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EFFECT OF CROSPOVIDONE ON THE WET GRANULATION ASPECTS OF ACETAMINOPHEN

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ABSTRACT

The effect of crospovidone on the characteristics of wet granulated acetaminophen was investigated. Powder blends of acetaminophen and crospovidone were wet granulated using hydroxypropyl methylcellulose as the binder and water as the granulating liquid. The sieve analysis data showed that as the level of crospovidone in the powder blend increased, there was an increase in the amount of fines in the particle distribution of the dried granulations. The bulk densities of formulae containing a higher level of crospovidone were generally lower although no clear trend was seen for the tap density values. Interference in the hydration of hydroxypropyl methylcellulose, and increase in the total surface area were considered as two possible mechanisms for the effect of crospovidone. The results of this study indicate that an interaction of both mechanisms may be responsible for the effect of crospovidone on the characteristics of wet granulated acetaminophen.

INTRODUCTION

Crospovidone, one of the newer disintegrants used in tablet formulations, is a crosslinked insoluble homopolymer of N-vinyl-2-pyrolidone. The superior disintegrating action of crospovidone is attributed to its tremendous swelling property in the presence of water[1]. Polyplasdone XL® and Polyplasdone XL-10® are two commercially available forms of crospovidone. Polyplasdone XL-10 has a very fine particle size distribution (90 percent less than 75µ).

In the wet granulation operation a disintegrant can be incorporated into the formulation in one of three ways: added to the powder blend before the wet granulation process, added after the wet granulation process during the final blending operation just prior to compression, or added in divided portions before and after the wet granulation process[2]. Agglomeration during the wet granulation process is caused by a complex interaction of several variables. In discussing these variables, Aulton and Banks[3] distinguished between apparatus variables, process variables and product variables. The product variables are related to the starting materials, the applied binder and the binder solvent.

During the scale-up work on a tablet formulation containing crospovidone, the observation was made that the amount of crospovidone used in the wet granulation step significantly affected the particle size distribution of the dried granulation. When the entire amount of crospovidone was included at the wet granulation step, the particle size distribution of the dried granulation had a high percent of fines, whereas when only one-half of the crospovidone amount was included in the wet granulation, the particle size distribution of the dried granulation was coarser and the granules appeared denser in nature. The granulation containing a high percent of fines resulted in a capping problem during compression whereas the coarser granulation could be compressed without any problem.

The objective of this study was to identify the mechanism by which crospovidone influences the characteristics of wet granulated acetaminophen which was selected for this study because it is similar in physical characteristics to the principal ingredient of the scale-up tablet. Therefore the results obtained in this study would be useful in understanding the wet granulation behavior of the scale-up formulation.

EXPERIMENTAL

The compositions of the powder blends and the amount of water used as the granulating liquid are shown in Table 1. The batch weights were adjusted such that the total batch weight was 750 g. The granulating liquid for Formulae 1, 2 and 3 was 120.4 ml of deionized water. Formulae 4, 5 and 6 had the same composition as Formulae 1, 2 and 3, respectively, except the hydroxypropyl methylcellulose was dispersed in deionized water and used as the granulating liquid. Formulae 7, 8 and 9 compositions were the same as Formula 2 except the water amounts were increased to

Table 1

Formula	Acetaminophen[1] (% w/w)	Polyplasdone[2] (% w/w)	HPMC 2910[3] 15 cps	Water (ml)
1	97.2	0.0	2.8	120.4
2	92.9	4.3	2.8	120.4
3	89.0	8.2	2.8	120.4
4	97.2	0.0	2.8[4]	120.4
5	92.9	4.3	2.8[4]	120.4
6	89.0	8.2	2.8[4]	120.4
7	92.9	4.3	2.8	132.4
8	93.9	4.3	2.8	144.5
9	92.9	4.3	2.8	156.5
10	89.0	8.2	2.8	138.5
11	89.0	8.2	2.8	154.5
12	89.0	8.2	2.8	174.6

[1]RPS France, Rhone-Poulence Inc., Chicago, IL.
[2]GAF Corporation, Wayne, NJ.
[3]The Dow Chemical Company, Midland, MI.
[4]Dispersed in water and used as the granulating liquid.

132.4, 144.5 and 156.5 ml, respectively, representing increases of 10, 20, and 30 percent over the amount used in Formula 2. Similarly, Formulae 10, 11 and 12 were the same as Formula 3 except the water amounts were increased to 138.5, 154.5 and 174.6 ml, respectively, representing increases of 15, 30 and 45 percent over the amount used in Formula 3.

Granulation Process

The powders were placed in a Littleford Lodige mixer[4] and mixed for three minutes. The granulating liquid (water or hydroxypropyl methylcellulose dispersion in water) was added in approximately 30 seconds while mixing. Mixing was continued for an additional four minutes, 30 seconds. The wet mass was then passed through a 16 mesh screen and dried in an oven[5] at 65°C for six hours to a moisture level of about 1 percent w/w.

Table 2
Particle Size Distribution Data for Acetaminophen-HPMC-Crospovidone Granulations

Formula No.	Percent Retained on Sieve No.						Geometric Mean Diameter (μ)
	20	40	60	80	100	Pan	
1	21.3	25.2	16.4	14.2	6.6	16.3	410
2	18.5	17.3	9.8	8.4	6.1	39.9	246
3	17.4	16.7	8.6	8.5	7.9	40.9	228
4	15.5	30.9	10.4	6.3	4.1	32.8	315
5	14.2	21.6	7.5	4.8	4.2	47.7	190
6	11.7	19.0	5.1	3.8	4.1	56.3	129
7	22.0	20.1	11.2	9.3	6.7	30.7	328
8	25.5	21.9	12.1	10.1	6.8	23.6	401
9	28.0	21.8	13.0	10.3	7.5	19.4	443
10	17.5	20.9	10.4	10.3	3.4	37.5	246
11	18.3	23.3	13.0	13.8	3.0	28.6	305
12	27.4	24.0	11.6	11.9	2.0	23.1	415

Sieve Analysis Procedure

U. S. standard sieve Nos. 20, 40, 60, 80 and 100 were used. For particle size analysis, a 10 g sample was placed in the top sieve and shaken on the ATM sonic sifter[6] for five minutes with the sift and pulse amplitudes set at 5. The fraction retained on each screen was determined and the geometric mean diameter of the granulation was calculated from the sieve analysis data.

Bulk and Tap Density Measurement Procedure

The granulation was poured through a funnel into a tared 50 ml graduated cylinder. The volume of the granulation was recorded. The graduated cylinder was weighed and the bulk density calculated as the ratio of the sample weight to the sample volume. The graduate was then tapped on the Eberhard Bauer D-7300 Esslingen[7] tap density apparatus. The tap density was calculated as the ratio of the sample weight to the final sample volume.

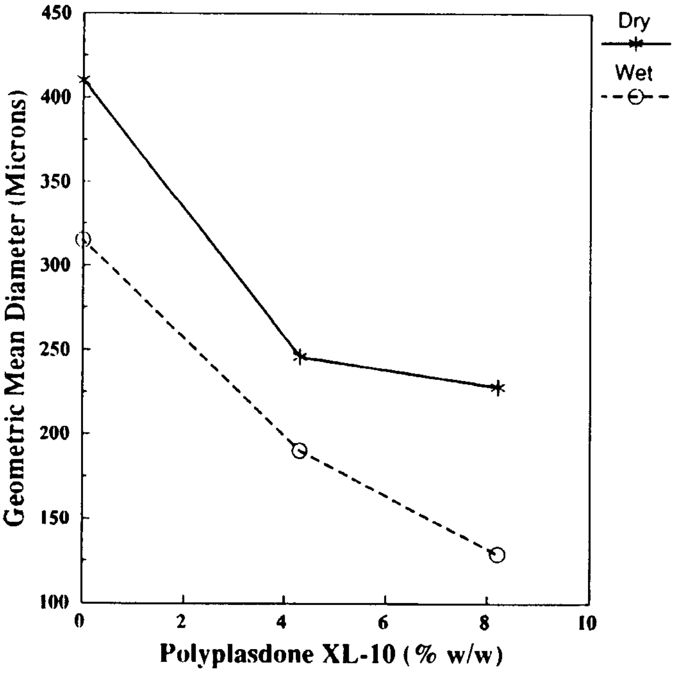

Figure 1 - Effect of Level of Polyplasone XL-10 and Method of Binder Addition on Geometric Mean Diameter of Acetaminophen Granulations

Surface Area Measurement Procedure

A single point BET method was used for the determination of the specific surface area of acetaminophen and Polyplasdone XL-10 using the Quantasorb[8] apparatus.

RESULTS AND DISCUSSION

The sieve analysis data shown in Table 2 indicate that as the level of Polyplasdone XL-10 in the powder blend is increased there is a decrease in the coarser fraction (>60 mesh) of the dried granulation with a corresponding increase in the amount of fines (<100 mesh).

The sieve analysis data for granulations prepared using a dispersion of hydroxypropyl methylcellulose in water (Formulae 4, 5 and 6) show a trend similar to the one observed for granulations prepared with water although tending to be smaller in size. The effect of the level of Polyplasdone XL-10 and the method of addition of the binder

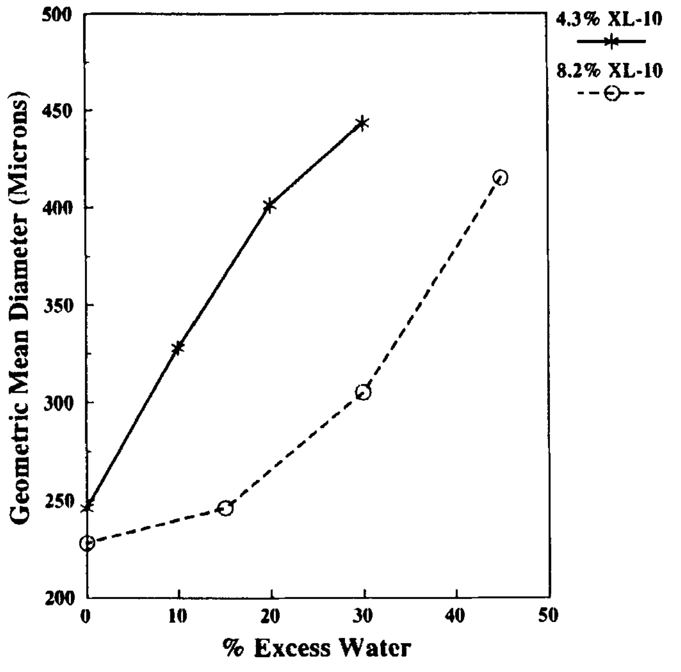

Figure 2 - Geometric Mean Diameter as a Function of Percent Excess Water for Two Levels of Polyplasdone XL-10

on the geometric mean diameter of the dried granulations is shown in Figure 1. The sieve analysis data for formulae containing 4.3 and 8.2 percent of Polyplasdone XL-10 prepared with additional water (Formulae 7, 8, 9 and 10, 11, 12, respectively) indicate that an increase in the amount of water results in an increase in the coarser fraction with a corresponding decrease in the amount of fines. A plot showing the effect of additional water on the geometric mean diameter of granulations containing the two levels of Polyplasdone XL-10 is shown in Figure 2. As can be seen from this plot the geometric mean diameter increases sharply with an increase in the amount of water for the granulations containing 4.3 percent Polyplasdone XL-10 whereas for the granulations containing 8.2 percent Polyplasdone XL-10 there is an initial gradual increase followed by a rapid increase in the geometric mean diameter.

Table 3 shows the bulk and tap density data for Formulae 1-12. Consistent with the changes in the particle size distribution the bulk density for granulations prepared using water as the granulating liquid (Formulae 1, 2 and 3) tends to decrease with an

Table 3
Bulk and Tap Density Data for Acetaminophen-HPMC-Crospovidone Granulations

Formula No.	Bulk Density (g/ml)	Tap Density (g/ml)
1	0.39	0.49
2	0.36	0.50
3	0.30	0.43
4	0.44	0.55
5	0.36	0.54
6	0.33	0.54
7	0.33	0.43
8	0.36	0.47
9	0.30	0.45
10	0.29	0.40
11	0.30	0.39
12	0.30	0.39

increase in the level of Polyplasdone XL-10. This trend in the bulk density values is also seen for the granulations prepared using a dispersion of hydroxypropyl methylcellulose in water (Formulae 4, 5 and 6). This trend is, however, not seen for the granulations containing either 4.3 or 8.2 percent of Polyplasdone XL-10 prepared with an additional amount of water (Formulae 7, 8, 9 or 10, 11, 12, respectively). The tap density values remained relatively constant independent of the Polyplasdone XL-10 level or the amount of water.

Since the granulations prepared using a dispersion of hydroxypropyl methylcellulose in water exhibited a difference in the particle size distribution with respect to the amount of Polyplasdone XL-10, it was considered that the mechanism of its influence may be more surface area related. If interference with the hydration process was the governing mechanism, the additional water should not have a significant effect since the water absorption capacity of Polyplasdone XL-10 is very high. To further identify the surface area effect, the specific surface area of acetaminophen and Polyplasdone XL-10 were measured. Acetaminophen was found

Table 4
Surface Area and Batch Weight/Water Amount and Surface Area/Water Ratios for Acetaminophen-Crospovidone-HPMC Powder Blends

Formula No.	Surface Area (m^2)	Batch Weight/ Water Amount (g/ml)	Surface Area/ Water Amount (m^2/ml)
1	365	6.24	3.03
2	393	6.24	3.27
3	421	6.24	3.49
4	365	6.24	3.03
5	394	6.24	3.27
6	421	6.24	3.49
7	394	5.67	2.98
8	394	5.19	2.73
9	394	4.80	2.52
10	421	5.43	3.04
11	421	4.87	2.72
12	421	4.31	2.41

to have a specific surface area of 0.5 m^2/g and Polyplasdone XL-10 a specific surface area of 1.42m^2/g. The total surface areas, and the batch weight/water amount and surface area/water amount ratios for the powder blends in Formulae 1-12 are shown in Table 4.

Since HPMC would be expected to hydrate its surface area was ignored in the calculation. As can be seen from the surface area values, at 4.3 percent w/w level Polyplasdone XL-10 increases the surface area of the powder blend from 365 m^2 to 393 m^2, and to 421 m^2 at 8.2 percent w/w level.

Carstensen and Zoglio[9] have proposed a model for the wet granulation process for a bolus type of granulation. A schematic diagram of the model is shown in Figure 3. According to their model, as the granulating liquid is added there are two

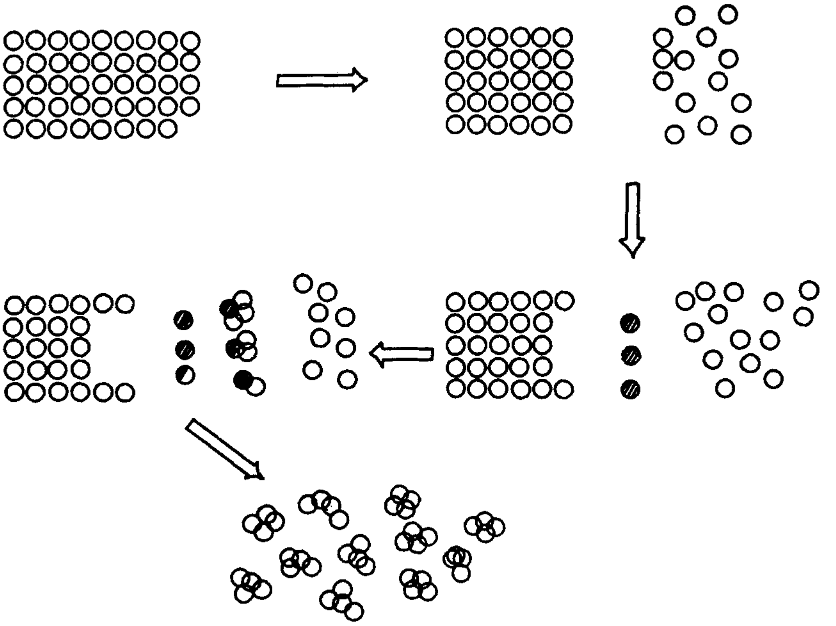

Figure 3 - Model for Bolus Type Granulation [reproduced from Pharm. Tech.,1985, Conference Proceedings (4)]

parts in the mixer, a bolus wetted part (shown as circles in a rectangle) and the unwetted primary particles (shown random). The next step involves shredding off of the nuclei (crossed-hatched particles) which combine with the primary particles resulting in granule growth. This process continues with mixing and eventually all the wet material gets distributed as equilibrium granules.

The effect of Polyplasdone XL-10 can be viewed in reference to the above model. Because of the its fine particle size, as the amount of Polyplasdone XL-10 in the powder blend is increased the number of particles in the powder blend is increased. When the granulating liquid is added, the fraction of the bolus wetted part decreases with an increase in the number of unwetted primary particles. The result is a fewer number of nuclei and a hindered granule growth. The effect of using an aqueous hydroxypropyl methylcellulose dispersion can also be considered in reference to the above model. In the hydration of hydroxypropyl methylcellulose, water molecules are bound to the polymer molecules therefore the dispersion would have a superior binding property but a diminished wetting capacity. This diminished wetting capacity

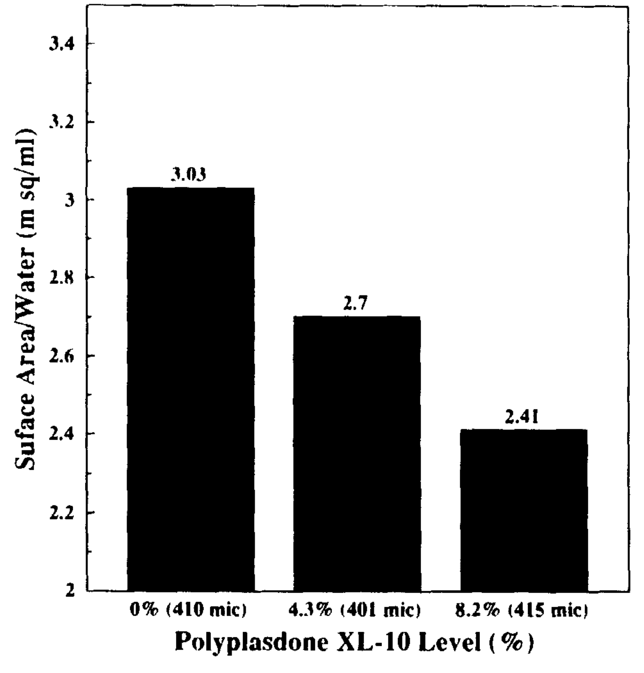

Figure 4 - Surface Area/Water Amount Ratios for Formulae 1, 8 and 12

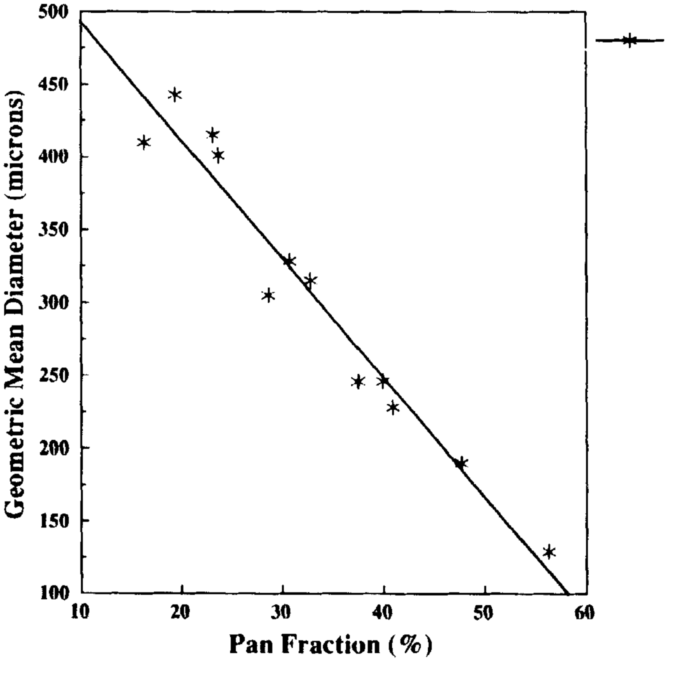

Figure 5 - Geometric Mean Diameter as a Function of Pan Fraction for Acetaminophen Granulation Formulae 1 - 12

would result in a smaller fraction of the wetted bolus part and a limited granule growth.

A plot of the surface area to water amount ratio for Formulae 1, 8 and 12 is shown in Figure 4. The surface area to water amount ratio for Formula 1 containing no Polyplasdone XL-10 is 3.03 m^2/ml. The particle size distribution and the geometric mean diameter of Formulae 1 and 8 are comparable although the surface area to water amount ratio for Formula 8 containing 4.3 percent Polyplasdone XL-10 is 2.73.m^2/ml. Similarly, the geometric mean diameter of Formula 12 containing 8.2 percent Polyplasdone XL-10 is comparable to the geometric mean diameter of Formula 1. The surface area/water amount ratio for this formula is 2.41 m^2/ml. If the mechanism of the effect of Polyplasdone XL-10 were strictly surface area related then the surface area/water amount ratio for Formula 1, 8 and 12 should be very close if a linear relationship is assumed. This negative deviation from linearity of the surface area/water amount ratio could be because of the high water absorption capacity of Polyplasdone XL-10. The geometric mean diameter data for Formulae 1-12 are plotted as a function of the corresponding pan fraction in Figure 5. It is interesting to note a statistically significant linear relationship ($R^2 = 0.97$) between these two factors.

CONCLUSION

Polyplasdone XL-10 has a significant effect on the particle size distribution of acetaminophen granulations. The mechanism of its influence appears to be related to a cumulative effect of its small particle size and high water absorption capacity. Through an increase in the amount of water it was possible to produce a coarser acetaminophen granulation containing Polyplasdone XL-10.

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