants.[12,13] While tablet disintegration is often a required precursor for drug dissolution, it in no manner guarantees that the drug substance will dissolve, and hence, be available for transport across gastrointestinal tissues. Therefore, it is therapeutically more appropriate to examine the stability properties of super disintegrants in the context of how the dissolution rate of a model drug from the tablet is affected by storage. Horhota *et. al.*[14] and Bolhuis *et. al.*[15] have investigated the dissolution behavior of tablets containing sodium starch glycolate upon aging, while the characteristics of croscarmellose sodium and crospovidone upon aging have not been examined. The studies by Horhota *et. al.* and Bolhuis *et. al.* were carried out for one or two months. Although elevated humidity and temperature conditions were included, it has been noted that unlike chemical decomposition, it is not possible to quantitatively relate dissolution results from storage under stress conditions to shelf life.[14]

Tablets can also be protected from high levels of humidity with the moisture impermeable container systems now available. Therefore, the rational design of tablets that maintain good dissolution rates upon storage would be aided if the stability characteristics of the super disintegrants were described after a prolonged period of storage.

Several investigators have examined the behavior of super disintegrants complying with the same compendial specifications, but produced by different manufacturers.[16-20] Since these products may be interchanged in a production setting, it is essential to study their behavior in the formulation after aging. None of the reported studies have examined the behavior of these compendially identical disintegrants after aging.

This study examined the influence of storage at 30°C for fourteen months on the effectiveness of super disintegrants' ability to promote drug dissolution from directly compressed tablets, using tablets with varied composite solubility and hygroscopicity. Two types of super disintegrants were obtained from different sources to examine if their dissolution behavior was similar in the various formulations upon aging. It was found that the behavior of the disintegrants prior to and after aging was similar. The origin of the compendially identical super disintegrants had very little, if any, impact on dissolution characteristics after storage. Improved understanding of these factors should help in developing better tablet formulations.

EXPERIMENTAL

Materials - The sodium starch glycolate (Primojel, lot no. 1023, Generichem Corp.; Explotab, lot no. 2709X, Edward Mendell

Co., Inc.), crospovidone (Polyplasdone XL, lot no. 1073-5, GAF Corp.; Kollidon CL, lot no. 70-0539, BASF Wyandotte Corp.), croscarmellose sodium (Ac-Di-Sol, lot no. T532, FMC Corp.), dicalcium phosphate dihydrate (Emcompress, lot no. 9156, Edward Mendell Co., Inc.; notated as dicalcium phosphate in all tables), spray dried lactose (lot no. 3RL304, Foremost), sorbitol (Sorbelite, lot no. 021362, Edward Mendell Co., Inc.), and magnesium stearate (lot no. 2255V15, Mallinckrodt, Inc.) were all USP/NF grade. The para-aminobenzoic acid (lot no. 041857, Aldrich Chemical Co.) was at least 99% pure.

Powder Blend - The super disintegrant and the para-aminobenzoic acid were jointly passed through a 35-mesh screen. The powders, except for the magnesium stearate, were then blended in a small planetary type mixer (Kitchen Aid, Model K5-A, Hobart Manufacturing Co.) for 10 minutes. The powder blend was then mixed with the magnesium stearate for 3 minutes.

Compression - The tablets were compressed with a single punch machine (Stokes F-4) to a targeted hardness of 12 kiloponds and a targeted mass of 500 mg. The actual tablet hardness mean was 12.0 kiloponds with a standard deviation of 0.7 kiloponds. The actual tablet weight was 497 mg with a standard deviation of 6 mg. A 1.11 cm standard concave punch and die set was used, with a bisect on the upper punch.

Storage - The tablets were packaged in high density polyethylene bottles with polypropylene screw caps. The packaged tablets were stored in a chamber with a controlled temperature of 30°C $\pm$ 2°C for fourteen months.

Hardness Determination - The tablet hardness was determined immediately after compression using an instrument (Model HT-300,

Key International, Inc.) that utilizes the principal of strain gauge linear force to ascertain the degree of tablet hardness. Ten tablets were tested for each batch and the mean and standard deviation were calculated. Hardness was measured in kiloponds (1 kilopond = 1.4 Strong-Cobb units = 9.8 newtons).

In Vitro Dissolution - Dissolution of the tablets was performed according to USP XXI using Apparatus 1. Six tablets were tested for each batch and the mean and standard deviation were calculated. The medium was 900 ml of deaerated phosphate buffer (pH = 7.4) with a temperature of 37°C ± 0.5°C. The basket rotated at 100 rpm. Automated sampling equipment removed the samples through a filter and analyzed them spectrophotometrically at 254 nm.

Hygroscopicity - The hygroscopicity of the finished powder blends was determined for the control formulations by storing the blends for 26 hours in 98% relative humidity at room temperature. The formulation which contained sorbitol as the main tablet component exhibited a 12% weight gain, the sorbitol plus dicalcium phosphate dihydrate formulation demonstrated a 7% weight gain, and the three other formulations did not display any appreciable weight gain.

RESULTS AND DISCUSSION

Table 1 gives the generalized tablet formulation used in this study. It consisted of 1% para-aminobenzoic acid as a tracer, 2% super disintegrant, 0.5% magnesium stearate as a lubricant, and 96.5% filler(s). Thirty tablet formulations were prepared. Each formulation contained one of the five principal excipient combinations, thereby varying the composite

TABLE 1: Generalized Tablet Formulation For All Batches

Excipient	% W/W
Para-aminobenzoic acid	1.00
Super disintegrant	2.00[a]
Main tablet component (sorbitol, lactose, or dicalcium phosphate, or equal parts of sorbitol and dicalcium phosphate, or equal parts of lactose and dicalcium phosphate	96.50
Magnesium stearate	0.50

[a]Control formulations substituted 2% additional "main tablet component" for the super disintegrant.

solubility or hygroscopicity of the formulation. Each formulation contained either one of five super disintegrants, or no disintegrant in the control batch.

Dissolution results at the 5 minute timepoint for the thirty formulations are presented in Table 2. Except for the formulations containing sorbitol as the main tablet component, as a general rule all of the super disintegrants behaved in a statistically similar manner at the $p = 0.01$ level before and subsequent to storage. While the tablets that contained disintegrant with sorbitol as the main tablet component did exhibit upon aging an average of an eight percent increase in the amount dissolved, the control formulation exhibited a

TABLE 2: Tablet Dissolution Results at 5 Minutes For Tablets Before and After Storage for 14 Months at 30°C, Sorted by the Main Tablet Component(s), and Then by Increasing Dissolution For the Aged Tablets

Main Tablet Component(s)	Disintegrant	% Dissolved ± S.D. Before Storage, at 5 Minutes	% Dissolved ± S.D. After Storage, at 5 Minutes	Significance Of Difference[a] Between Initial And Aged Tablets	Significance Of Difference[b] Between Tablet Disintegrants For the Aged Tablets
Sorbitol	Sodium Starch Glycolate[c]	53.8 ± 1.8	61.8 ± 1.5	$p < .01$	
"	No Disintegrant	56.0 ± 1.0	63.4 ± 1.4	$p < .01$	
"	Sodium Starch Glycolate[d]	59.4 ± 2.1	65.6 ± 3.3	$p < .01$	
"	Crospovidone[f]	63.4 ± 1.5	70.3 ± 1.5	$p < .01$	
"	Crospovidone[e]	61.8 ± 1.4	73.0 ± 1.4	$p < .01$	
"	Croscarmellose Sodium	65.5 ± 1.2	75.8 ± 1.9	$p < .01$	
Lactose	No Disintegrant	22.3 ± 0.8	17.8 ± 1.0	$p < .01$	
"	Sodium Starch Glycolate[d]	90.8 ± 0.8	91.6 ± 1.6	Not significant	
"	Sodium Starch Glycolate[c]	92.9 ± 2.0	93.5 ± 1.6	Not significant	
"	Crospovidone[f]	94.5 ± 0.6	94.4 ± 1.0	Not significant	
"	Croscarmellose Sodium	94.9 ± 0.7	95.9 ± 1.3	Not significant	
"	Crospovidone[e]	97.6 ± 0.6	97.1 ± 1.3	Not significant	
Sorbitol/Dicalcium Phosphate	No Disintegrant	26.9 ± 0.9	34.3 ± 1.7	$p < .01$	
"	Sodium Starch Glycolate[c]	68.2 ± 1.3	74.1 ± 3.3	$p < .01$	
"	Sodium Starch Glycolate[d]	77.1 ± 2.5	80.3 ± 3.3	Not significant	
"	Crospovidone[e]	77.5 ± 3.3	81.1 ± 2.2	Not significant	
"	Crospovidone[f]	79.4 ± 5.5	81.7 ± 5.5	Not significant	
"	Croscarmellose Sodium	80.4 ± 1.6	86.7 ± 2.8	$p < .01$	
Lactose/Dicalcium Phosphate	No Disintegrant	11.6 ± 0.4	10.9 ± 0.4	$p < .05$	
"	Sodium Starch Glycolate[c]	91.1 ± 0.5	93.4 ± 1.0	$p < .01$	
"	Crospovidone[f]	93.9 ± 2.0	94.2 ± 1.0	Not significant	
"	Sodium Starch Glycolate[d]	92.9 ± 1.8	95.1 ± 2.0	Not significant	
"	Croscarmellose Sodium	96.1 ± 1.8	96.7 ± 0.8	Not significant	
"	Crospovidone[e]	97.3 ± 1.0	98.0 ± 1.3	Not significant	
Dicalcium Phosphate	No Disintegrant	9.0 ± 0.5	8.7 ± 0.6	Not significant	
"	Sodium Starch Glycolate[d]	93.4 ± 1.2	94.1 ± 1.2	Not significant	
"	Sodium Starch Glycolate[c]	94.5 ± 1.6	95.5 ± 1.1	Not significant	
"	Croscarmellose Sodium	96.1 ± 1.1	95.6 ± 0.5	Not significant	
"	Crospovidone[f]	95.9 ± 0.9	96.4 ± 0.6	Not significant	
"	Crospovidone[e]	96.5 ± 0.9	97.7 ± 1.2	Not significant	

[a]The statistical significance was tested using a Student's t test at the $p = 0.05$ and $p = 0.01$ levels.
[b]The statistical significance was calculated by the least significant difference method at the $p = 0.01$ level. A line connecting data indicates that the results were not significantly different.
[c]Edward Mendell Co., Inc.
[d]Generichem Corp.
[e]BASF Wyandotte Corp.
[f]GAF Corp.

TABLE 3: Tablet Dissolution Results at 5 Minutes For Tablets Stored For 14 Months at 30°C, Sorted by Disintegrant Used and Then by Increasing Dissolution

Disintegrant	Main Tablet Component(s)	% Dissolved ± S.D. After Storage, at 5 Minutes	Statistical Significance[a]
None	Dicalcium Phosphate	8.7 ± 0.6	
"	Lactose/Dicalcium Phosphate	10.9 ± 0.4	
"	Lactose	17.8 ± 1.0	
"	Sorbitol/Dicalcium Phosphate	34.3 ± 1.7	
"	Sorbitol	63.4 ± 1.4	
Sodium Starch Glycolate[b]	Sorbitol	65.6 ± 3.3	
"	Sorbitol/Dicalcium Phosphate	80.3 ± 3.3	
"	Lactose	91.6 ± 1.6	]
"	Dicalcium Phosphate	94.1 ± 1.2	
"	Lactose/Dicalcium Phosphate	95.1 ± 1.2	]
Sodium Starch Glycolate[c]	Sorbitol	61.8 ± 1.5	
"	Sorbitol/Dicalcium Phosphate	74.1 ± 3.3	
"	Lactose/Dicalcium Phosphate	93.4 ± 1.0	]
"	Lactose	93.5 ± 1.6	
"	Dicalcium Phosphate	95.5 ± 1.1	]
Crospovidone[d]	Sorbitol	70.3 ± 1.5	
"	Sorbitol/Dicalcium Phosphate	81.7 ± 5.5	
"	Lactose/Dicalcium Phosphate	94.2 ± 1.0	]
"	Lactose	94.4 ± 1.0	
"	Dicalcium Phosphate	96.4 ± 0.6	]
Crospovidone[e]	Sorbitol	73.0 ± 1.4	
"	Sorbitol/Dicalcium Phosphate	81.1 ± 2.2	
"	Lactose	97.1 ± 1.3	]
"	Dicalcium Phosphate	97.7 ± 1.2	
"	Lactose/Dicalcium Phosphate	98.0 ± 1.3	]
Croscarmellose Sodium	Sorbitol	75.8 ± 1.9	
"	Sorbitol/Dicalcium Phosphate	86.7 ± 2.8	
"	Dicalcium Phosphate	95.6 ± 0.5	]
"	Lactose	95.9 ± 1.3	
"	Lactose/Dicalcium Phosphate	96.7 ± 0.8	]

[a]The statistical significance was calculated by the least significant difference method at the p = 0.01 level. A line connecting data indicates that the results were not significantly different.
[b]Generichem Corp.
[c]Edward Mendell Co., Inc.
[d]GAF Corp.
[e]BASF Wyandotte Corp.

similar increase in dissolution rate, demonstrating that the increased dissolution was independent of the super disintegrants. Therefore, the data indicates that tablet solubility and hygroscopicity do not influence the effectiveness of super disintegrants in a time dependent fashion. However, it has been noted[18] that hygroscopic ingredients decrease the effectiveness of super disintegrants in promoting dissolution in freshly prepared tablets. Table 3 demonstrates that when the data is organized in a manner to permit analysis for the impact of tablet composite hygroscopicity, that after storage the more hygroscopic formulations dissolve significantly slower than do the nonhygroscopic formulations.

Table 2 also shows the statistical significance of the differences between the super disintegrants in a given formulation, allowing an analysis of whether the source of the sodium starch glycolate or crospovidone influences the performance of these disintegrants after storage of the tablets. The two sodium starch glycolate products behave significantly different ($p=0.01$) in two out of the five formulations upon aging, as do the the two crospovidone materials. Therefore this data is statistically inconclusive as to whether the compendially identical disintegrants behave differently. The sodium starch glycolate products exhibited a variation of not more than 6.2% in a given formulation, while the crospovidone materials demonstrated a maximum inequality of 3.8%. This indicates that whereas some statistical differences were found when the behavior of the compendially identical super disintegrants were compared, from a practical viewpoint the pharmacopoeially identical materials behaved similarly.

CONCLUSIONS

The results of this study suggest that prolonged storage of tablets at 30°C does not affect the dissolution efficiency of the super disintegrants in direct compression formulations. The ability of the super disintegrants to resist change during tablet storage was independent of the composite solubility or hygroscopicity of the formulation. However, the decrease in super disintegrant effectiveness in promoting tablet dissolution that has been observed, prior to storage, to be related to composite hygroscopicity persisted after storage. The data also imply that super disintegrants that meet the same compendial specifications, but that are manufactured by different companies, will maintain similar properties upon tablet aging.

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