Effect of Molecular Weight of Hydrolyzed Gelatin on Its Binding Properties in Tablets: A Technical Note

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Introduction

In solid state pharmaceuticals, particle size enlargement is an important unit operation and is performed to impart degree of functionality to particles. These functions include improved flowability, compressibility, and compactability. Binder is an essential component in this process to impart these properties.

Gelatin, obtained by hydrolysis of collagen, is a conventionally used binder. Tablets obtained using gelatin as binder have shown high tensile strength.[1-3] Hence, hydrolyzed gelatins, with low molecular weight and viscosity can be used to produce soft and uniform granules with good compressibility and compactability. Hydrolyzed gelatins differ in molecular weights and viscosities but are analytically identical and are spray dried to produce a low-density powder. Spray-dried hydrolyzed gelatins offer ease of handling and improved rheological properties. Obiroch and Shotton[4] studied the effect of hydrolyzed gelatin on compression characteristics and reported that hydrolyzed gelatins, without regard to their molecular weight, yielded more strongly bonded compacts. Reading and Spring[5] reported the effects of binder film characteristics on granule and tablet properties, using high molecular weight hydrolyzed gelatin. They observed that the distribution of the binders to the point of contacts was important to impart mechanical strength to compacts. This distribution was inhibited by the high viscosity of binder. Also there was no correlation observed between physical properties of binder films and their granule and compact properties. Hence, rather than film characteristics, the binders should be evaluated for their ability to improve handling properties, compressibility, and compactability of granules.

The aim of the present study was to evaluate the potential of hydrolyzed gelatins (Byco-A, Byco-O, and Byco-C) to be used as binding agents in wet granulation technique and the effect of their molecular weight on binding ability. Their performance was compared with conventionally used pharmaceutical-grade type B gelatin, which is prepared by treatment of ossein or skin stocks with a calcium hydroxide-alkaline process. Various evaluation parameters were studied, including micromeritic and mechanical properties, and compression and compaction behavior. Paracetamol, a poorly compressible drug with capping tendency, was chosen as a model drug.

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Materials and Methods

Materials

Paracetamol IP, Lactose IP, sodium starch glycolate (Primogel, FMC Corp, Philadelphia, PA), magnesium stearate, and colloidal silicon dioxide (Aerosil 200; Degussa) were gift samples from Get-Rid Pharma, Pune, India. Hydrolyzed gelatins (Byco products) were the generous gift samples of Croda Healthcare (East Yorkshire, UK). All other chemicals and reagents were analytical grade and used as received.

Methods

Determination of Viscosity

Viscosity was determined at 25°C of 4%, 6%, and 8% wt/vol concentration levels by Cell and Tube viscometer (Ostwald's viscometer, Yash Enterprises, Pune, India).[4-6] Relative viscosities were determined by comparing with water (Table 1).

Preparation of Granules

Batches of a basic formulation (50 g each) were prepared with the following composition: Paracetamol IP (66.67% wt/wt), Lactose IP (20.83% wt/wt), Byco (8% wt/wt), Primogel (4% wt/wt), magnesium stearate (0.33% wt/wt), and Aerosil 200 (0.17% wt/wt). Three types of hydrolyzed gelatins (Byco-A, Byco-O, and Byco-C) were studied. Paracetamol and lactose were thoroughly mixed and granulated with binder solution (4 mL of 8% wt/vol) in purified water by manual kneading for 10 minutes. The wet and coherent masses obtained were manually screened through no. 12 mesh and dried in a hot air oven at 50°C for 2 hours. Then, the semidried masses obtained were resieved through

Table 1. Viscosity Measurements of Binder Solutions

Binders	Viscosity (mPa.s) ± SD			Molecular Weight (Da)*
	4% wt/vol	6% wt/vol	8% wt/vol	
Byco-O	1.09 ± 0.009	1.10 ± 0.006	1.16 ± 0.012	1000-2000
Byco-A	1.22 ± 0.003	1.29 ± 0.007	1.30 ± 0.004	2500-4000
Byco-C	2.08 ± 0.029	2.18 ± 0.005	2.27 ± 0.019	10 000-12 000
Gelatin	3.06 ± 0.044	3.75 ± 0.042	4.11 ± 0.012	15 000-250 000

*As given in technical literature supplied by Croda Healthcare, East Yorkshire, UK.

Table 2. Micromeritic Properties of the Granules

Binders	Compressibility Index ± SD	Hausner Ratio ± SD	Angle of Repose ± SD (θ°)	Circularity Factor ± SD	Roundness ± SD
Byco-O	12.50 ± 0.165	1.14 ± 0.04	33.27 ± 0.46	1.57 ± 0.35	0.67 ± 0.17
Byco-A	14.54 ± 0.416	1.17 ± 0.03	32.74 ± 0.45	1.75 ± 0.75	0.65 ± 0.11
Byco-C	15.59 ± 0.872	1.22 ± 0.05	31.45 ± 0.58	1.54 ± 0.29	0.70 ± 0.11
Gelatin	18.73 ± 0.487	1.19 ± 0.03	27.45 ± 0.71	1.56 ± 0.37	0.65 ± 0.12

no. 16 mesh and no. 30 mesh sequentially, and finally dried in a hot air oven at 40°C overnight. These granules were analyzed for loss on drying (LOD) and then subjected to micromeritic and mechanical characterization.

Evaluation of Granules

Loss on Drying

Dried granules (1 g) were kept at 105°C in an oven (Kumar Industries, Mumbai, India) and dried up to constant weight. LOD was calculated using the following formula[7]:

$$\% \text{ LOD} = 100(\textit{Initial Weight} - \textit{Final Weight})/\textit{Initial Weight} \quad (1)$$

Micromeritic Properties

The granules were assessed for bulk density, tapped density, compressibility index, and Hausner ratio using Tapped density tester (USP) (model ETD 1020, Electrolab, Mumbai, India). Also, angle of repose (θ) was determined using the fixed funnel method[8] to evaluate flowability. The granules (50 in number) were observed under stereomicroscope (Zeiss Stemi 2000-C, Zeiss, Oberkochen, Germany), and their roundness and circularity factor (CF) were measured using Biovis (Image plus, Version 1.50, Expert Vision Labs, Mumbai, India) software.

$$CF = \pi(\textit{major axis})^2/4(\textit{area}) \quad (2)$$

$$\text{Roundness} = (\textit{perimeter})^2/4\pi(\textit{area}) \quad (3)$$

The observations of micromeritic properties are summarized in Table 2.

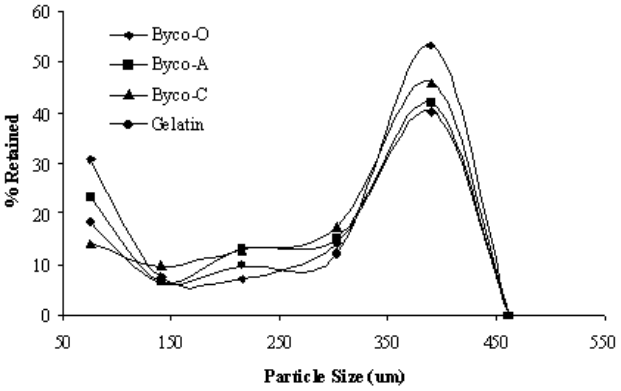

Figure 1. Frequency distribution curves of particle size analysis.

Particle size analysis of the granules (20 g) was done using no. 30, 40, 60, 80, and 100 ASTM (American Standards of Testing Materials) meshes. The frequency distribution curves of this study were plotted against mean particle size (Figure 1).

Mechanical Properties

Friability

Friability of granules was determined by the method described by Deodhar et al,[9] in which 10-g granules were placed with 20 polyethylene balls in a ball mill (Seema Enterprises, Pune, India) and rotated for 5, 10, 20, and 30 minutes, with sieve analysis done at each time interval. The friability index (FI) as a function of time was determined using the Rubinstein equation.[10]

$$FI = [(d_g)_t/(d_g)_0] \times 100 \quad (4)$$

where $(d_g)_t$ is the mean geometric diameter after time t, and $(d_g)_0$ is the initial mean geometric diameter.

Table 3. Disintegration Time and Hardness of Tablets

	Parameters	
Binders	**Disintegration Time ± SD (minutes)** (At 50 kg/cm^2 pressure)	**Hardness ± SD (N)** (At 50 kg/cm^2 pressure)
Byco-O	3.39 ± 0.036	89.86 ± 0.971
Byco-A	3.89 ± 0.317	102.16 ± 1.04
Byco-C	4.52 ± 0.068	131.36 ± 1.18
Gelatin	6.29 ± 0.07	160.33 ± 1.52

Crushing Strength

Crushing strength of granules was determined as described by Jarosz and Parrott[11] using the mercury load cell method on specially fabricated crushing strength apparatus (Seema Enterprises, Pune, India).

Compressional Properties

Heckel Plot

Primogel, magnesium stearate, and Aerosil 200 were added to the granules used for micromeritic and mechanical characterization and then mixed well. These granules (150 ± 5 mg) were compressed at different pressures up to constant density of compacts using a hydraulic press (Spectralab, Mumbai, India) with an 8-mm flat-faced punch and die set. For hydrolyzed gelatins, constant density was observed at lower pressures (10 to 60 kg/cm^2), while for conventional gelatin, constant density was achieved at higher pressure values (10 to 110 kg/cm^2). Around 40 compacts were prepared for each formulation and then stored in vacuum chambers for 24 hours to allow for elastic recovery. The data obtained were processed using the Heckel equation,[11-13] and mean yield pressure (P_y ie, 1/k) was obtained.

$$\ln(1/1-\rho_r) = kP + A \quad (5)$$

where ρ_r is relative density and k and A are constants.

Compactability of Granules

For compactability assessment, the force (F) required for diametral breaking of the compacts was determined using a diametral hardness tester (model PTB, Pharmatest, Hyderabad, India).

The tensile strength (σ_t) of the compacts was calculated using the following equation:[14]

$$\sigma_t = 2F/\pi D T \quad (6)$$

where F is hardness (in Newtons) and D and T are the diameter and thickness of the compacts (in mm), respectively.

Data analysis was performed by fitting the data in the Leuenberger equation.[15] A nonlinear plot of tensile strength with respect to product of compaction pressure (P) and relative density (ρ_r) was obtained using statistical software (UNISTAT, Megalon, Novato, CA).

$$\sigma_t = \sigma_{tmax}(1 - e^{-\gamma P \rho r}) \quad (7)$$

where σ_{tmax} is tensile strength (kg/cm^2) when $P \rightarrow \infty$ and $\rho_r \rightarrow 1$, and γ is compression susceptibility.

Disintegration Test

The disintegration behavior of compacts compressed at variable pressures was studied in distilled water at 37°C using disintegration tester USP (ED-2L Electrolab, Mumbai, India). The observations are shown in Table 3.

Results and Discussion

Preliminary studies were performed to optimize the binder concentration. It was observed that gelatin yielded a very viscous solution at 10% wt/vol concentration. Such high viscosity introduced variations because of uneven distribution and produced very hard granules. On the other hand, hydrolyzed gelatins, at 6% wt/vol concentration, yielded soft, fragile granules, which were difficult to handle. Hence, binder solution of 8% wt/vol concentration was used for their comparative evaluation.

No significant increase in viscosity was observed with increase in concentration of polymer. However, at the same concentration, viscosity of hydrolyzed gelatin was found to increase with an increase in molecular weight, as shown in Table 1.

Granules, prepared by the wet granulation technique, were evaluated for LOD, which was observed to be in the range of 1% to 2% wt/wt for all batches. Micromeritic properties (ie, compressibility index, Hausner ratio and angle of repose) revealed no significant differences (Table 2). Also, roundness and circularity factor values were between 0.65 to 0.70 and 1.54 to 1.75, respectively (Table 2). Particle size analysis of granules revealed similar frequency distribution curves, although the percentage of fines (below 75 μm) varied to a certain extent (Figure 1).

Friability index and analysis of change of friability index with time were calculated to determine surface and core strength of granules. It was observed that friability index was a linear function of time, with decreasing friability index. Hence, the data were fitted into a linear regression equation.

Table 4. Mechanical Properties of the Granules

Binders	Crushing Strength (g) ± SD	Friability After 5 Minutes(FI_5)	Friability Rate (β_1)	Initial Friability (C)	r
Byco-O	326.47 ± 93.76	52.75	1.501	58.59	0.9888
Byco-A	405.36 ± 89.45	51.23	1.337	57.10	0.9984
Byco-C	389.00 ± 105.34	50.04	1.369	57.12	0.9995
Gelatin	620.18 ± 98.87	60.21	1.842	69.52	0.9646

$$FI = -\beta_1 t + C \quad (8)$$

where $ß_1$ is friability rate and C is initial friability, which reflect the rate of generation of fines and the surface strength of granules, respectively. It was observed that the FI after 5 minutes and friability rate were significantly higher in the case of conventional gelatin, indicating formation of noncohesive granules, which readily shed off particles from their surfaces (Table 4). This finding may be attributed to the radial gradient in binder distribution across the granule.

The radial gradient in the binder concentration in the granules causes changes in the strength at different points across the radius of the granule, thus leading to differing surface and core strengths. This variation is influenced by the properties of the binder such as viscosity.[2] Granules produced using Byco-O generated fines at a faster rate, although surface strength was slightly high (58.59). This finding may be owing to higher chances of surface migration of the low viscosity solution of Byco-O. Byco-A has shown a relatively lower rate of fines generation and high tensile strength, which may be attributed to uniform distribution of binder as observed by Deodhar et al.[9]

The resistance of granules to crushing provides uniform granule size regardless of the extent and type of normal handling during processing. It can be determined by various methods.[11,16,17] The data obtained using Jarosz and Parrott load cell are shown in Table 4. It was observed that the crushing strength of granules prepared using hydrolyzed gelatin was significantly lower than the crushing strength of those prepared using conventional gelatin, indicating the hard nature of granules in the latter case.

Compressibility and compactability of granules were evaluated by mathematical treatment of the compressional study data by 2 techniques: Heckel plot studies (Figure 2) and Leuenberger equation fitting. As suggested by York and Pilpel[17] and Kurup and Pilpel,[18] the Heckel equation is a sensitive tool to study compressibility of soft materials. It describes the relationship of the compact density to the applied pressure. The reciprocal value of the slope (k) represents the mean yield pressure (P_y) by which a substance resists the deformation process. The value of the intercept (C) describes the movement of granules or particles at the beginning of compression.[18] In the case of hydrolyzed

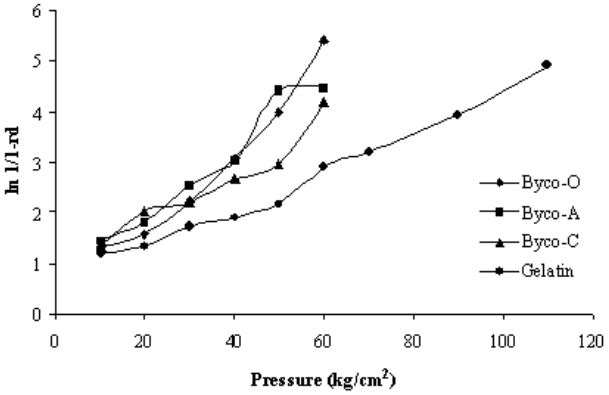

Figure 2. Comparative Heckel plots of hydrolyzed gelatins and conventional gelatin.

gelatins in which the granules are very soft, significant reduction in volume was observed at very low pressure. On the basis of P_y values for different granules, the compressibility may be ranked as Byco-O > Byco-A > Byco-C > gelatin. As shown in Figure 2, relative densities of hydrolyzed gelatins increased significantly at low pressure values, indicating soft granules formed as compared with gelatin. The Leuenberger equation, which correlates the compressional force with relative density and tensile strength of the compact, analyzes the ability of granules to be compressed into compacts of specified strength (ie, compactability expressed as σ_{tmax}). It also provides an expression, γ, quantifying compressibility and known as compression susceptibility. The properties of drug substance, diluents, and binder concentration of granules affect both compressibility and compactability. Compression susceptibility values did not show significant difference among the 3 hydrolyzed gelatins. P_y is a parameter sensitive enough to discriminate between the different grades as compared with compression susceptibility. Sensitivity of P_y may be because the determination of P_y depends on low pressure range data as compared with the Leuenberger plot, which uses nonlinear regression and includes data of high pressure range. According to P_y values data, compressibility of the granules increased with a decrease in molecular weight of the hydrolyzed gelatins (Table 5). This increase in compressibility may be due to a reduction in crushing strength with a decrease in molecular weight. The low strength granules fractured faster and a significant increase in particle-particle contact occurred, thus requiring lower pressure to yield a compact.

Table 5. Compressibility and Compactability of Granules

	Compressibility		Compactability		
Binder	Mean Yield Pressure (P_y) ± SD(kg/cm^2)	Compression Susceptibility (γ) ± SD($\times 10^{-2}$)	σ_{tmax} ± SD(N/cm^2)	r^2	Significance
Byco-O	5.04 ± 1.01	2.47 ± 0.30	766 ± 9.64	0.71	0.0006
Byco-A	7.65 ± 2.24	2.63 ± 0.46	787 ± 18.79	0.76	0.0003
Byco-C	8.53 ± 2.17	2.73 ± 0.20	959 ± 13.05	0.76	0.0001
Gelatin	13.59 ± 3.70	3.79 ± 0.02	1168 ± 4.17	0.72	0.0000

Compactability of the granules was found to be a direct function of molecular weight of gelatin, which governs the viscosity. The σ_{tmax} values for Byco-O and Byco-A did not show significant variations as their molecular weights are close to each other as compared with Byco-C and conventionally used gelatin.

Disintegration tests were performed for each of the formulations compressed at variable pressures.[19] Although the tensile strength of compacts varied according to the molecular weights of binders used, no significant differences in disintegration time at a given pressure were observed for different types; however, gelatin showed slightly higher disintegration time. Disintegration time values of compacts compressed at 50 kg/cm^2 pressure are given in Table 3.

Conclusion

Hydrolyzed gelatins (Byco-A, Byco-O and Byco-C), when used as binders, yielded soft, uniform granules with good flow properties. As the molecular weight and viscosity of hydrolyzed gelatins increased, the compressibility of granules decreased and their compactability increased. The balance between compressibility and compactability of granules may be achieved by careful monitoring of the molecular weight of hydrolyzed gelatins that can serve as potential binders.

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