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THE EFFECT OF MOLECULAR STRUCTURE ON THE FUNCTION OF SODIUM STARCH GLYCOLATE IN WET GRANULATED SYSTEMS

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ABSTRACT

The effect of variation in the degree of cross-linkage and extent of substitution on the disintegrant properties of sodium starch glycolate in wet granulated systems has been examined. The rates of mixing shear were evaluated for their effect on the ability of the disintegrants to function after granulation. In addition, the effect of varying the intragranular and extragranular concentration of the disintegrants was investigated. The results indicate that increased rates of mixing shear adversely effect sodium starch glycolates. In addition, the current commercial specifications for a marketed sodium starch glycolate seem to be optimal in this regard. It also seems evident that a

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mixture of disintegrant within and around the granule is desirable in wet granulated systems.

Previous papers have discussed the importance of raw materials specifications in defining the fitness for use of many pharmaceutical excipients (1-6). We have recently initiated a study concerning the effect of variation of degree of cross-linkage and extent of substitution on the disintegrant action of sodium starch glycolate in direct compression systems. Further details of this study will be provided in a paper focussed on standard raw materials tests for disintegrants and their relative differences in direct compression systems (7).

EXPERIMENTAL

Table I lists the specifications for each of the modified sodium starch glycolates. Fifteen modifications were selected for this study and their composition is represented in the grid by "X's" in Table I. The modifications that were supplied[1] were confirmed by standard organic sodium determinations (8). For the purpose of this paper, individual modified sodium starch glycolates will be referred to by their coordinates in Table I. The first number indicates the horizontal position in the grid (degree of cross-linkage), while the second number indicates the vertical position (degree of carboxymethylation). Thus, the modification

1. Roquette Freres, Lille, France

coded 5-1 has the least amount of cross-linkages and the least amount of carboxymethylation of all the modfications. The sample coded 1-5 has the most amount of cross-linkages and the most amount of carboxymethylation of all the modifications. The sample coded 3-3 is the current commercial specifications for a marketed sodium starch glycolate.[2]

The modified disintegrants were incorporated into an aspirin formulation as listed below:

Aspirin (crystalline)[3]	50%
National 1551 Starch[4]	5%
Stearic Acid[5]	2%
Sodium starch glycolate[1]	2% (intragranular)
" " "	2% (extragranular)
Dibasic Calcium phosphate[6]	19.5%
Hydrous Lactose[7]	19.5%
TOTAL----	100.0%

The aspirin, binder (National 1551), one-half the disintegrant (2%), the calcium phosphate and the lactose were added together in a mixer. The granulating fluid was distlled water (90ml/kg). There were three mixing conditions used: for "low-shear" mixing, a planetary mixer[8] was used at a low setting (#2) and mixing times were no less than eight but no more than eleven minutes. For

2. Explotab, Edward Mendell Co., Inc., Carmel, NY
3. Ruger Chemical Co., Irvington, NJ
4. National Starch Co., Plainfield, NJ
5. Ruger Chemical Co., Irvington, NJ
6. Stauffer Chemical Co., Westport, CT
7. Foremost Foods Co.,San Francisco, CA
8. Kitchen-Aid, K-5A mixer,

Table I

CHEMICAL MODIFICATIONS OF SODIUM STARCH GLYCOLATE STUDIED*

Degree of Substitution	Coordinates	Cross-linkage +30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	X		X		X
-14%	2		X	X		
0	3	X	X	$\underline{X}$	X	X
+21%	4			X	X	
+38%	5	X		X		X

*note- Modifications synthesized are represented by an "X".

"medium-shear" conditions, the same planetary mixer was used at a high setting (#10). The mixing times for this condition were no less than seven minutes and no more than ten minutes. For "high-shear" conditions, a rapid mixer[9] was used at it's maximum setting. This mixer has both plows and blades and is similar to other rapid mixers in this regard. The mixing times for this system was no less than seven minutes but no more than eight minutes.

The granulate was then sieved through a 6-mesh screen, and placed in a cirulating-current oven[10] at 40°C. until the moisture content

9. Erweka Rapid Lab Mixer, Erweka Apparatabau, West Germany
10. Blue M Oven, Blue M Co.,Blue Island, Illinois

was 5% (about 1½ hours). The dry granulate was then milled[11] and sieved to remove fines.

The remaining disintegrant and the lubricant were added in proportion and the formulation mixed[12]. The formulations were then tableted on a rotary tablet press[13]. The tablets were then tested for weight[14], hardness[15], disintegration[16] and dissolution[17] (according to U.S.P. Specifications).

The modified sodium starch glycolates were also incorporated into an acetaminophen formulation as listed below:

Acetaminophen[18]	50%
National 1551 Starch[4]	5%
Stearic Acid	2%
Sodium Starch Glycolate	1,2 or 3%(intragranular)
" " "	3,2,or 1%(extragranular)
Calcium Phosphate Dihydrate	qs
	100%

As shown in the formulation above, the modified disintegrants were incorporated into the systems at an intra/extragranular ratio of 25/75, 50/50 and 75/25, for each of the modifications. The drug, binder, disintegrant and calcium phosphate were added

11. Fitzpatrick Co.,Chicago, Illinois
12. WAB Turbula Mixer, WABachoven Co.,Basel, Switzerland
13. Stokes B-2 Tablet Press, Stokes-Penwalt Co.,Warminster, PA
14. Mettler H-8 Balance, Mettler Co.,Switzerland
15. Erweka Hardness Tester, Erweka Apparatabau, West Germany
16. U.S.P. Apparatus, with discs.
17. Dissograph, Hanson Research Co.,Northridge, CA
18. Ruger Chemical Co., Irvington, NJ

together in a palnetary mixer as before, and mixed at a setting #5 on the mixer for no less than eight minutes, and no more than 12 minutes. The resultant granulate was dried, milled and sieved as before, and tableted on the same tablet press. The physical tests done on the tablets were identical to those described above.

RESULTS AND DISCUSSION

The tablet weights for the systems made at all three mixing conditions were essentially the same and were $\pm$ 2% of the mean (approx. 885mg).

The tablet hardnesses for the three systems also were equivalent for all practical purposes and were $\pm$ 1.5kg. from the mean (approx. 7kg.)

The tablet disintegration data for all three systems and all fifteen modified sodium starch glycolates are listed on Tables II-IV. From these data, it is clear that the upper right quadrant of the grid (lower cross-linkage and carboxymethylation) is favored over the rest and that a plateau of sorts exists around the center of the grid (the commercial specifications). The disintegration times, in general, tend to increase as the rate of shear or mixing speed increases.

Figs. 1-3 show the dissolution profiles for the aspirin formulations made at the three mixing conditions. From these it is apparent that the rates of mixing have a marked effect on the rate of release of drug from the tablets. In addition, it seems

Table II

Disintegration Times of Planetary Mixer (slow) Granulated Aspirin Formulations

Levels	Coordinates		+30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	mean	4.1 min.		3.8		1.6
		range	3.8-4.7		3.2-4.3		1.5-1.8
-14%	2			3.9	1.3		
				3.3-4.7	1.0-1.6		
0	3		2.2	1.4	1.2	2.4	1.8
			1.9-2.6	1.0-1.6	0.9-1.5	1.0-2.9	1.4-2.1
+21%	4				2.9	1.3	
					2.5-3.3	0.9-1.5	
+38%	5		6.1		2.4		4.8
			5.4-6.3		1.8-2.4		4.3-5.1

Table III

Disintegration Times of Planetary Mixer (fast) Granulated Aspirin Formulations

Levels	Coordinates	+30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	mean 4.7 min. range 4.5-5.1		12.2 9.8-14.3		6.8 6.4-7.1
-14%	2		3.4 2.9-3.6	2.3 1.9-2.4		
0	3	14.5 14.1-15.5	3.9 3.4-4.6	1.8 1.5-2.1	1.9 1.1-2.3	3.8 3.4-4.3
+21%	4			11.2 10.4-12.0	5.1 4.6-6.9	
+38%	5	4.3 3.9-4.5		4.6 4.0-12.0		5.8 5.3-6.6

Table IV

Disintegration Times for Rapid Lab Mixer Granulated Aspirin Formulations

Levels	Levels Coordinates	+30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	mean 13.6 range 8.2-15.6		21.3 16.4-24.1		22.6 18.1-24.6
-14%	2		9.3 7.9-10.8	10.8 9.1-12.7		
0	3	17.9 16.7-24.9	18.4 16.2-20.3	8.1 5.1-8.8	11.1 10.5-12.0	12.7 10.2-15.2
+21%	4			19.6 15.3-21.8	16.5 12.5-14.5	
+38%	5	12.4 11.8-16.1		17.2 13.1-19.5		18.9 13.8-21.4

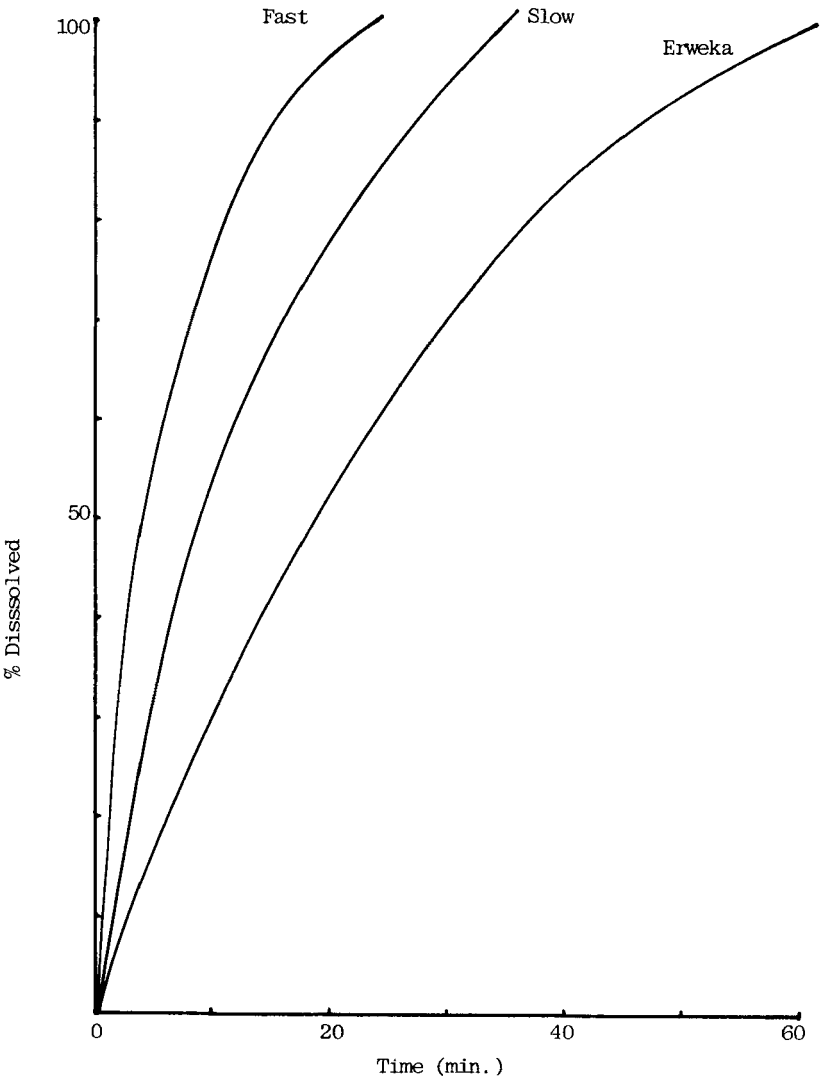

Fig. 1
Dissolution Curves for ASA Formulation (W.G.) for
Sodium Starch Glycolate 1-5

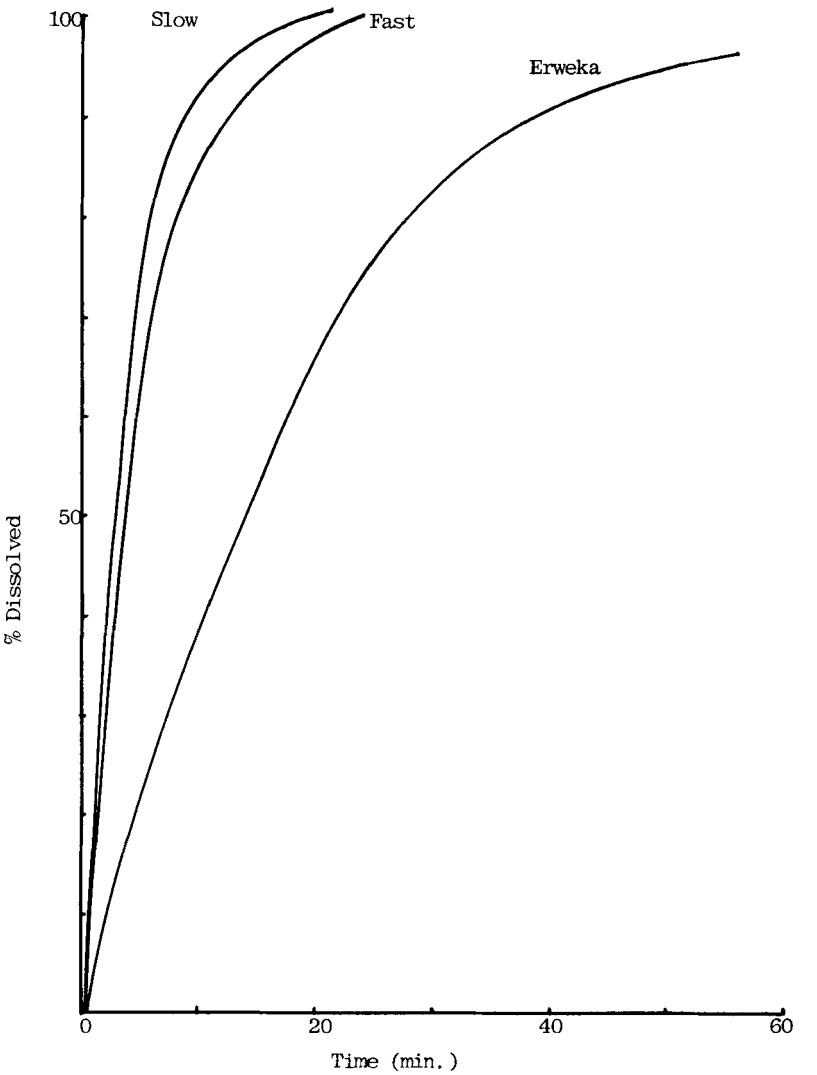

Fig. 2
Dissolution Curves for ASA Formulation (W.G.) for Sodium Starch Glycolate 3-3.

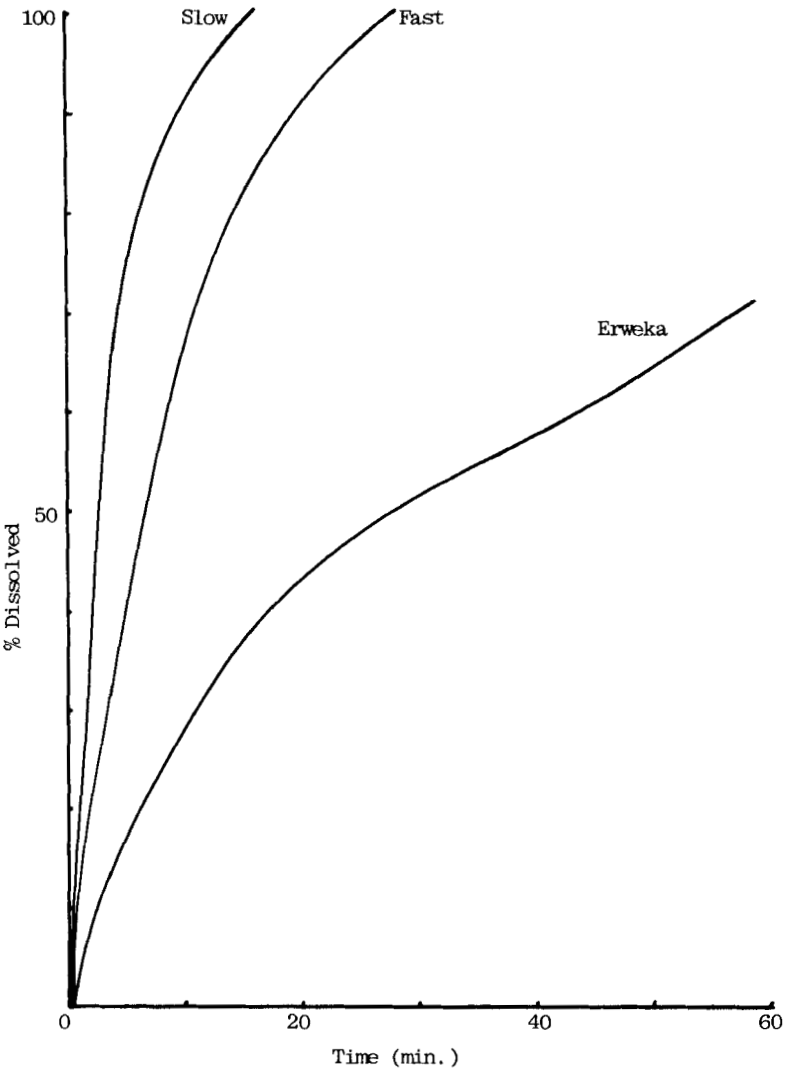

Fig. 3
Dissolution Curves for ASA Formulation (W.G.) for Sodium Starch Glycolate 5-1.

Table V

Disintegration Times for Acetaminophen Formulation (25% Intra/75% Extragranular)

Level	Level		+30%	+18%	0	-12%	-30%
Level	Coordinates		1	2	3	4	5
-31%	1	mean	4.4 min.		4.2		2.9
-14%	2			3.7	4.1		
0	3		3.7	3.4	5.1	5.2	2.7
+21%	4				2.9	4.4	
+38%	5		4.8		4.5		2.1

Table VI

Disintegration Times for Acetaminophen Formulation (50% Intra/50% Extragranular)

Level	Level Coordinates	+30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	3.4 min.		4.1		3.7
-14%	2		3.3	4.6		
0	3	2.5	3.4	5.9	3.3	2.9
+21%	4			3.4	4.2	
+38%	5	3.4		5.2		2.3

Table VII

Disintegration Times for Acetaminophen Formulation (75% Inra/25% Extragranular)

Level	Level / Coordinates		+30% 1	+18% 2	0 3	-12% 4	-30% 5
-31%	1	mean	9.7		11.3		8.9
-14%	2			12.4	12.2		
0	3		11.1	9.8	10.4	12.2	12.9
+21%	4				14.4	13.2	
+38%	5		12.1		9.9		7.2

clear from these data that the current commercial specifications for this disintegrant are optimal.

The tablet weights for the acetaminophen systems were also essentially the same, with all weights being $\pm$4% of the mean (approx. 570mg.). The tablet hardnesses were also equivalent and were $\pm$2kg. of the mean for each system (25/75, 50/50 and 75/25 intra/extragranular ratios).

Tables V-VII show the disintegration data for the three systems. In general, the disintegration times increase as the percentage of intragranular disintegrant increases. This may be due to some of the disintegrant acting as a binder within the granule. It is also evident that the center of the grid (the commercial specifications) seem to be optimal for the 75/25 system although no real conclusions can be made with the other systems. However, it seems that lower levels of cross-linkage and substitution are favored when compared to higher levels of cross-linkage and substitution, for the remaining two systems.

CONCLUSIONS

With the current proliferation of cross-linked, substituted polymers intended for pharmaceutical systems, it has become increasingly important to monitor the raw material specifications and the molecular specifications of these substances. This paper clearly identifies the effect which even minor changes in molecular structure can have on the performance of so called "inert" excipients. Although

most prudent manufacturers have rigorous raw materials control standards, the verification of molecular specifications is rarely, if ever accomplished.

This study clearly shows that for at least one excipient, it is necessary to maintain strict control over the molecular structure of the commercial product to maintain consistent quality. There is an obvious need for further studies of this type on the effect of variation of molecular structure on the performance of many pharmaceutical excipients.

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