Studies on Spray-Dried Mixtures of Chitosan and Hydrolyzed Gelatin as Tablet Binder: A Technical Note

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INTRODUCTION

Hydrolyzed gelatins (HG) are cold water–soluble and have good adhesion properties, but do not readily form gels. Both acidic and basic functional groups are present in the small peptides of HG. HG differ in molecular weights and viscosities, but are analytically identical and are spray dried to produce a low-density powder.[1,2] Recently Kokil et al[3] reported the effect of molecular weights of HG on their binding properties in tablets. It was observed that HG (Byco A, Byco O, and Byco C) when used as binders yielded soft, uniform granules with good compressibility but poor compactability. The compactability of granules was found to increase with increase in molecular weight and viscosity of HG.

Use of polymer mixtures as binders has been reported by various workers. Both water-soluble and water-insoluble polymers have been shown to possess excellent binding properties.[4] Serra and Robles[5] observed that the compactability of microcrystalline cellulose/calcium carbonate/polyvinyl pyrrolidone spray-dried mixtures was equal to or greater than that of pure microcrystalline cellulose and their compactibility increased with increase in mixing efficiency in the following order: spray dried > wet massing > tumble mixing.

Chitosan (CH) is a cationic polysaccharide, obtained by alkaline N-deacetylation of chitin, the principal component in crustaceans, which is insoluble in water but soluble in weakly acidic media. CH is not only readily and economically processed from naturally abundant chitin, but is also nontoxic, biodegradable, and multifunctional. It is structurally analogous to cellulose and has been evaluated as a direct tablet compression aid and sustained release excipient. Although CH has been evaluated as a directly compressible tablet excipient, virtually all formulations developed to date necessitated addition of other ingredients to facilitate compression.[6-8] Upadrashta and Katikaneni[9] studied CH as a tablet binder in comparison with other cellulose binders such as sodium carboxymethyl cellulose (Na CMC), hydroxypropylmethyl cellulose (HPMC), and methyl cellulose (MC). They reported that, on the basis of relative binder efficiency, the binders can be ranked in the order as HPMC > CH > MC > Na CMC. Sawayanagi et al[10] reported the hardness of the tablets follows the following order: CH > MCC > chitin. Although reports are available on the possibility of CH as a directly compressible agent, the compressibility of CH needs to be improved in order to make it acceptable to formulator.[11,12]

So to improve poor compactibility of HG as a binder, CH, having inadequate compressibility, has been selected. It was hypothesized that CH, being a cationic biopolymer, may form a complex with anionic functional groups of HG through electrostatic interactions and the resultant mixture may exhibit better compactibility as compared with HG alone. To form such possible complexes between CH and HG, the spray-drying technique was employed because of its simplicity, ease of operation, and economy in terms of cost and time.

In the present study, CH and HG (Byco C, Croda Healthcare, East Yorkshire, UK) were mixed in solution forms at sundry ratios as 1:1 (batch A), 1:2 (batch B), 1:3 (batch C), and 1:4 (batch D) wt/wt, respectively and then spray-dried. Spray-dried mixtures of CH and HG were analyzed for parameters such as moisture content, viscosity, Fourier transform infrared (FTIR), and surface topography. These spray-dried mixtures were further evaluated as binding agents in the wet granulation technique. Paracetamol, a poorly compressible drug with known capping tendency, has been chosen as a model drug.

MATERIALS AND METHODS

Materials

Hydrolyzed gelatin (Byco C; molecular weight 10 000 to 12 000 Da) was a generous gift by Croda. Chitosan (85% deacelyated) was a gift sample from Marine Chemicals Pvt Ltd, Kochin, India. Paracetamol IP, lactose IP, sodium starch glycolate (Primogel; FMC Corporation, Philadelphia, PA), magnesium stearate, and colloidal silicon dioxide (Aerosil 200; Degussa Corp, Piscataway, NJ) were gift samples from Get-Rid Pharma, Pune, India. All other chemicals and reagents were analytical grade and used as received.

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Methods

CH (1 g) was dissolved in 75 mL acetic acid solution (1% vol/vol). HG (1 g) was dissolved in 25 mL of distilled water. Then these 2 aqueous solutions were mixed together to obtain a final homogeneous solution of concentration 2% wt/wy (batch A, CH:HG: 1:1 wt/wt). Likewise, mixtures of CH and HG were prepared for 3 other ratios: 1:2 (batch B), 1:3 (batch C), and 1:4 (batch D) wt/wt, respectively. Then these mixtures were spray dried using a laboratory scale spray dryer (Jay Instruments Systems Pvt Ltd, Mumbai, India). For spray drying of aqueous solutions or suspensions, the outlet temperature should be higher than the boiling point of water.[13] Optimum inlet temperature for spray drying of CH and HG mixtures in an aqueous system was found to be in the range of 165°C to 185°C. If the inlet temperature was set below 140°C,or the pump rate chosen was faster than 6 to 7 mL/minute, the solvent in the droplets could not be fully evaporated. It was observed that some of liquid droplets were attached inside the wall of the expansion chamber. Hence the inlet temperature was optimized to 180°C and the pump rate was controlled at 4 to 6 mL/minute, respectively. When the liquid was fed to the nozzle with a peristaltic pump, atomization occurred by the force of the compressed air, disrupting the liquid into small droplets. The droplets, together with hot air, were blown into a chamber where the solvent in the droplets was evaporated and discharged out through an exhaust tube. Spray-dried products were obtained as free-flowing off-white powders and were easily soluble in water.

Characterization of Spray-dried Mixtures of CH and HG

Moisture Content

Moisture content of CH, HG, and spray-dried mixtures of CH and HG was determined using Karl Fischer Titrator (Veego Matic D, Veego Instruments Cooperation, Mumbai, India) and end point was detected visually.

Viscosity Determination

Viscosities of aqueous solutions of CH, HG, and their spray-dried mixtures (1% wt/vol and 2% wt/vol) were determined at 25°C using Brookfield's viscometer (Brookfield ENG, Labs Inc, Stoughton, MA) (Table 1).

Infrared Spectroscopy

IR spectra of plain CH, HG, and batch A were taken by using instrument JASCO V 5300 FT-IR (Tokyo, Japan) (Figure 1). The pellets were prepared on a KBr-press (Spectralab, Mumbai, India). The spectra were scanned over the wave number range of 4000 to 400 cm^{-1}.

Table 1. Viscosity of Binder Solutions of Spray-dried Mixtures

Batch (CH:HG wt/wt)	Viscosity ± SD (mPa.s) (at 25°C)	
	1% wt/vol	2% wt/vol
D (1:4)	26.73 ± 0.11	80.63 ± 1.51
C (1:3)	31.50 ± 1.32	85.33 ± 0.57
B (1:2)	36.43 ± 4.20	94.33 ± 0.57
A (1:1)	44.40 ± 0.10	108.00 ± 7.47
HG (Byco C)	2.08 ± 0.03*	2.27 ± 0.02†

*Viscosity of 4% wt/vol solution.
†Viscosity of 8% wt/vol solution.

Surface Topography

Surface topography of CH, HG, and batch D was examined using scanning electron microscopy (SEM). Powders were placed on the SEM stage, coated under an argon atmosphere with gold-palladium, and observed with SEM (Stereoscan S120, Cambridge, UK; acceleration voltage 4 kV). Gold coating was done using sputter coating unit (VG-Microtech, Uckfield, UK). The thickness of the coating was approximately 20 nm. The photomicrographs of these samples are shown in Figure 2.

Preparation of Granules

The powder mixture for granulation contained the following (for 100 g each batch): Paracetamol IP (66.67 g), lactose IP (26.83 g), spray-dried mixture (A/B/C/D) (4 g), Primogel (2 g), magnesium stearate (0.33 g), and Aerosil 200 (0.17 g). Paracetamol and lactose were thoroughly mixed and granulated with binder solution of polymer mixture (34 mL of 4% wt/vol solution) 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 no. 16 mesh and no. 30 mesh sequentially, and finally dried in a hot air oven at 40°C overnight.

Evaluation of Granules

Loss on Drying (LOD)

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 following formula.[14]

$$\%LOD = \frac{100(Initialweight - Finalweight\ )}{Initialweight}$$

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,

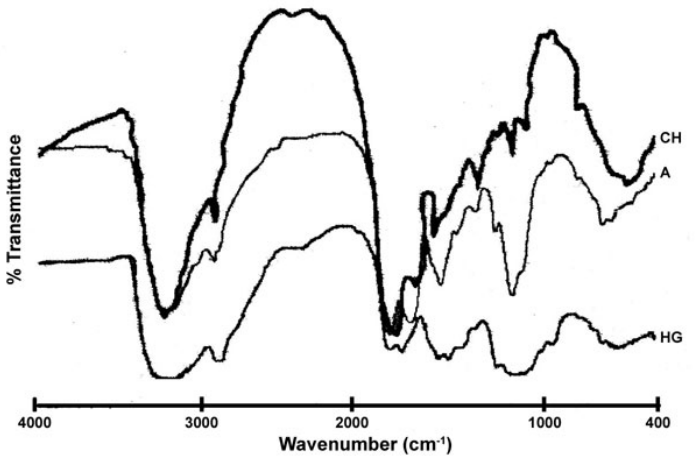

Figure 1. Infrared spectra of chitosan (CH), batch A, and hydrolyzed gelatin (HG).

India). Also angle of repose (θ) was determined, using the fixed funnel method to evaluate flowability. The granules (50 in number) were observed under stereomicroscope (ZEISS Stemi 2000-C, Oberkochen, Germany) and their roundness and circularity factor (CF) were measured using Biovis software (Image plus v 1.50, Expert vision labs, Mumbai, India).

$$CF = \frac{\pi\ (majoraxis)^2}{4(area)}$$

$$Roundness = \frac{(perimeter)^2}{4\pi\ (area)}$$

The observations of micromeritic properties are summarized in Table 2.

Particle size analysis of the granules (20 g) was done using no. 30, no. 40, no. 60, no. 80, and no. 100 ASTM meshes.

Mechanical Properties

(a) Friability

Friability of granules was determined by the method described by Deodhar et al,[15] in which 10 g of granules were placed with 20 g polyethylene balls in a ball mill and rotated for 5, 10, 20, and 30 minutes, with sieve analysis done at each time interval. The friability index (FI) was determined using the Rubinstein equation[16] as a function of time.

$$FI = \left[\frac{(d_g)_t}{(d_g)_0}\right] \times 100,$$

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

(b) Crushing Strength

Crushing strength of granules was determined by the mercury load cell method as described by Jarosz and Parrott[17] using specially fabricated crushing strength apparatus (Seema Enterprises, Pune, India).

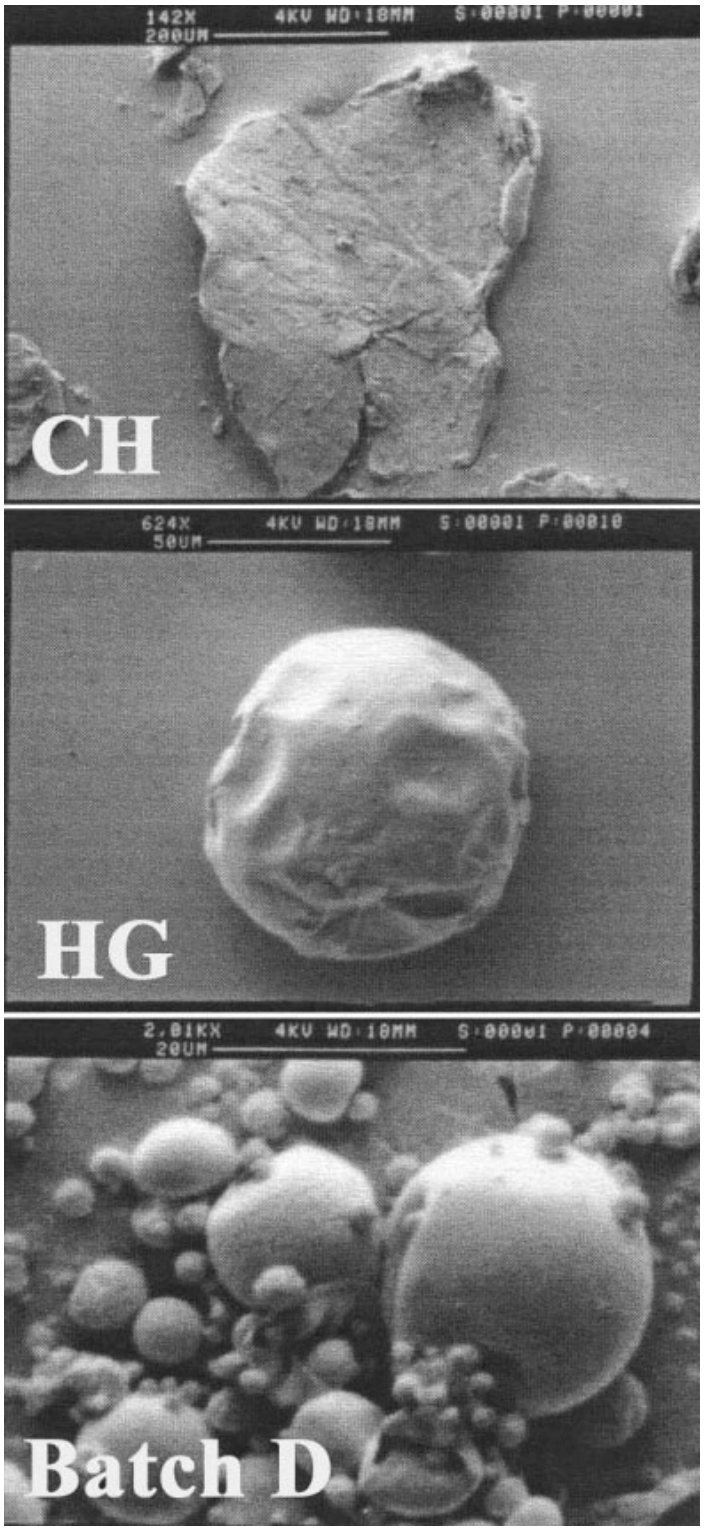

Figure 2. Photomicrographs of chitosan (CH), hydrolyzed gelatin (HG), and batch D.

Table 2. Micromeritic and Mechanical Properties of the Granules

	Micromeritic Properties					
Batch (CH:HG wt/wt)	LOD (% wt/wt)	Compressibility Index ± SD	Housner Ratio ± SD	Angle of Repose ± SD (θ°)	Roundness ± SD	Circularity Factor ± SD
D (1:4)	1.30	14.28 ± 0.016	1.16 ± 0.001	35.53 ± 0.28	0.70 ± 0.10	1.61 ± 0.20
C (1:3)	1.31	23.68 ± 0.016	1.31 ± 0.008	33.96 ± 0.62	0.58 ± 0.10	1.65 ± 0.17
B (1:2)	1.84	19.44 ± 0.016	1.24 ± 0.001	32.64 ± 0.18	0.59 ± 0.07	1.53 ± 0.21
A (1:1)	2.07	13.33 ± 0.016	1.15 ± 0.002	30.15 ± 0.04	0.62 ± 0.13	1.67 ± 0.12
HG*	1.26	15.59 ± 0.872	1.22 ± 0.050	31.45 ± 0.58	0.70 ± 0.11	1.54 ± 0.29

	Mechanical Properties				
Batch (CH:HG wt/wt)	Crushing Strength ± SD (g)	Friability Index after 5 Minutes (FI_5)	Friability Rate (β_1)	Friability Constant (C)	r
D (1:4)	490 ± 13.06	83.75	1.1809	87.24	0.916
C (1:3)	506 ± 29.09	85.88	1.0519	87.35	0.915
B (1:2)	556 ± 16.86	90.05	1.0558	90.28	0.865
A (1:1)	737 ± 20.29	92.87	0.9882	93.60	0.887
HG*	389 ± 105.34	50.04	1.3690	57.12	0.999

*Byco C (concentration as a binder was 8% wt/wt).

Compressional Properties

(a) Heckel Plot

Primogel, magnesium stearate, and Aerosil 200 were add 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. Around 40 compacts were prepared for each formulation and then stored in vacuum chambers for 24 hours to allow elastic recovery. The data obtained were processed using the Heckel equation[18,19] and mean yield pressure (P_y i. e. 1/k) was obtained.

$$Ln\left(\frac{1}{1-\rho_r}\right) = kP + A,$$

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

(b) Compactibility of Granules

For compactibility assessment, the force (F) required for diametral breaking of the compacts was determined using diametral hardness tester (model PTB, Pharmatest, Hyderabad, India). The tensile strength (σ_t) of the compacts was calculated using following equation.[20]

$$\sigma_t = \frac{2F}{\pi DT},$$

where F is hardness (in Newton) 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.[21] A nonlinear plot of tensile strength with respect to product of compaction pressure *(P)* and relative density *(ρ_r)* was obtained using a statistical software (UNISTAT, Megalon, Novato, CA).

$$\sigma\ t = \sigma_{tmax}\ (1-e^{-\gamma P \rho r}),$$

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

Disintegration Test

The disintegration behavior of compacts compressed at variable pressures was studied in distilled water at 37°C ± 0.5°C with the help of disintegration tester USP (ED-2L Electrolab, Mumbai, India). The observations are shown in Table 3.

Dissolution Test

Granules (150 ± 5 mg) were compressed at pressure of 40 kg/cm^2 for 1 minute. These compacts were subjected for the dissolution studies using USP 24 type I dissolution test apparatus (TDT 08L, Electrolab, Mumbai, India). The study was performed in 0.1 M HCl (900 mL) at 37 ± 0.5°C temperature at 100 rpm (n = 6).

Results and Discussion

Earlier study revealed that HG, as a binder, has inadequate compactibility.[3] It was thought that polymer mixtures might

Table 3. Compressibility and Compactability of Granules and Disintegration Time (DT) and Hardness of Tablets

	Compressibility		Compactability*		At 50 kg/cm^2 Pressure	
Batch (CH:HG wt/wt)	Mean Yield Pressure (P_y) ± SD (kg/cm^2)	Compression Susceptibility (γ) ± SD ($\times 10^{-2}$)	σ_{tmax} ± SD (N/cm^2)	r^2	D. T. ± SD (Minutes)	Hardness ± SD (N)
D (1:4)	3.46 ± 0.34	4.71 ± 0.63	1696.87 ± 212.16	0.80	2.40 ± 0.04	89.36 ± 0.83
C (1:3)	4.75 ± 1.10	5.80 ± 3.09	2016.25 ± 165.18	0.81	5.11 ± 0.04	90.90 ± 6.65
B (1:2)	8.51 ± 0.10	3.26 ± 0.18	2298.32 ± 139.11	0.76	8.00 ± 0.31	94.16 ± 5.80
A (1:1)	10.39 ± 2.27	4.94 ± 3.02	2299.36 ± 423.36	0.70	13.20 ± 0.1	97.90 ± 3.14
HG†	8.53 ± 2.17	2.73 ± 0.20	959 ± 13.05	0.76	4.52 ± 0.068	131.36 ± 1.18

* $P < .01$.

†Byco C (concentration as a binder was 8% wt/wt).

improve the compactibility. Although CH can be directly compressed, the resultant tablets, generally, are friable and soft.[10] CH, which has inadequate compressibility, was chosen because of its cationic nature that may help in molecular interactions with HG. Spray-drying technique has been successfully used in the pharmaceutical industry to process powders since it offers a means of obtaining powders of predetermined particle size and shape.[22] In a preliminary study, physical mixtures of CH and HG were prepared using different ratios. When such physical mixtures were evaluated as binder in tablets, the granules showed capping and lamination tendency. Therefore spray-drying technique was employed to obtain free-flowing powder mixtures of CH and HG.

Within the range of observed operating parameters, spray drying was satisfactory and yielded free-flowing powder mixtures of these 2 polymers. The percent yield after spray drying for all batches was in between 40% and 65% wt/wt. The moisture content of CH and HG was 7.3% wt/wt and 10.8% wt/wt, respectively and that of the spray-dried mixtures of CH and HG was in the range of 2.14% to 3.20% wt/wt, indicating sufficient drying with fair efficiency in terms of percent yields. Viscosities of spray-dried mixtures of CH and HG were significantly higher as compared with plain HG, even at 4% and 8% wt/vol concentration, owing to presence of CH. Within the same concentration range, viscosity of spray-dried mixtures increased with relative increase in CH content. Also viscosities of 2% wt/vol solutions were much higher than that of 1% wt/vol solutions for all the 4 batches of spray-dried mixtures, as shown in Table 1. FTIR spectroscopy was employed to study molecular interactions between CH and HG in the spray-dried mixtures. IR spectrum of batch A (CH:HG:: 1:1 wt/wt) showed a sharp peak at 1651 cm^{-1} and its increased intensity may be attributed to NH_3^+ of CH. This seems to be in good agreement with the increase of H^+ species. Also batch A showed sharp peak at 1556 cm^{-1} with slightly more intensity as compared with HG. The peak at 1078 cm^{-1} was more intense as compared with CH as well as HG due to bending of carbonyl or hydroxyl bonds. This seems to indicate the complexation via H-bond formation between CH and HG (Figure 1). The photomicrograph of CH showed irregularly shaped particles in the range of 50 to 200 μm while the particles of HG were spheres with pitted surface and the particle size varied between 50 and 100 μm. Incorporation of CH in HG solution and subsequent spray drying resulted in more smooth spheres without any surface pits. It may be attributed to the increased viscosity and elasticity due to CH, which allowed uniform expansion of the droplet during spray drying (Figure 2).

Preliminary studies were performed to optimize the binder concentration in the form of solution. High viscosity of binder solution was likely to introduce variations because of uneven distribution and also produced very hard granules. The prototype level of binder in all the granulates was 4% wt/wt.

Granules prepared by wet granulation technique were evaluated for LOD, which was observed to be in the range of 1% to 2.1% wt/wt for all the batches (Table 2). Micromeritic properties (ie, compressibility index and Hausner ratio) revealed no significant differences, but the angle of repose for batch A was low as compared with other batches. Also roundness and circularity factor values were between 0.58 to 0.70 and 1.53 to 1.67, respectively (Table 2). Particle size analysis of granules revealed no significant differences (data not shown).

Crushing strength decreased with increasing HG content in spray-dried mixtures and was lowest for plain HG. Friability index decreased linearly with time. It was observed that friability index after 5 minutes and initial friability were significantly higher in the case of batch A. With increasing concentration of HG, crushing strength was observed to reduce, indicating formation of soft granules that were susceptible to fracture at lower loads. Similarly, friability index at 5 minutes reduced with increasing concentration of HG in spray-dried mixtures, indicating formation of noncohesive granules, which readily shed off particles from their

surfaces (Table 2). This might be attributed to radial gradient in binder distribution across the granule, as suggested by Deodhar et al.[15] Also the crushing strength of granules prepared using high concentration of HG (batch D) was significantly lower than batch A, indicating hard nature of granules formed in the latter case owing to higher CH content.

The Heckel equation describes the relationship of the compact density to the applied pressure.[19] Relative density of batch D increased significantly at low pressure suggesting weak granules as compared with other batches (Figure 3). The properties of drug substance, diluents, and the binder concentration of granules affect both compressibility and compactibility. On the basis of P_y values for different granules, the compressibility may be ranked as batch D > batch C > batch B > batch A (Table 3), however they are not significantly different. P_y is a more sensitive parameter to discriminate between the different batches as compared with compression susceptibility since the later takes into account reduction in volume at high pressures where the discrimination of compressibility is quite less.[3] It 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 decrease in concentration of CH (Table 3). The σ_{tmax} values (indicating compactibility) were found to increase with relative increase in the concentration of CH. However, it was interesting to note that this effect of CH on compactibility was more prominent up to a certain concentration, beyond which CH did not contribute to an increase in compactibility. This was evident from the observation that relative increase in σ_{tmax} values from batch D to batch C, and from batch C to batch B was significant, while there was only marginal increase in σ_{tmax} values from batch B to batch A. This increase in crushing strength with increase in CH content (up to a ceiling value)

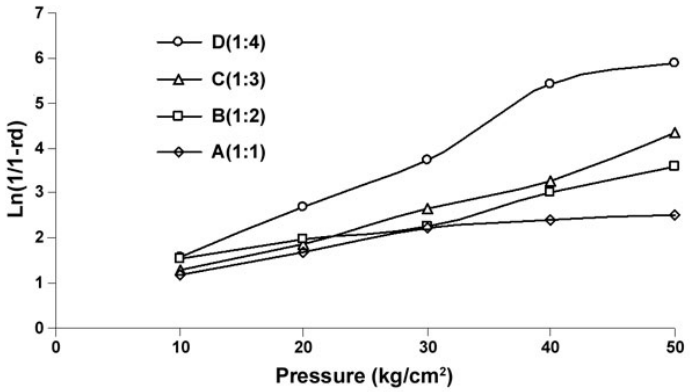

Figure 3. Comparative Heckel plots spray-dried mixtures (A, B, C, D) of chitosan (CH) and hydrolyzed gelatin (HG).

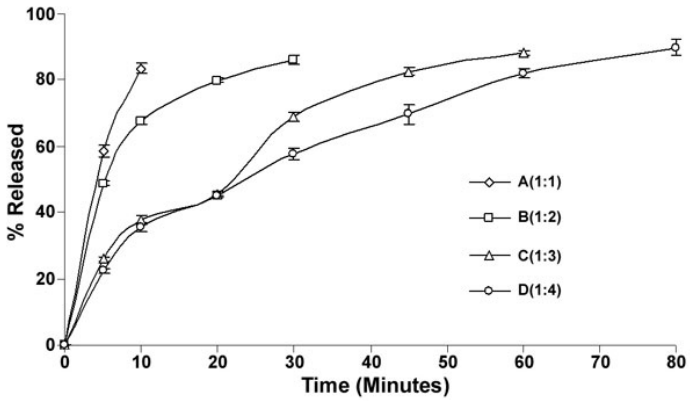

Figure 4. Comparative dissolution profiles of spray-dried mixtures (A, B, C, D) of chitosan (CH) and hydrolyzed gelatin (HG).

could be attributed to formation of low-strength granules that fractured faster and significant increase in particle-particle contact occurred, thereby resulting in enhanced formation of cold wielding bonds between adjacent particles. Once the upper limit of such bond formation was reached, further addition of CH in the granules (eg, batch A) did not cause any significant change in tensile strength of compacts.

The mean hardness values for all the batches were in the range of 89 to 98 N, although the mean hardness value was found to decrease with increasing HG content of the compacts. Disintegration tests were preformed on each formulation at variable pressures.[23] Disintegration time values at a given pressure (50 kg/cm^2) are shown in Table 3. The disintegration time increased in batches with decrease in HG, and the order of disintegration time was observed as batch A > batch B > batch C > batch D. Disintegration time of compacts was found to depend on HG, which is a water-soluble component. At higher concentrations of HG in compacts, disintegration time in distilled water was significantly less. On the contrary, the dissolution of compacts in 0.1 M HCl (Figure 4) revealed that with increasing concentration of CH, rate of drug dissolution increased. This may be ascribed to high solubility of cationic CH in acidic media,[7,9] leading to burst effect within a short period of time.

CONCLUSION

The results of this investigation showed that spray drying of CH and HG resulted in free-flowing powder, which exhibited improved compressibility and compactibility, thereby suggesting the potential of such spray-dried mixtures of CH and HG as binder in tablets. Optimization of CH:HG ratio needs to be undertaken on a case basis, depending on the presence of other excipients in the formulation.

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