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Process and formulation characterizations of the thermal adhesion granulation (TAG) process for improving granular properties

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Abstract

In this study, we demonstrate the feasibility of using the thermal adhesion granulation (TAG) method to improve granular properties for preparing highly compressible excipients as direct tabletting aids. The TAG method subjects a mixture containing excipients, such as microcrystalline cellulose (MCC), lactose, starch, or dibasic calcium phosphate (DCP), under closed conditions with a low moisture content and low content of polyvinyl pyrrolidone (PVP) as a binder, to heating during mixing by tumble rotation to produce highly compressible granules. Results demonstrated that a closed system is more efficient than an open system at such a low moisture content, and both water and ethanol were able to fulfill the role of a granulation liquid, but water was more appropriate than ethanol for successfully producing granules suitable for use as direct tabletting aids by the TAG method. It was also found that a 5% moisture content in the powder mixture containing MCC and PVP is optimal in the TAG process to produce granules with the desired characteristics for pharmaceutical applications. On the contrary, increasing the moisture content led to further decreases in the mean size and deterioration of the flowability. It was further demonstrated that the TAG process is able to imbue these commonly used diluents with more-desirable physical characteristics of granules for direct tabletting, enabling the processing of these commonly used diluents with 50% PVP into directly compressible matrix materials.

Keywords: Thermal adhesion granulation method; Compressible; Polyvinyl pyrrolidone; Mechanical properties; Direct tabletting aids

1. Introduction

The flowability and compressibility of powdered materials are improved by dry or wet granulation in the presence of a binder in dry or solution form, respectively. Wet granulation is by far the most often employed method for granulation. A novel granulation method, moisture-activated dry granulation (MADG), involving agglomeration and moisture distribution was described (Ullah et al., 1987). This process is designated a moist granulation technique (MGT), and it was compared to conventional granulation (Railkar and Schwartz, 2000). The application of MGT to an immediate-release dosage form showed the advantages of wet granulation such as increased particle size and better flow (Railkar and Schwartz, 2001b), and the development of controlled-release dosage forms for those materials with poor compressibility and flowability, such as acetaminophen (APAP), was further proven to be feasible (Railkar and Schwartz, 2001a).

In a patent assigned to Wei-Ming Pharmaceutical Company (Yeh and Yeh, 2004), a novel granulation method, designated a thermal adhesion granulation (TAG) method, was described. The process was designated TAG since it differs from the traditional wet granulation approach in several important aspects: (1) in TAG, a low amount of moisture is added to the tabletting mixture containing diluent excipients and binder, whereas in wet granulation the binder is generally dissolved in the granulation fluid then mixed with the diluent excipients; (2) TAG resembles a "dry" process in that the moisture content (water or organic solvent requirement) is significantly less than that in wet granulation; (3) with the exception of the drying step, wet granulation is typically conducted at ambient temperature, whereas in TAG the tabletting mixture is heated to promote the formation of the adhesive binder, such as PVP, for enlarging granules; (4) wet granulation involves significant post-granulation steps of drying and milling to form the desired granules; these steps are unnecessary with the TAG process due to the low amount of

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moisture introduced to the tabletting mixture; and (5) conventional granulation methods are typically conducted in a partially open system, while TAG is preferably conducted in a closed system.

With the MGT, a low level of moisture (2.0–3.6%) is manually introduced from a squeeze bottle with continued mixing and is distributed in the powder mixture composed of the drug, PVP (a binder), and hydroxypropyl cellulose (HPC, a controlled-release material). Lactose or dicalcium phosphate is then added, followed by microcrystalline cellulose (MCC, a moisture-absorbing material), and mixing is continued for 5 min. The granulation is passed through a screen and then transferred to a twin-shell blender for blending with Cab-O-Sil and then magnesium stearate before tabletting (Railkar and Schwartz, 2000, 2001a,b). In the TAG method, granules are formed during mixing of the moist powder under continuous tumble rotation as the powder mass flows within the container with heating (Yeh and Yeh, 2004). Thus, this provides an alternative method for improving granular properties to prepare direct tabletting aids or formulations using a binder as a finely divided powder with a low moisture level or with a pharmaceutically acceptable solvent to granulate diluent excipients or active substances in a closed system which is subjected to heating and mixing by tumble rotation. The influences of the formulation and process factors employed in the thermal adhesion granulation on the physical characteristics of the resulting granules were thoroughly examined in this study.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose grade 101 (MCC, Microcel® PH 101, Wei-Ming, Taipei, Taiwan), lactose (lactose anhydrous, Borculo), starch (starch 1500, Colorcon), dibasic calcium phosphate anhydrous (Fujicalin SG, Fuji Chemical), dibasic calcium phosphate dihydrate (DCP, Innophos, Chicago, IL, USA), hydroxypropyl cellulose (Klucel® EXF, Aqualon), and polyvinyl pyrrolidone (PVP K30, Kollidon®, BASF) with a particle size range of 10–50 μm as binders were used as received. Powder characteristics, including the mean particle size, angle of repose, bulk density, tapped density, and compressibility index, of all excipients used in this study and the corresponding tablet properties, such as tensile strength, friability, and disintegration time, were determined and are summarized in Table 1. The water content of all materials was controlled to ≤3%.

2.2. Thermal adhesion granulation (TAG) method

The binder/diluent mixture was first moisturized with water or ethanol (by weight of the total mixture) via a fine spray and briefly blended. The mixture was next placed in a prewarmed glass bottle, sealed, and heated by an infrared lamp to raise the surface temperature of the vessel to 90–105 °C for water or 70–90 °C for ethanol while being mixed under tumble rotation (the bottle was subjected to a rolling motion about a horizontal axis) for 3–20 min until granules had formed. During granulation, the bottle was also briefly shaken periodically to allow any accumulated vapor condensation on the inner surface of the bottleneck and bottom portions to come in contact with the powder mass. The resulting granules were then immediately screened through a size-24 mesh (800 μm). The resulting granules could be used directly upon cooling, or in certain cases if so desired, were further dried by the infrared lamp or other means as necessary. Granules so obtained were stored in desiccators until their mechanical properties were measured. Detailed formulations listed in Table 2 were designed to examine the feasibility of the TAG method by comparing processing variables including an open versus a closed system, inclusion or exclusion of a disintegrant, and the granulating fluid (water or alcohol). The influences of formulation variables including the moisture level (Table 3), binder level (Table 4), and diluent type (Tables 5 and 6) on the resulting granular and tablet properties employing the TAG method were examined by the same procedures described above.

2.3. Measurement of mean particle size

The particle size distributions were evaluated by sieve analysis. Powder samples subjected to sieve analysis using a nest of standard sieves of 37–800 μm were agitated for 10 min on a sieve shaker (ERWEKA, AR400, Heusenstamm, Germany), and data

Table 1
Powder physical characteristics of excipients and physical properties of the corresponding tablets

Property	MCC 101	Lactose	Starch	DCP
Mean size (μm)	50	90	80	113
Angle of repose (°)[a]	54.33 ± 1.53	40.33 ± 0.58	40.68 ± 0.58	41.33 ± 0.58
Bulk density (g/mL)[a]	0.256 ± 0.002	0.635 ± 0.006	0.623 ± 0.007	0.387 ± 0.002
Tapped density (g/mL)[a]	0.397 ± 0.002	0.811 ± 0.011	0.784 ± 0.006	0.455 ± 0.002
Compressibility index (*C*%)[a]	35.58 ± 0.71	21.63 ± 0.34	20.56 ± 0.21	14.94 ± 0.14
Tensile strength (MPa)[b]	2.677 ± 0.49	NT[c]	0.191 ± 0.02	NT
Friability (%)	0.20	NT	1.03	NT
Disintegration (s)	>900	NT	<420	NT

MCC, microcrystalline cellulose; DCP, dibasic calcium phosphate.
[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$.
[c] NT, not tablettable at a compression force of 500 kg (49 MPa).

Table 2
Physical properties of granules and tablets produced by different methods in terms of the binder, wetting solution, and system conditions

	Closed system				Open system	
	Percent (%) composition					
	A	A-1	Q	R	T	U
MCC 101	90	86.85	90	90	90	90
PVP K30	10	9.65	10	–	10	10
HPC	–	–	–	10	–	–
Crospovidone	–	3.5	–	–	–	–
	Method of wetting					
	5% Water	5% Water	1.5% Ethanol	1.5% Ethanol	5% Water	1.5% Ethanol
Mean size (μm)	205.08 ± 129.56	129.18 ± 94.22	66.85 ± 61.85	88.03 ± 41.73	50.68 ± 31.54	43.78 ± 35.79
Angle of repose (°)[a]	42.67 ± 0.58[c]	45.33 ± 0.58[c]	47.67 ± 0.58[c]	51.00 ± 1.00	47.67 ±± 0.58[c]	49.67 ± 0.58
Bulk density (g/mL)[a]	0.205 ± 0.003[c]	0.199 ± 0.002[c]	0.231 ± 0.001[c]	0.216 ± 0.001	0.250 ± 0.002	0.292 ± 0.003[c]
Tapped density (g/mL)[a]	0.255 ± 0.001[c]	0.241 ± 0.001[c]	0.320 ± 0.002[c]	0.287 ± 0.001[c]	0.329 ± 0.002[c]	0.400 ± 0.004
Compressibility index (*C*%)[a]	19.69 ± 0.88[c]	17.41 ± 0.43[c]	27.77 ± 0.18[c]	24.70 ± 0.23[c]	23.88 ± 0.28[c]	27.01 ± 0.26[c]
Tensile strength (MPa)[b]	3.08 ± 0.33	3.79 ± 0.19[c]	2.46 ± 0.17	2.54 ± 0.15	1.85 ± 0.46[c]	2.14 ± 0.39[c]
Friability (%)	0	0.2	1.02	0	0.40	0
Disintegration (s)	>900	<180	>900	>900	>900	>900

MCC, microcrystalline cellulose; PVP, polyvinyl pyrrolidone; HPC, hydroxypropyl cellulose.
[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$; A-1: +3.5% intragranule disintegrant.
[c] $p < 0.02$ versus MCC 101 in Table 1.

of the retained weight were then obtained for each sieve size. A log-normal plot of cumulative weight percentage versus the respective average mean size of the two sieve sizes was used to determine the mean size of the distribution (the size of 50%) and its geometric standard deviation (the antilog ratio of [size of 86%/size of 50%]).

2.4. Determination of the bulk density, tapped density, and compressibility index of granules

Bulk and tapped densities were measured using an A.B.D. Fine Particle Characteristics Measuring Instrument (Tsutsui, Tokyo, Japan). The weight of a 100-g sample was placed in a 100-mL funnel cylinder and tapped until a constant volume was observed, and then the volume was recorded and calculated as follows:

$$\text{Bulk density (g/mL)} = \frac{\text{weight of samples (g)}}{\text{volume occupied before tapping (mL)}},$$

$$\text{Tapped density (g/mL)} = \frac{\text{weight of samples (g)}}{\text{volume occupied after tapping (mL)}}.$$

Both densities were averaged from three determinations. The compressibility index (*C*%) was calculated from the bulk and tapped density results using the following formula:

$$C\% = \left[\frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}}\right] \times 100\%.$$

Table 3
Physical properties of granules and tablets produced with microcrystalline cellulose (MCC) and polyvinyl pyrrolidone (PVP) (90:10) under different moisture contents

	Percent (%) composition/formulation		
	L	M	N
MCC 101	90.0	90.0	90.0
PVP K30	10.0	10.0	10.0
Moisture content (%)	5	10	15
Mean size (μm)	193.73 ± 113.59	146.42 ± 100.79	132.34 ± 91.81
Angle of repose (°)[a]	44.67 ± 0.58[c]	50.00 ± 1.00	56.33 ± 0.58
Bulk density (g/mL)[a]	0.209 ± 0.002[c]	0.234 ± 0.001[c]	0.239 ± 0.002[c]
Tapped density (g/mL)[a]	0.258 ± 0.001[c]	0.301 ± 0.001[c]	0.294 ± 0.001[c]
Compressibility index (*C*%)[a]	19.17 ± 0.58[c]	22.31 ± 0.17[c]	18.61 ± 0.23[c]
Tensile strength (MPa)[b]	3.28 ± 0.40[c]	2.76 ± 0.21	3.20 ± 0.29[c]
Friability (%)	0.20	0	0
Disintegration (s)	>900	>900	>900

[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$.
[c] $p < 0.02$ versus MCC 101 in Table 1.

Table 4
Physical properties of granules and tablets produced with microcrystalline cellulose (MCC) and polyvinyl pyrrolidone (PVP) with a 5% moisture content

	Percent (%) composition/formulation		
	E	F	G
MCC 101	95.0	90.0	85.0
PVP K30	5.0	10.0	15.0
Mean size (μm)	125.32 ± 86.37	225.06 ± 154.62	332.45 ± 188.19
Angle of repose (°)[a]	49.33 ± 1.53	43.00 ± 1.00[c]	41.33 ± 1.00[c]
Bulk density (g/mL)[a]	0.216 ± 0.001[c]	0.213 ± 0.002[c]	0.223 ± 0.004[c]
Tapped density (g/mL)[a]	0.291 ± 0.001[c]	0.253 ± 0.002[c]	0.245 ± 0.004[c]
Compressibility index (*C*%)[a]	25.58 ± 0.23[c]	15.59 ± 0.29[c]	9.11 ± 0.74[c]
Tensile strength (MPa)[b]	3.32 ± 0.47[c]	3.13 ± 0.21	3.53 ± 0.26[c]
Friability (%)	0.20	0.40	0
Disintegration (s)	>900	>900	>900

[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$.
[c] $p < 0.02$ versus MCC 101 in Table 1.

Table 5
Physical properties of granules and tablets produced with different diluents and polyvinyl pyrrolidone (PVP) at a 5% moisture content

	Percent (%) composition/formulation			
	A	B	C	D
MCC 101	90.0			
Lactose		90.0		
Starch			90.0	
DCP				90.0
PVP K30	10.0	10.0	10.0	10.0
Mean size (μm)	205.08 ± 129.56	271.53 ± 203.26	379.94 ± 185.56	195.82 ± 123.52
Angle of repose (°)[a]	42.67 ± 0.58[c]	35.00 ± 1.00	38.33 ± 0.58	32.00 ± 0.00[c]
Bulk density (g/mL)[a]	0.205 ± 0.003[c]	0.524 ± 0.004[c]	0.443 ± 0.003[c]	0.454 ± 0.002[c]
Tapped density (g/mL)[a]	0.255 ± 0.001[c]	0.561 ± 0.005[c]	0.458 ± 0.001[c]	0.505 ± 0.003[c]
Compressibility index (*C*%)[a]	19.69 ± 0.88[c]	6.52 ± 0.08[c]	3.17 ± 0.69[c]	10.08 ± 0.86[c]
Tensile strength (MPa)[b]	3.08 ± 0.38	2.24 ± 0.80[c]	1.08 ± 0.16[c]	1.16 ± 0.12[c]
Friability (%)	0	0.60	0.81	1.42
Disintegration (s)	>900	<375	<190	<180

MCC, microcrystalline cellulose; DCP, dibasic calcium phosphate; PVP, polyvinyl pyrrolidone.
[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$.
[c] $p < 0.02$ versus the respective diluents in Table 1.

2.5. Preparation and characterizations of tablets

To characterize tablets made using the excipients, granules, and direct tabletting aids described in this study, tablets (11.3 mm discoid, 0.5 g) were produced with compression of 49 MPa (500 kg/cm^2) using a Sankyo Pio-Tech SK-02 Tablettability Tester (Japan). Tablet hardness was tested using the same instrument and tensile strength was calculated as follows: Tensile strength = $2P/\pi Dh$, where P is the load necessary to cause fracture; D is the tablet diameter; and h is its thickness. The friability of tablets was tested on a Roche Friabilator by Aikho (AE-20, Japan; 20 rpm; 5 min; $n = 10$). The initial (W_i) and final weights (W_f) of the tablet samples were recorded, and the corresponding friability was calculated as follows:

$$\text{Friability (\%)} = \left[\frac{(W_i - W_f)}{W_i}\right] \times 100.$$

The disintegration time of tablets was measured according to the US Pharmacopoeia (USPXXIII) with six tablets for a period of 30 min using a tablet disintegration tester ($n = 6$) by Shin Gwon (model SK-0004, Taipei, Taiwan).

2.6. Statistical analysis

All data are reported as the mean ± S.D. The data were statistically evaluated using ANOVA, paired *t*-test, and independent *t*-test for unpaired observations. Differences were considered significant at $p < 0.05$.

3. Results and discussion

3.1. Feasibility of thermal adhesion granulation (TAG)

The desired formulations and process conditions for the production of direct tabletting aids by the TAG method were

Table 6
Physical properties of granules and tablets produced with a high percentage of polyvinyl pyrrolidone (PVP) and different excipients with a 5% moisture content

	Percent (%) composition			
	H	I	J	K
MCC 101	50.0			
Lactose		50.0		
Starch			50.0	
DCP				50.0
PVP K30	50.0	50.0	50.0	50.0
Mean size (μm)	151.48 ± 163.75	183.18 ± 182.99	140.58 ± 152.98	171.55 ± 163.54
Angle of repose (°)[a]	49.00 ± 1.00[c]	44.33 ± 3.51	38.67 ± 1.16	38.33 ± 0.58
Bulk density (g/mL)[a]	0.296 ± 0.002[c]	0.430 ± 0.001[c]	0.425 ± 0.001[c]	0.415 ± 0.001[c]
Tapped density (g/mL)[a]	0.385 ± 0.001[c]	0.523 ± 0.001[c]	0.531 ± 0.001[c]	0.495 ± 0.001[c]
Compressibility index (*C*%)[a]	23.08 ± 0.56[c]	17.82 ± 0.07[c]	19.97 ± 0.21[c]	16.12 ± 0.17
Tensile strength (MPa)[b]	6.93 ± 0.94[c]	6.47 ± 1.09[c]	4.36 ± 0.91[c]	1.28 ± 0.32[c]
Friability (%)	0	0.20	0.20	0.40
Disintegration (s)	>900	>900	>900	>900

MCC, microcrystalline cellulose; DCP, dibasic calcium phosphate; PVP, polyvinyl pyrrolidone.
[a] Mean ± S.D., $n = 3$.
[b] Mean ± S.D., $n = 10$.
[c] $p < 0.02$ versus their parent materials in Table 1.

examined. MCC 101 and PVP at a 90:10 weight ratio were used as the basic formulation, and the influences of a 5% moisture content (formulations A and T) and 1.5% ethanol (formulations Q and U) on the physical properties of the resulting granules and tablets were compared in either a closed (formulations A and Q) or open system (formulations T and U). The physical properties of the respective granules and tablets given in Table 2 demonstrate that regardless of which solvent (5% water or 1.5% ethanol) was used to moisturize the powder mixture, the physical characteristics of the resulting granules, mainly the mean size, flowability, and compressibility index, improved more significantly in the closed than in the open system. Furthermore, the increase in the mean size and the improvements in flowability and the compressibility index of the resulting granules moisturized with 5% water were more significant than those with 1.5% ethanol in both systems, but the closed system produced more-desirable results. This indicates that in order to successfully produce granules suitable for use as direct tabletting aids by the TAG method, a closed system is more efficient at forming the adhesive binder (PVP) than an open system at such a low moisture content, and both water and ethanol were able to fulfill the role of a granulation liquid, but water was more appropriate than ethanol.

However, results in Table 2 also illustrate that the disintegration time exceeded 900 s for all tablets produced with granules by the TAG method in both the closed and open system moisturized with 5% water or 1.5% ethanol. The influence of adding crospovidone intragranularly at 3.5% as a disintegrant (formulation A-1 in Table 2) on improving the disintegration of tables produced with the resulting granules was examined. Results illustrate that the mean size decreased and the flowability and compressibility index somewhat deteriorated in the corresponding granules in comparison with those with no disintegrant added. This was probably because absorption of moisture by the disintegrant resulted in decreased efficiency in the formation of the adhesive binder (PVP) for granulation. Nevertheless, the disintegration time of tablets produced with the corresponding granules was shortened from >900 to <180 s. This indicates that the addition of a disintegrant to the powder mixture used for TAG is not only workable without extensively decreasing the efficiency of forming the adhesive binder by water and heating for granulation but also fulfills the role of a disintegrant by significantly improving the disintegration of tablets.

An alternative binder of HPC supplied by Aqualon was evaluated for its possible use in the TAG process in the same proportion as PVP to MCC 101 (10:90) moisturized with 1.5% ethanol (formulation R). Results are given in Table 2 and demonstrate that favorable granules were produced in terms of the mean size, flowability, and compressibility index in comparison with those using PVP as the binder. This demonstrates the applicability of the TAG process for producing tablettable granules containing other binders even when using a solvent such as ethanol, which has a lower moisturization efficiency of forming adhesive binders for granulation.

The feasibility of the TAG process in a closed system with a low moisture content was confirmed. When subjected to heating, the added water or ethanol plus the inherent moisture in the powder mass vaporized in the closed system to maximize the use of the granulating solution, leading to successful granulation with the minimal addition of moisture or solvent. It is believed that heating the powder mass might also result in the transfer of a certain amount of the inherent moisture in the diluents to the binder. As described in Section 2, the vessel was briefly shaken periodically during granulation to allow any accumulated vapor condensation on the inner surface of the vessel (mainly around the bottleneck and bottom) to contact with the powder mass, indicating that the preferred implementation of TAG is such that the heat distribution on the surface of the granulation vessel should be, in some manner, slightly non-uniform, such that when the powder mass is heated, the evolved water or solvent vapor can condense on a portion of the inner surface of the vessel which is comparatively cooler. Since binders, such as PVP, are generally

hygroscopic, any moisture present in the system, especially in the form of condensation, will be scavenged by the binder, which then becomes sticky and tacky with heating to form the adhesive binder. Because the binder was uniformly pre-dispersed among the diluents as a fine powder prior to granulation, the increasing adhesiveness of the binder results in the cohesion of neighboring particles and ultimately the formation of granules as the powder mixture is mixed within the processing vessel. The optimal temperature range for TAG is system-specific, and depends on factors such as the type and the amount of diluents, the binder, and granulation liquid used. For example, when an organic solvent rather than water is used as the granulation liquid, a lower temperature may be needed.

3.2. Processing MCC with a fixed amount of PVP at different moisture contents

In a closed system, PVP at a fixed ratio (10%) was mixed with MCC 101 at three different moisture levels (5%, 10%, and 15%) and was then subjected to the TAG process (formulations L, M, and N, respectively, Table 3). The physical characteristics of the resulting granules and tablets are illustrated in Table 3 and demonstrate that the mean size of granules unexpectedly decreased with an increasing moisture content in the powder mixture. This was also reflected by an increase in the angle of repose with respect to a decrease in the mean size of the corresponding granules. However, the compressibility index of the resulting granules and the tensile strength of the corresponding tablets did not follow the same trends as those with respect to the mean size and angle of repose. This can possibly be explained by the excess moisture during the TAG process being absorbed onto the MCC fibers leading to the fraction of moisture used as the granulating liquid not proportionally increasing with an increasing moisture content in the powder mixture. We concluded that a 5% moisture content in the powder mixture containing MCC 101 and PVP is optimal in the TAG process for producing granules with desirable characteristics for pharmaceutical applications. On the contrary, an increase in moisture content unnecessarily led to a further decrease in the mean size and deterioration of flowability.

3.3. Processing MCC with various amounts of PVP at a fixed moisture content

PVP K30 at three different percentages of 5%, 10%, and 15% (formulations E, F, and G in Table 4, respectively) was mixed with MCC 101 and then subjected to TAG with a 5% moisture content, and the results are summarized in Table 4. As expected, the mean particle size and flowability increased with the additional amount of PVP incorporated in the powder mixture due to the binding role of PVP, which enlarged the granules at the same moisture content of 5%. However, differences in tensile strengths among the tablets produced with these three kinds of granules were statistically insignificant ($p > 0.05$), but significantly differed from those of tablets produced with only MCC PH 101 ($p < 0.02$). Thus, it was further confirmed that the low moisture content was appropriate for initiating enlargement of the grain size and regulating the mean particle size by adjusting the amount of binder added to the TAG process.

3.4. Processing various diluents with a fixed amount of PVP and a fixed moisture content

The TAG method was applied to process various diluents with a fixed amount of PVP at a 5% moisture content, and the results are given in Table 5. In a comparison of the physical characteristics of the granules with the original materials and their corresponding tablets listed in Table 1, it is clearly demonstrated that the mean size of the resulting granules increased, and the compressibility index and flowability, reflected by the angle of repose, improved for all diluents in the TAG process. Results further indicate that the TAG process with the addition of low moisture preserves the binding capability of the resulting MCC granules to form tablets with desired tensile strengths, which was reported to deteriorate when subjecting MCC particles to wet granulation (Sherwood et al., 2000). Those resulting granules of lactose and DCP processed by TAG with PVP as the binder were tablettable compared to the inability to form tablets with either of the original materials. Furthermore, the tensile strength of tablets produced with starch granules processed by TAG significantly increased in comparison to those tablets produced from starch granules without TAG processing. Preferably, the disintegration of the respective tablets produced from the resulting granules of lactose, DCP, and starch processed by the TAG method with such a high percentage of PVP was not hindered, and all fell within an acceptable range for pharmaceutical applications. Thus, we concluded that the TAG process is able to imbue these commonly used diluents with improved physical characteristics of granules that are desirable for tabletting.

3.5. Processing PVP with various diluents as matrix material

When a large quantity of viscous materials, such as PVP and HPMC, is granulated with water or ethanol in a high shear mixer by pouring or in a fluidized bed by spraying to produce the matrix materials, it usually becomes so viscous that it hinders the formation of desired granules with the former, whereas with the latter, the resulting granules are sponge-like when water is used and hard when ethanol is used (Liu et al., 1993). Therefore, in order to evaluate the potentials of applying TAG to process PVP with various diluents to produce matrix material, PVP was processed by TAG with various diluents, including MCC (formulation H), lactose (formulation I), starch (formulation J), and DCP (formulation K) at a 1:1 weight ratio with a 5% moisture content. Results are given in Table 6 and show that the mean size increased and the flowability improved for all resulting granules in comparison to those of the original materials of each individual component. However, a decrease in the mean particle size and accordingly a decrease in the flowability were noted compared to each respective granule listed in Table 5 which were produced with a 10% PVP content. Nevertheless, the tensile strengths of tablets produced with three of those resulting granules containing 50% PVP (formulations H–J) were signif-

icantly higher than those containing 10% PVP (formulations A–C). Only an insignificant increase in the tensile strength of tablets produced with granules processed with DCP by TAG was shown with an incremental amount of PVP from 10% (formulation D) to 50% (formulation K). With PVP optimally being used as the matrix material, the disintegration of the corresponding tablets produced with each of those granules was obviously hindered as reflected by all of the disintegration times exceeding 900 s.

Taking the role that PVP plays as a binder into consideration, it was interesting to find that the enlargement of granular size by TAG at the same moisture level (5% in this case) was at a decreased efficiency with an increasing PVP content (10% to 50%) in the powder mixture. Since PVP was the most hygroscopic material among the ingredients in the powder mixture, that can possibly explain why the number of PVP particles that could be plastically heated after water absorption and then bind to neighboring particles to produce granules would be expected to decrease with an increasing PVP amount as a result of competing for the same amount of water. Thus, a lower amount of PVP being moisturized led to the formation of larger granules at the same water level.

It is known that the compact strength of tablets made of MCC (Avicel PH 101) is attributed mainly to intermolecular forces as a result of plastic deformation, those made of starch (Sta-Rx 1500) to plastic deformation and a rougher surface texture, and those made of lactose (α-monohydrate) to fragmentation and a limited extent of plastic deformation (Karehill and Nyström, 1990a,b). Therefore, it is believed that the tensile strengths of tablets made of formulations H–J markedly increased compared to their parent materials and formulations A–C due to an increase in the PVP content from 0 to 10% and then to 50%, which played a major role as a binder in increasing the compact strength by plastic deformation (Nyström et al., 1993; Kibbe, 2000; Kachrimanis and Malamataris, 2005). Nevertheless, the tensile strength of tablets made of formulation D was found to insignificantly ($p > 0.05$) differ from that of formulation K. This could be attributed to DCP serving as a fragmenting material (Nyström et al., 1993) that fragments during compression leading to the formation of a similar bonding surface area that predominately bonds by intermolecular distance forces for compact strength, which is consistent with results reported by Schmidt and Herzog (1993).

4. Conclusions

The thermal adhesion granulation technique was shown herein to be a useful method and was successfully applied to prepare highly compressible materials for direct tabletting aids. The results obtained indicated better particle sizes, flowability, and tensile strengths for direct compression tablets compared with the parent materials. In this study, we suggest the evaluation and application of the thermal adhesion granulation method to prepare or develop controlled-release dosage forms. It was concluded that the thermal adhesion granulation method is quite simple and convenient with low moisture and binder contents in a closed system for preparing highly compressible materials or for modifying the poor characteristics of excipients.

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