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RESEARCH PAPER

Comparative Evaluation of Granules Made with Different Binders by a Fluidized Bed Method

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ABSTRACT

Granules were prepared using three different binders, pregelatinized starch (PGS), gelatin (GEL), and polyvinylpyrrolidone (K30) by a fluidized bed method. As a quantitative measurement of mechanical strength or abrasion resistance, granules were subjected to a friability test for certain periods of time, and friability indexes (FI) as a function of time were calculated. The data obtained were analyzed by applying standard mathematical models. According to the derived parameters of the logistic and Weibull models, which fit best to the data, mechanical strength of granules made with K30 was observed to be lower than that of the granules of PGS and GEL which have similar values of model parameters. Flow properties, consolidation, and compressibility behaviors of unfriabled (UFR) and friabled (FR) granules, which were selected based upon their Weibull time parameter, were investigated as comparative. The flow rate of granules decreased due to diminishing particle size depending on binder type and friability, but the values of angle of repose were within the acceptable limits. Regarding consolidation behavior, the change of relative density vs. the number of taps, i.e., packing rate for FR granules of GEL was slower than that of its UFR form, whereas FR granules of PGS and K30 showed faster change in relative density compared to their UFR forms. According to the parameters obtained from the Heckel equation, PGS and K30 were found to produce softer, more plastic and readily deformable granules than GEL, and the compressibility of their FR forms was not influenced negatively.

Key Words: Wet granulation; Fluidized bed; Binder; Pregelatinized starch; Gelatin; Polyvinylpyrrolidone; Friability; Compressibility.

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INTRODUCTION

The production of tablets of high quality in large scale production requires a tablet mass with excellent properties regarding mixing homogeneity, flowability and compactability, etc. A granulation of the drug and excipients before tableting has been and still is the common procedure to ensure good properties in the tablet mass. Although the granulation process has been extensively studied, there is still a lack of knowledge concerning the compression characteristics of granulated materials and granule properties that are of decisive importance for the mechanical strength of tablets. The mechanical strength of tablets compressed from a granulated product is governed by both formulation parameters, primarily type and amount of binder, and process conditions during the granulation. Granulations made by roller compaction, wet massing, and spray drying give tablets of different mechanical strength.[1] Since 1970, the fluidized bed granulation process has come into vogue because it has the advantage that in the fluid bed powders can be dry-mixed, while at the end of the process drying is rather simple.[2] It has been shown that fluidized bed granulation results in less granule hardness and greater plastic deformability that is important for the compactness of the granules.[3]

Abrasion resistance and strength are important physical properties of the tablet granules. Failure to withstand handling can result in poor granule flow, gross tablet weight variation, and unsatisfactory compression. Abrasion resistance or friability has been used to evaluate granule strength. A friability index (FI) has been numerically calculated by using a friability test as the change in the mean particle size before and after the test.[4] The FI is a parameter that defines a single point. However, the friability event of the granules shows a continuity as a function of time during the sieving and mixing periods after the drying process at the industrial manufacturing stage.[5,6] Therefore a mathematical modeling of the curve of the FI values vs. time would provide better understanding, for evaluating the effects of the formulation and process variables by using the model parameters.

In this study, the granules were made with different binders by a fluidized bed method. The friability of the granules was studied as a function of time and then the data were analyzed by applying different mathematical models. Consolidation (packing) and compressibility behaviors and flow properties of the granules before and after friability test were examined comparatively.

EXPERIMENTAL

Materials

Powder materials used were lactose (Meggle GmbH, Germany), starch potato (BDH Chemicals Ltd., England), microcrystalline cellulose (Avicel PH 102) (FMC Corp., USA), and microfine cellulose (Elcema F 150) (Degussa GmbH, Germany). Aqueous solutions of gelatin (Difco Laboratories, USA), pregelatinized starch (Avebe BA, The Netherlands), and polyvinylpyrrolidone (Kollidon-30) (BASF AG, Germany) were used as binders.

Mixture Composition and Granulation Process by Fluidized Bed Method

As shown in Table 1, the basal powder mixture consists of lactose, starch, microcrystalline cellulose, and microfine cellulose. Pregelatinized starch (PGS), gelatin (GEL), and polyvinylpyrrolidone (K30) were used as binders in the form of aqueous solutions of 9% w/w.

The operating conditions at the fluidized bed apparatus (Glatt Lufttechnische Apparate Type: Uniglatt, Fabr.Nr:2858, Binzen/Germany) are given in Table 2. The basal powder mixture was placed on the retention screen and mixed for 5 min. The binder solution was sprayed onto the powder mixture being fluidized in the warm air stream entering from the bottom. After the spraying process was finished, the temperature of inlet air was elevated to 60°C and drying was conducted continuously in the same vessel until the exhaust air temperature reached 60°C. The duration of granule preparation by the fluidized bed method was about 120 min. Dried granules were sieved through a 3-mm sieve to remove oversize granules and subjected to the analysis given below.

Table 1. Formulation for the granulation.

Ingredient	Amounts per batch (g)	Percent amounts
Lactose	60.0	38.40
Starch	67.5	43.20
Microcrystalline cellulose	15.0	9.61
Microfine cellulose	7.5	4.80
Binder[a] (dry)	6.15	3.94

[a]PGS, GEL, and K30 were used as binders in the form of aqueous solution of 9% w/w.

Table 2. Operating conditions at the fluidized bed apparatus.

Conditions	
Batch size	150 g
Nozzle diameter	1.4 mm
Spray rate	1.0–1.5 g/min
Spray air pressure	1.0–1.5 atm
Inlet air flap	15 < (adjusted according to fluidization of powder mass)
Inlet air temperature	25–30°C
Gun position	16 cm (from powder bed surface)
Drying temperature	60°C

Determination of Average Particle Size

The sieving method was used for measuring particle size distribution. Seventy-five grams of granules were placed on a series of successively smaller sieves (0.841, 0.595, 0.420, 0.250, 0.149, and 0.074 mm) and vibratory motion applied at an amplitude of 1.0 mm on a Retsch sieve shaker (Retsch KG, Germany) with interruption for 10 min.

The portion of the sample retained on each sieve was weighed. The cumulative percentage greater than the stated size against size was plotted on a logarithmic probability grid. The average particle size of granules was determined as the geometric mean.[7,8]

Determination of Granular Friability

The granular friability was determined using the friability test with Erweka friabilator (JEL, J. Engelsmann A.G., Germany) suggested by Rubinstein and Musikabhumma.[4] Seventy-five grams of the granules was placed in the friabilator together with 10 rubber balls of 15 mm diameter. The apparatus was rotated at 25 rpm for 5, 10, 20, 30, 45, 60, and 90 min. The granules after test were named friabled (FR) and the granules before test were named unfriabled (UFR). The FR granules were transferred to the nest of sieves and the average particle size was determined as before. The FI values for each friability testing time were calculated from Eq. (1). The harder the granules, the greater the value of the FI index.

$$\mathrm{FI} = \frac{\text{Average particle size of FR granules}}{\text{Average particle size of UFR granules}} \quad (1)$$

Table 3. Applied mathematical models to the friability data of granules.

Model	Equation
Exponential decay[a]	$\mathrm{FI} = \alpha e^{-kt}$
Weibull[b]	$\mathrm{FI} = 1 - e^{-(t/\tau_d)^{\beta}}$
Logistic[c]	$\mathrm{FI} = \dfrac{\alpha}{1+\gamma e^{-\beta t}}$

t, Time.
[a]The curve starts at α and decays to a plateau with a rate constant k.
[b]τ_d, time at which FI equals to 0.632; β, shape factor.
[c]The curve starts at $\alpha/(1+\gamma)$ and decreases to a lower limit of α when t is large.

The mathematical models, shown in Table 3, were fitted to the friability data, that is, FI vs. time, with the nonlinear regression module of Statistica 5.0 for Windows (Statsoft, OK, USA). In non-linear regression analysis, the estimation methods were the simplex, quasi-Newton, and Hooke–Jeeves pattern moves that minimize the sum of the squared deviation about the predicted values, i.e., loss function. The model parameters with their standard errors and descriptive statistics of regression for each model were determined. Depending on the estimations, a suitable mathematical model to describe the curves of friability data was determined. The derived parameters of the model were employed for the comparison of granules made with different binders.

Determination of the Flow Properties of Granules

The flow rate was determined with Erweka flow tester (JEL, J. Engelsmann A.G., Germany) by weighing the same quantity at each time (35 g) of FR and UFR granules ($n = 10$). The angles of repose of FR and UFR granules were determined by the dynamic angle of repose method by using 100 mL of the granules ($n = 5$).[7]

Determination of Consolidation Behavior of Granules

Ten milliliters of the granules was gently sifted into a 10-mL graduated cylinder through a funnel. Then the weight of 10 mL was determined, the bulk density (BD) being calculated thereafter. The graduated cylinder was tapped from a height of 25 mm and

the resulting reduction in volume was measured after repeating this procedure 5, 10, 20, 50, 75, 100, 120, 200, 300, 400, and 500 times until achieving unchanged volume reduction and then the tapped density (TD) was calculated. The natural logarithm of the number of taps (N_t) was plotted against the double ln of the relative density change (A) [Eq. (3)] and the parameters of the regression lines were determined.[9,10]

$$A = \frac{\text{TD} - \text{BD}}{\text{TD}} \tag{2}$$

Determination of Compressibility Behavior of Granules

For this purpose, a 12-mm flat face punch and a hand operated hydraulic press (Ucler, Turkey) were used. The appropriate amounts of granules were pressed at 60.17, 120.3, 180.5, 240.7, 300.9, and 361 MPa. When the desired pressure was reached, it was kept at this value for 20 sec. The height of the compact was measured accurately and the volume was calculated ($n = 3$). The data were analyzed by the Heckel equation (11). The equation may be written as

$$\ln \frac{V_p}{V_p - V_\infty} = KP + \ln \frac{V_0}{V_0 - V_\infty} \tag{3}$$

$$\ln \frac{V_p}{V_p - V_\infty} = KP + \ln I \tag{4}$$

where V_p is the volume of the compact at each pressure applied, V_∞ is the true volume of the compact (without pores), V_0 is the initial granule volume, and P is the applied pressure. K is determined from the slope and I from the intercept of a plot of $\ln(V_p/(V_p - V_\infty))$ vs. P.

RESULTS AND DISCUSSION

Granules were prepared by the formulation given in Table 1. Lactose and starch were used as filling agents. Both of them are cohesive powders which can cause flow problems and hence unacceptable variation in tablet weight during compression. Therefore, it is preferable that they be granulated. Microcrystalline cellulose and microfine cellulose are the direct tableting agents which provide the compacts with high mechanical strength even at low pressures. In granulating, microcrystalline cellulose makes the consistency of the wet mass less sensitive to variations in water content and overworking. Microcrystalline cellulose added to a wet granulation improves bonding on compression and reduces capping and friability of the tablet. Microfine cellulose (especially F and P series of Elcema) can also be used in wet granulation to produce harder granules and to improve the compressibility of the granules. However, unlike microcrystalline cellulose, it possesses poor dilution potential, losing its compressibility rapidly in the presence of noncompressible materials.[12] Based on these considerations, microcrystalline cellulose was used along with microfine cellulose at the ratio of 2:1 in the formulation.

The results of the friability tests of granules are seen in Table 4. As the time for abrasion of granules became longer, FI values decreased rapidly, followed by a slow change in the FI values. This is why solid bridges between the primary particles which have been constituted upon drying are broken, and component particles segregate and then milling between particles starts, so the change of the FI values vs. time continues in an almost steady state. The curves showing the change of the FI values vs. time are depicted in Fig. 1. The standard mathematical models in Table 3 were applied for the parametric representation of the friability curves. These models are exponential decay model, Weibull model, and logistic model, of which, the last two describe sigmoidal curves.[13,14]

After fitting these models to the friability data, the selection for the best-fit model was based on the comparisons of the following features of the models: (1) higher determination coefficient, (2) smaller absolute difference between each fitted and actual FI values, and (3) smaller residual mean square (Table 5). Considering these criteria, the logistic

Table 4. Friability data of the granules made with different binders and average particle size of the UFR granules.

	FI		
Time	PGS UFR 0.110 mm	GEL UFR 0.240 mm	K30 UFR 0.180 mm
5	0.8636	0.9375	0.7222
10	0.7500	0.8750	0.6111
20	0.6591	0.7083	0.4722
30	0.6591	0.6667	0.3889
45	0.5818	0.6667	0.3778
60	0.5818	0.6250	0.3333
90	0.5136	0.5208	0.2778

model with the lowest residual mean squares was that which fit best to the friability data of granules, while the second best was the Weibull model with the highest determination coefficients and the lower R_{max} values. The derived parameters of these models are given in Table 5. These parameters were compared as PGS-GEL, PGS-K30, and GEL-K30 using *t*-test, and the results are shown in Table 6.

In the logistic model, α values show the lower limits of the curves while the β parameter along with the γ parameter determines the course of the curves.[13] In the order PGS–GEL–K30, β values decreased (0.03312–0.02635–0.02419) and γ values increased (0.4490–0.4946–0.7088). The α values were 0.5242, 0.5307, and 0.2688 in the same order. As the α and γ parameters of the granules made with K30 were found significantly different from those of PGS and GEL granules ($P < 0.05$), β values were not significantly different ($P > 0.05$). Two parameters, β and τ_d, of the Weibull model describe the shape of the curve and time, respectively.[14] The shape parameter, β, lower than 1, characterizes the curve as one with greater initial slope than is consistent with the exponential (0.3189–0.4144–0.4756 for PGS–GEL–K30). The time parameter, τ_d, represents the time interval necessary to decrease the FI value to 0.632. τ_d values for granules made with PGS, GEL, and K30 were respectively 32.56, 46.61, and 8.31 min and significantly different for all granules considered ($P < 0.05$). Depending on the applied formulation and process conditions, the derived parameters of these two models show that the granules made with K30 are more friable or have lower strength against

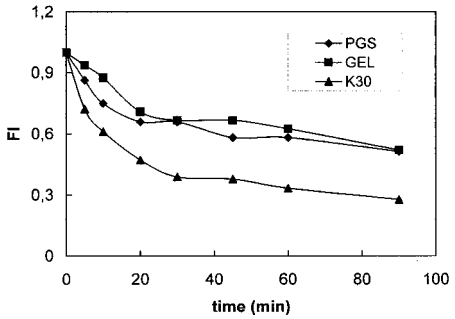

Figure 1. Friability curves of the granules.

Table 5. Parameters of the mathematical models and descriptive statistics of regression for the friability data of granules.

Model	Statistics[a]	PGS	GEL	K30
Exponential decay	r^2	0.8400	0.8569	0.8713
	α	0.8078	0.9022	0.6907
	S.E.	0.03728	0.04418	0.05378
	k	5.873×10^{-3}	6.769×10^{-3}	0.01304
	S.E.	1.230×10^{-3}	1.348×10^{-3}	2.715×10^{-3}
	R_{max}	0.07914	0.06536	0.07495
	RMS	2.641×10^{-3}	3.524×10^{-3}	0.01743
Weibull	r^2	0.9668	0.9483	0.9899
	τ_d	32.56	46.61	8.307
	S.E.	2.783	5.443	0.5860
	β	−0.3189	−0.4144	−0.4756
	S.E.	0.0290	0.05350	0.0257
	R_{max}	0.0260	0.03130	0.01687
	RMS	3.696×10^{-3}	9.610×10^{-3}	2.561×10^{-3}
Logistic	r^2	0.9595	0.9480	0.9908
	α	0.5242	0.5307	0.2688
	S.E.	0.04306	0.07611	0.02990
	γ	−0.4490	−0.4946	−0.7088
	S.E.	0.03530	0.05215	0.02360
	β	0.03312[b]	0.02635[b]	0.02419
	S.E.	0.01622	0.01711	7.182×10^{-3}
	R_{max}	0.03033	0.04150	0.02477
	RMS	4.720×10^{-4}	5.900×10^{-4}	4.660×10^{-4}

[a] r^2, determination coefficient; R_{max}, maximum residual in absolute size between fitted and actual FI values; RMS, residual mean square; S.E., standard error of model parameters, α, k, τ_d, β and γ.
[b] $P > 0.05$.

Table 6. Comparisons of the derived model parameters of granules by *t*-test (two-sided) ($n = 7$).

Granules	Difference logistic α	*t*	Difference logistic β	*t*	Difference logistic γ	*t*
PGS–GEL	−0.0065	0.07432	0.00677	0.2871	0.0456	0.7241
PGS–K30	0.2554[a]	4.871	0.00893	0.5034	0.2598[a]	6.118
GEL–K30	0.2619[a]	3.203	0.00216	0.1164	0.2142[a]	3.742
	Weibull τ_d		Weibull β			
PGS–GEL	−14.05[a]	2.298	0.0955	1.569		
PGS–K30	24.25[a]	8.256	0.1567	4.044[a]		
GEL–K30	38.30[a]	6.996	0.0612	1.031		

[a] $P < 0.05$.

abrasion than the granules of other binders. The results for the granules made with PGS and GEL were not significantly different. This implies that the shapes of the curves and the rate of the change of the FI values with time of these granules are similar to each other. However, the granules made with PGS achieved the FI values of 0.632 in shorter time than did the granules of GEL.

Following are the results of the investigations carried out to see if the initial properties of granules change or not because of friability or abrasion, which would occur during handling of granules before tableting. For this purpose, UFR granules and FR granules, which were selected based upon their Weibull time parameter, τ_d, that is, having FI values of approximately 0.632, were used.

Figure 2 shows the particle size distribution of granules. The values reported are 16% (fine particles), 50% (geometric mean), and 84% (coarse particles) (Table 7). The particle size distributions of FR granules of PGS and K30 were narrower than those of their UFR granules.The granules of GEL showed wider size distribution for its FR form. As the larger granules of PGS were primarily broken, the smaller granules of GEL were also primarily broken, and the size of the larger granules of GEL was not apparently decreased. The change of particle size distribution of FR granules of K30 indicated more homogeneous friability behavior that is even changing in size of smaller and larger granules.

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to ensure efficient mixing and acceptable weight uniformity for the compressed tablets. Flow properties of the UFR and FR granules are given in Table 8. Depending on the use of different binders, the flow

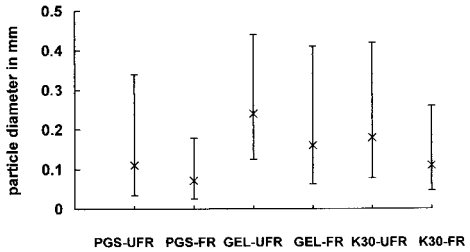

Figure 2. Particle size distributions of granules. *X*: 50% (geometric mean), upper limit: 84% (coarse particles), lower limit: 16% (fine particles).

Table 7. Particle size distribution (mm).

	$d_{16\%}$	d_{mean}	$d_{84\%}$
PGS–UFR	0.034	0.110	0.340
FR	0.026	0.071	0.180
GEL–UFR	0.130	0.240	0.440
FR	0.062	0.160	0.410
K30–UFR	0.077	0.180	0.420
FR	0.046	0.110	0.260

rates of the UFR granules were found significantly different from each other ($P < 0.001$). Within FR granules, the granules of K30 with the lowest flow rate showed the significant difference from the FR granules of PGS and GEL which have similar flow rates ($P < 0.001$). When the UFR and FR forms of granules were compared by using paired *t*-test for each binder, the flow rates were found to change significantly ($P < 0.001$). Decreasing flow rates of FR granules were caused by increasing cohesive and frictional forces between particles as these became smaller.

Table 8. Flow properties of the UFR and FR granules and comparisons by *t*-test.

Binder type	UFR granules Flow rate (g/sec)	FR granules (Mean ± 95% CI[a])	Significance UFR–FR
PGS	4.83 ± 0.112	3.96 ± 0.197	0.000[c]
GEL	5.88 ± 0.110	3.94 ± 0.0763	0.000[c]
K30	3.32 ± 0.763	2.06 ± 0.154	0.000[c]
	Significance		
PGS–GEL	0.000[c]	0.968	
PGS–K30	0.000[c]	0.000[c]	
GEL–K30	0.000[c]	0.000[c]	
	Angle of repose (α) (mean ± 95% CI)		
PGS	28.0 ± 1.84	28.1 ± 0.851	0.956
GEL	32.6 ± 1.19	29.5 ± 1.52	0.004[b]
K30	28.2 ± 2.13	28.1 ± 1.32	0.864
	Significance		
PGS–GEL	0.001[b]	0.111	
PGS–K30	0.968	1.000	
GEL–K30	0.001[b]	0.117	

[a]Confidence interval.
[b]$P < 0.01$.
[c]$P < 0.001$.

Values for angles of repose $\leq 30^\circ$ generally indicate a free-flowing material and angles $\geq 40^\circ$ suggest a poorly flowing material.[7] UFR granules of GEL had the angle of repose of 32.6° and this value was significantly different from those of other UFR granules ($P < 0.01$). However, FR forms of the granules did not show any significant difference in the values of angle of repose. According to the paired comparisons, the granules of GEL were the only ones showing difference its UFR–FR forms ($P < 0.01$) (Table 8).

Slope values of the relative density change vs. the number of taps, i.e., packing rates for UFR and FR granules, are given in Table 9. Among UFR granules, the packing rate of granules made with GEL was different from that of granules made with K30, while it was also different from that of granules of PGS in the case of FR granules ($P < 0.05$) and its packing rate decreased. The same consolidation behavior also occurred when UFR granules of GEL were compared with its FR form ($P < 0.05$). This may be attributable to a segregation between smaller and larger granules due to a wide size range (see Fig. 2, Table 7) or a tendency of fine particles to form stable arches or bridges that result in an increase in void space.[7,15] Such a consolidation behavior would possibly cause an increase in the upper punch distance in the die. Michoel et al.[16] have also stated that the first step during tablet formation is the consolidation of the powder to become a closely packed system, and a slow packing rate will result in uneven densities within the tablet because deformation already occurs before close packing is achieved in the whole powder system. However, unlike GEL granules, the packing rate of FR granules made with PGS was higher than that of its UFR form resulting from diminishing size of particles and narrower particle size range (see Fig. 2, Table 7), because the smaller granules are able to form a closer, more intimate packing than are larger granules.[7] Within the FR granules, the granules of PGS had the highest packing rate, which would be an advantage in the first phase in the process of compression. The granules of K30 come between the granules of PGS and GEL regarding packing rate.

Table 10 summarizes the results obtained from Heckel equation [Eqs. (3,4)] for describing the compressibility of the granules made with different binders. The Heckel equation describes the relationship of the compact density to the applied pressure. The rate of density increase with applied pressure is proportional to the volume fraction of pores.[11] In our study, volume reduction of the compacts was used instead of density increase under the applied pressure in Heckel equation. The reciprocal value of the slope of Eq. (4) ($P_y = 1/K$) represents the mean yield pressure

Table 9. Consolidation parameters of the UFR and FR granules and comparisons by *t*-test (two-sided).

Binder type		Slope ± 95% CI	*t* (UFR–FR)	r^2
PGS	UFR	$0.09089 \pm 3.933 \times 10^{-3}$	2.410[a]	0.9650
	FR	$0.1070 \pm 2.930 \times 10^{-3}$	—	0.9940
GEL	UFR	$0.1056 \pm 6.090 \times 10^{-3}$	7.952[a]	0.9827
	FR	$0.0460 \pm 3.534 \times 10^{-3}$	—	0.9376
K30	UFR	$0.08529 \pm 5.819 \times 10^{-3}$	0.4280	0.9760
	FR	$0.09469 \pm 6.478 \times 10^{-3}$	—	0.9638
	t (UFR)	*t* (FR)		
PGS–GEL	1.671	10.63[a]		
PGS–K30	0.645	1.497		
GEL–K30	2.343[a]	5.730[a]		

[a] $P < 0.05$.

Table 10. The constants determined from the Heckel equations for the UFR and FR granules and comparisons by *t*-test (two-sided).

Binder type		$K \pm 95\%$ CI $(MPa)^{-1}$	*t*[a]	$I \pm 95\%$ CI	*t*[a]	P_y (MPa)	r^2
PGS	UFR	$10.87 \times 10^{-3} \pm 3.130 \times 10^{-3}$	0.845	0.8110 ± 0.6360	0.518	91.99	0.9753
	FR	$13.15 \times 10^{-3} \pm 8.150 \times 10^{-3}$		0.5320 ± 1.593		76.05	0.9017
GEL	UFR	$8.792 \times 10^{-3} \pm 4.792 \times 10^{-3}$	1.085	0.9110 ± 1.027	1.409	113.7	0.9660
	FR	$7.111 \times 10^{-3} \pm 3.111 \times 10^{-3}$		1.351 ± 0.6490		140.6	0.9417
K30	UFR	$13.74 \times 10^{-3} \pm 3.260 \times 10^{-3}$	0.381	0.7300 ± 0.7110	1.409	72.78	0.9805
	FR	$14.38 \times 10^{-3} \pm 5.620 \times 10^{-3}$		0.8200 ± 0.8139		69.54	0.9850
		UFR		FR			
		t (*K*)	*t* (*I*)	*t* (*K*)	*t* (*I*)		
PGS–GEL		1.356	0.324	2.231	1.514		
PGS–K30		1.913	0.271	0.4034	0.482		
GEL–K30		3.033[b]	0.551	4.544[b]	1.805		

[a] *t* is calculated for UFR–FR pair.
[b] $P < 0.05$.

by which a substance resists the deformation process. The value of intercept (I) describes the movement of the granules or particles at the beginning of the compression. The constant is a measure of densification due to the particles slipping over each other during rearrangement, which mainly depends on size, shape, but also on hardness of the particles.[17] Regarding I values, any significant difference was not observed within the granules considered in UFR and FR forms ($P > 0.05$). Slope values of the granules made with GEL and K30 were found to be significantly different from each other in their UFR and FR forms ($P < 0.05$). The granules made with GEL gave the lowest slope values and accordingly the highest mean yield pressures, indicating that the granules could be hard and less plastic and much force would possibly be needed to deform them. In its FR form, P_y value increased further. This can also be a result of the slow packing rate and the wide size range of granules of GEL (see Table 9, Fig. 2). As seen in Table 10, the higher slope values and lower P_y values for granules made with PGS and K30 indicate that the granules are softer and more plastic and could deform readily. In their FR forms, decreasing P_y values imply that their compressibility behaviors were not influenced negatively due to contribution of higher packing rates and narrower size distributions of these FR granules (see Table 9, Fig. 2). It has

been reported that mean yield pressures below 80 MPa are regarded as an indication of mainly plastic flow.[17] Therefore FR form of granules made with PGS and UFR–FR forms of the granules made with K30 seem to deform by mainly plastic flow, since the mean yield pressures are lower than 80 MPa.

CONCLUSION

According to the parameters of the applied mathematical models, the mechanical strength of granules made with K30 was lower than that of the granules made with PGS and GEL which have similar values of model parameters. However, regarding consolidation and compressibility behaviors, FR forms of K30 and also PGS presented more affirmative properties beyond protecting initial properties of their UFR forms, while the initial properties of the granules of GEL changed negatively in its FR form. This emphasizes the importance of binder type. Different binders have different binding properties. In this study, same concentrations and amounts of binders were used for the granulation under the same process conditions. Therefore, we have thought that the concentration of individual binder and the amount of it to be added to the formulation may have to be optimized to obtain similar binding of the primary particles. Such an optimization can be performed advantageously by the mathematical modeling for the evaluation of binders through the friability rates of the granules produced.

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