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COMMUNICATION

Statistical Comparison of High-Shear Versus Low-Shear Granulation Using a Common Formulation

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ABSTRACT

Experimental combinations from the ranges assigned to the independent factors were studied using both a low-shear (planetary) mixer and a high-shear mixer for granulation. The independent factors studied were X_1 *calcium phosphate/mannitol ratio,* X_2 *pregelatinized starch,* X_3 *magnesium stearate,* X_4 *mixer type, and* X_5 *compression pressure. To optimize the tablet properties fully, the experimental range was varied from* -2 *to* $+2$ *experimental units, with the exception of* X_4*, which was assigned* -1 *for the planetary mixer and* $+1$ *for the high-shear mixer. Drug dissolution did not seem to be affected by mixer type, but tablet hardness was affected by mixer type.*

Key Words: *Granulation mixer; Optimization.*

INTRODUCTION

The techniques of optimization in pharmaceutical dosage form design are well documented (1–4). Schwartz et al. (5,6) developed a technique by which a formulation with optimum properties could be obtained through computer-assisted data analysis. They used the result of a statistically designed series of experiments, based on five independent variables, as input into a computer. Down et al. (7) used a desktop computer for product optimization. Their method offered rapid access and versatility to large-scale computing facilities, which frequently are not readily accessible. Sequential prediction analysis (8) has been suggested for optimizing multiple potency systems with invariant tablet weight. In another study (9), key variables in dosage form design were determined employing two interrelated statistical techniques: correlation analysis and principal component analysis.

EXPERIMENTAL

The formulation was comprised of drug A (9.7% w/w), drug B (5.6%), mannitol (17.8%), calcium phos-

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Table 1

Independent Variables and Experimental Range

Variable	Name	−2	−1	0	1	2
X_1	Calcium phosphate/mannitol ratio	93.6/80	113.6/60	133.6/40	153.6/20	173.6/00
X_2	Starch pregelatinized	2 mg	3 mg	4 mg	5 mg	6 mg
X_3	Magnesium stearate	0.750 mg	1.125 mg	1.5 mg	1.875 mg	2.250 mg
X_4	Mixer type	—	Planetary (−1)	—	High intensity (+1)	—
X_5	Compression pressure	1.2 tons	1.6 tons	2.0 tons	2.4 tons	2.8 tons

Current operating levels: X_1 = 133.6/40; X_2 = 4 mg; X_3 = 1.5 mg; X_4 = high intensity; X_5= 2.25 tons.
Important interactions X_1 X_2, X_2 X_3.

phate dihydrate (50.7%), intragranular starch (8.9%), pregelatinized starch (1.0%), color (0.2%), extragranular starch (4.9%), and magnesium stearate (0.7%). The independent variables and the experimental range are given in Table 1 to enable full optimization of tablet properties.

Each experiment consisted of a batch of 6000 tablets. Wet granulation was carried out in a high-shear (BPMC 10-L Granulator-Baker Perkins Chemical Machinery, England) or low-shear (Hobart, Philadelphia, PA) granulator at low speeds. The granulations were tableted on a rotary press (Manesty Betapress, Manesty Machines Limited, Liverpool, England). The responses (dependent variables) measured included geometric granulation surface area (*a*, m^2/g), mathematically calculated from the quantitative mesh profile and the tapped density; dissolution rate for drug A (*b*, % dissolved); dissolution rate for drug B (*c*, % dissolved); disintegration time (*d*, min); tablet hardness (*e*, Kp); tablet friability (*f*, % weight loss); tablet weight variation (*g*, standard deviation [SD]); and tablet thickness variation (*h*, SD).

Dissolution rates were determined in 0.1 N hydrochloric acid with USP apparatus 2 at 50 rpm. Tablet disintegration time, breaking strength, and friability were measured with commonly employed equipment.

However, to compare the effects of mixer type, the region ''close'' to the current production settings, given in Table 1, was studied using both types of mixers. Here, the experimental region studied using both a low-shear mixer ($X_4 = -1$) and a high-shear mixer ($X_4 = +1$), is shown in Table 2, the fractional factorial portion not including axial and center points listed in Table 1.

The notation of X_1 to X_5 conforms to the nomenclature for these factors (independent variables) listed in Table 1. The actual values of the factors that were fitted to the data are given by the Z_1 to Z_5 values (−1, 1). The transformations of the factors in X to the coded Z's are done to make the data more interpretable. The effect of this is that the results are applicable only if the changes made in the independent variables are in the ranges given in Table 2.

RESULTS AND DISCUSSION

The data used to optimize the tablet properties are given in Table 3. The data generated from the experimental combinations of the independent variables from Table 2 are presented in Table 4.

Discussed below are the results of the characterization for responses (dependent variables) *a*, *b*, *c*, and *e*.

Surface Area

The important factors are X_1, X_2, and X_4. Changes in the factors X_3 and X_5 over the ranges listed above did not cause statistically significant changes in the surface area of the granulation.

Table 2

The Experimental Region

Factor	Study Range
X_1	116.9/56.7 (2.06) to 150.5/23.3 (6.45)
Z_1	−1 to 1
X_2	3.5 mg to 4.5 mg
Z_2	−1 to 1
X_3	1.13 mg to 1.88 mg
Z_3	−1 to 1
Z_5	1.88 tons to 2.63 tons
X_5	−1 to 1

Table 3

Data Generated from Optimization

	X_1	X_2	X_3	X_4	X_5	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*
1	1	−1	−1	−1	1	1771	93.0	83.3	2.60	13.8	0.06	0.002	0.03
2	1	1	−1	−1	−1	563	95.4	90.9	4.90	21.2	0.18	0.001	0.02
3	−1	−1	1	−1	1	1286	100.0	93.8	4.10	13.7		0.007	0.09
4	−1	1	1	−1	−1	392	63.0	46.6	31.10	21.6	0.18	0.002	0.02
5	−1	−1	−1	1	−1	785	100.0	90.4	3.98	17.6	0.08	0.001	0.02
6	−1	1	−1	1	1	629	94.1	81.5	19.10	27.5	0.31	0.001	0.01
7	1	−1	1	1	−1	1295	94.4	87.9	3.30	17.8	0.15	0.002	0.02
8	1	1	1	1	1	613	60.5	37.1	27.00	30.1	0.13	0.001	0.01
9	−2	0	0	1	0	445	98.0	87.2	11.28	24.0	0.05	0.002	0.03
10	2	−2	0	1	0	471	96.9	84.6	2.73	20.1	0.15	0.003	0.04
11	0	2	0	1	0	843	99.4	81.1	3.78	20.9	0.06	0.002	0.02
12	0	0	0	1	0	762	93.4	95.8	8.00	27.9	0.13	0.003	0.04
13	0	0	−2	1	0	634	98.5	97.0	6.70	17.6	0.07	0.001	0.02
14	0	0	2	1	0	634	85.9	75.8	9.57	20.0	0.05	0.004	0.06
15	0	0	0	1	−2	485	100.0	89.3	7.62	19.8	0.08	0.002	0.02
16	0	0	0	1	2	344	90.8	79.4	12.27	19.8	0.18	0.002	0.02
17	0	0	0	−1	0	1075	98.6	90.0	4.33	24.6	0.13	0.001	0.01
18	0	0	0	1	0	499	80.4	69.9	20.48	29.3	0.17	0.002	0.03
19	0	0	0	−1	0	414	100.0	100.0	11.10	24.6	0.07	0.002	0.02
20	0	0	0	1	0	896	97.2	91.4	6.10	24.3	0.09	0.002	0.03
21	0	0	0	1	0	780	100.0	93.0	2.00	20.0	0.02	0.020	0.02
22	0	0	0	1	0	750	98.0	91.0	2.00	20.0	0.02	0.020	0.02

An equation that can be used to predict the effect on surface area of changing the important factors over the ranges listed above is

$$\text{Surface Area} = 1003 + 143.648\,(Z_1) - 525.35\,(Z_2)$$

if the planetary mixer is used and

$$\text{Surface Area} = 803.44 + 143.648\,(Z_1) - 209.36\,(Z_2)$$

if the high-intensity mixer is used.

Table 4

Data Used for Mixed Type Comparison

	X_1	X_2	X_3	X_4	X_5	*a*	*b*	*c*	*e*
1	1	−1	−1	−1	1	1771	93.0	83.3	13.8
2	1	1	−1	−1	−1	563	95.4	90.9	21.2
3	−1	−1	1	−1	1	1286	100.0	93.8	13.7
4	−1	1	1	−1	−1	392	63.0	46.6	21.6
5	−1	−1	−1	1	−1	785	100.0	90.4	17.6
6	−1	1	−1	1	1	629	94.1	81.5	27.5
7	1	−1	1	1	−1	1295	94.4	87.9	17.8
8	1	1	1	1	1	613	60.5	37.1	30.1

In the above equations and all equations that follow, Z_1 and Z_2 (and Z_3 and Z_5 if they are important for the response) take values from −1 to 1; they correspond to the values listed above them in the previous listing of the experimental region. The coefficients of the *Z*'s estimate the effect on granulation surface area of changing the corresponding factor from its current value ($Z = 0$) to a high value ($Z - 1$). For example, from the fitted equation for the planetary mixer, the effect of increasing pregel starch (pregelatinized starch) from 4 mg ($Z_1 = 0$) to 4.5 mg ($Z_1 = 1$) is to decrease the surface area by 525.35. Likewise, changing the pregel starch from 4 mg ($Z_1 = 0$) to 3.5 mg ($Z_1 = -1$) has the effect of increasing the surface area by the same amount. Note the interaction between the mixer type and the pregel starch (Z_2); there is a much greater effect on surface area of changes in the starch when using the planetary mixer. These two equations are plotted as contour plots in Fig. 1.

Drug Dissolution

The important factors are again the pregel starch (X_2) and the magnesium stearate (X_3). Changes in the process

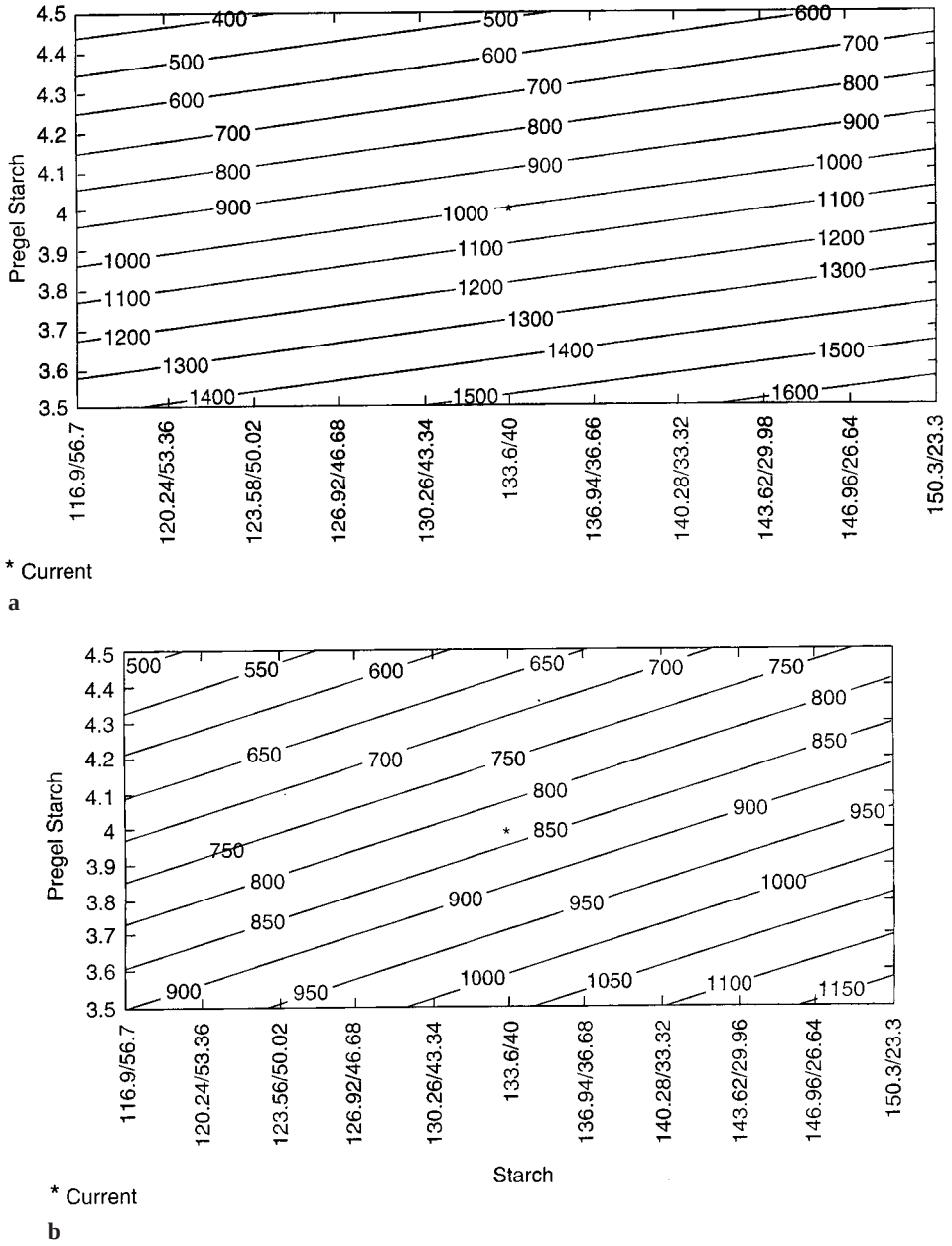

Figure 1. (a) Contour plot of surface area as a function of calcium phosphate/mannitol ratio and pregel starch with planetary mixer; magnesium stearate at 1.5 mg and pressure 2.25 tons. (b) Contour plot of surface area as a function of calcium phosphate/mannitol ratio and pregel starch with high-intensity mixer; magnesium stearate at 1.5 mg and pressure 2.25 tons.

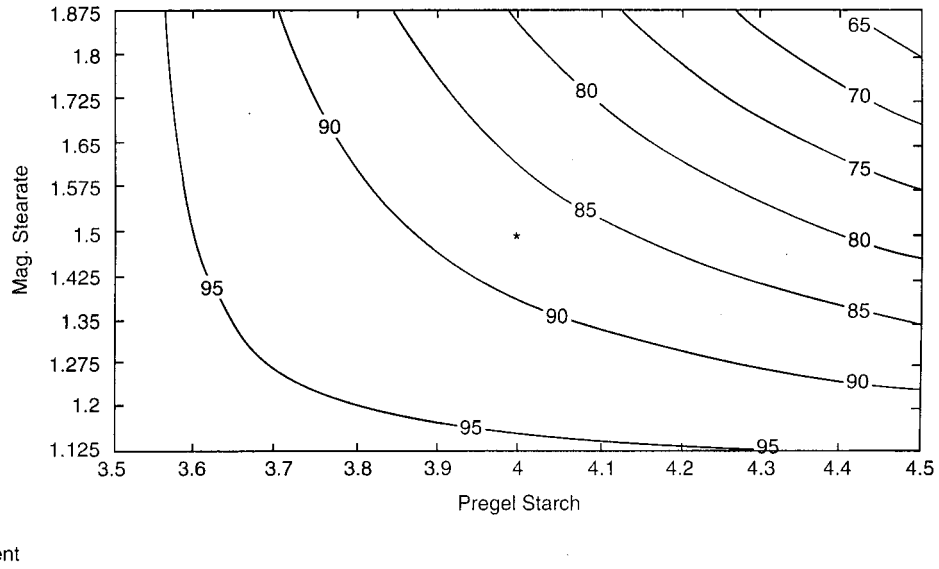

Figure 2. Contour plot of drug A dissolution as a function of magnesium stearate and pregel starch with calcium phosphate/mannitol ratio at 133.6/40 and pressure at 2.25 tons with either mixer type.

factors calcium phosphate/mannitol (X_1) and compression pressure (X_5) over the ranges listed above did not cause statistically significant changes in the percentage dissolution of this drug, nor did dissolution seem to be affected by the mixer type.

An equation that can be used to predict the effect on dissolution of changing the important factors over the ranges listed above is

$$\% \text{ Drug A Dissolved} = 87.55 - 9.3\,(Z_2) - 8.075\,(Z_3) - 8.43\,(Z_2)(Z_3)$$

We note that there is an interaction between the pregel starch and the magnesium stearate, and that the effect of increasing either or both is to decrease the percentage dissolved. This equation is plotted as a contour plot in Fig. 2.

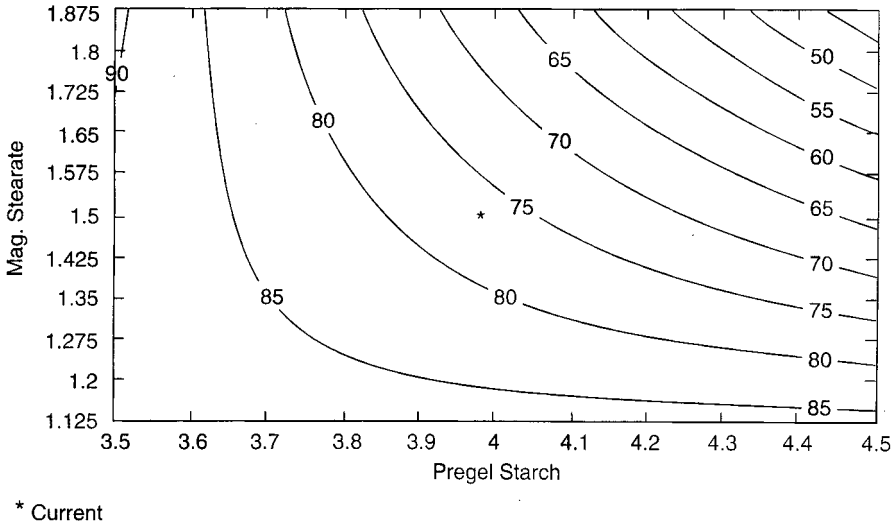

Figure 3. Contour plot of drug B dissolution as a function of magnesium stearate and pregel starch with calcium phosphate/mannitol ratio at 133.6/40 and pressure at 2.25 tons with either mixer type.

Drug B Dissolution

The important factors are again the pregel starch (X_2) and the magnesium stearate (X_3). Changes in the process factors calcium phosphate/mannitol (X_1) and compression pressure (X_5) over the ranges listed above did not cause statistically significant changes in the percentage dissolution, nor did dissolution seem to be affected by the mixer type.

An equation that can be used to predict the effect on dissolution of changing the important factors over the ranges listed above is

$$\% \text{ Drug B Dissolved} = 76.44 - 12.41\,(Z_2) - 10.09\,(Z_3) - 12.09\,(Z_2)(Z_3)$$

We note that there is an interaction between the pregel starch and the magnesium stearate, and that the effect of

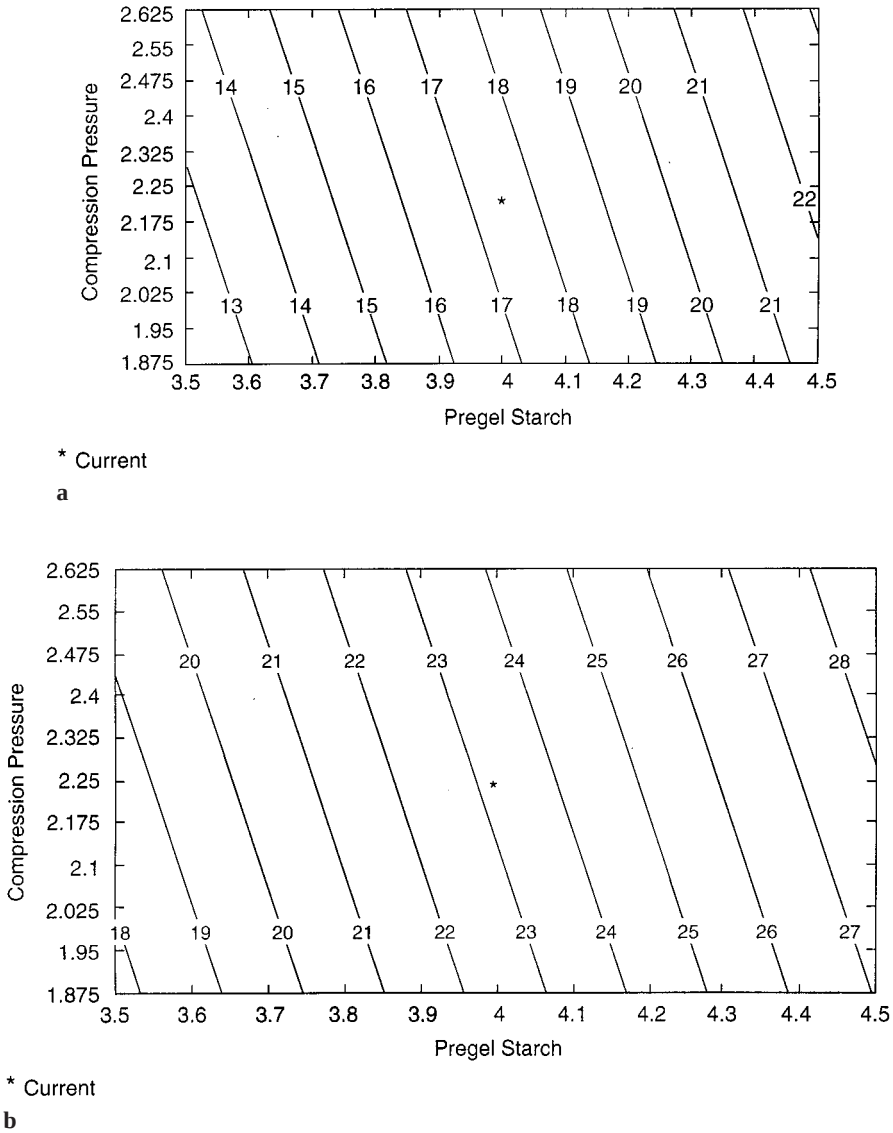

Figure 4. (a) Contour plot of table hardness as a function of compression pressure and pregel starch with planetary mixer; magnesium stearate at 1.5 mg and calcium phosphate/mannitol ratio at 133.6/40. (b) Contour plot of table hardness as a function of compression pressure and pregel starch with high-intensity mixer; magnesium stearate at 1.5 mg and calcium phosphate/mannitol ratio at 133.6/40.

increasing either or both is to decrease the percentage dissolved. This equation is plotted as a contour plot in Fig. 3.

Tablet Hardness

Because of the choice of the combinations run, there are two competing interpretations of the data. This is because the effect of compression pressure is confounded with the effect of the interaction of the pregel starch with mixer type. In either interpretation, the largest effect was observed on changing the pregel starch, and the next largest was due to mixer type. However, because of the confounding, it is not possible to determine if the next, and only other, effect is compression pressure or the interaction of the two larger effects.

Interpretation 1 yields the equations

$$\text{Hardness} = 17.58 + 4.69\,(Z_2) + .86\,(Z_5)$$

for the planetary mixer

and

$$\text{Hardness} = 23.25 + 4.69\,(Z_2) + .86\,(Z_5)$$

for the high intensity mixer

Harder tablets come from running the same conditions, but mixing with the high-intensity mixer, but in either mixer, both pregel starch and compression pressure increase the hardness. The effect of increasing compression pressure is small compared to increasing the pregel starch.

The second interpretation would be that important factors were the pregel starch (X_2) and mixer type only, and that there is an interaction between the mixer type and the pregel starch. It makes sense that, if pregel starch and mixer type have an effect, then they may interact also. In this interpretation, the equation for describing the effects on hardness would be

$$\text{Hardness} = 17.58 + 3.83\,(Z_2)$$

for the planetary mixer

and

$$\text{Hardness} = 23.25 + 5.55\,(Z_2)$$

for the high-intensity mixer

The mixer effect is the same as in interpretation 1; however, the effect of the pregel starch is greater in the high-intensity mixer than in the planetary mixer. Interpretation 1 is plotted in Figs. 4a and 4b, and interpretation 2 is plotted in Fig. 5.

CONCLUSION

Drug dissolution did not seem to be affected by mixer type, but was affected by the formulation factors pre-

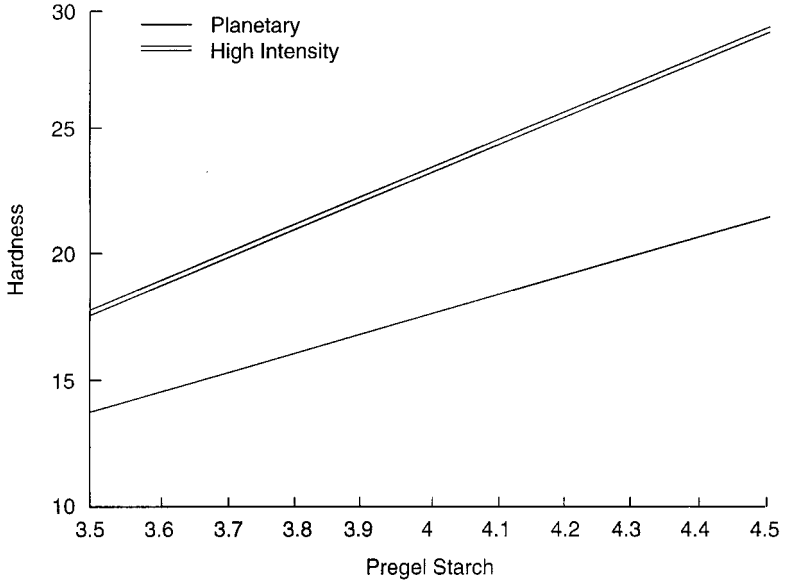

Figure 5. The effect of mixer type and pregel starch on hardness assuming interpretation 2 (mixer-by-starch interaction).

gelatinized starch (X_2) and magnesium stearate (X_3) and by the interaction between the two in that the effect of increasing either or both decreased drug dissolution. Tablet hardness was affected by the factors pregelatinized starch (X_2) and mixer type (X_4) and possibly by the interaction between the two. The equations for describing the effects on hardness are Hardness = 17.50 + 3.83 (Z_2) for the planetary mixer, and Hardness = 23.25 + 5.55 (Z_2) for the high-intensity mixer. The low-shear mixer yielded a larger granulation surface area than the high-shear mixer.

Equivalent tablet properties were obtained on a commercial scale with granulating water/time equal to 0.05 ml/tablet/5 min for the low-shear mixer and 0.045 ml/tablet/3 min for the high-shear mixer. Therefore, the processing of this tablet formulation was amenable to either mixer with minor modifications.

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