Drug Development and Industrial Pharmacy, 33:1273–1284, 2007

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701542390

informa
healthcare

A Cross-Performance Relationship Between Carr's Index and Dissolution Rate Constant: The Study of Acetaminophen Batches

Tu Lee
Department of Chemical and Materials Engineering, and Institute of Materials Science and Engineering, National Central University, Jhong-Li City, Taiwan, R. O. C.

Fu Bin Hsu
Department of Chemical and Materials Engineering, National Central University, Jhong-Li City, Taiwan, R.O.C.

The aim of this paper is to promote a simple and scalable approach to accelerate the formulation development of wet granules using acetaminophen batches as a model system. Only two thorough experiments with five processing steps of: crystallization → dry blending → wet granulation → drying → dissolution, were required to establish a specific linear relationship between the overall effect of the particle size distribution and the dissolution performance for a given formulation of any batch of acetaminophen. With this specific linear relationship at hand, dissolution rates of the granules prepared from batches of acetaminophen with various particle size distribution could be predicted without the need of doing any wet granulation, drying and dissolution for the same formulation. It was found that the Carr's Index, *C*, an overall manifestation of particle size distribution, of only a few grams of the dry blended acetaminophen was good enough to be linearly related to the dissolution rate constant, *k*, of the formulated granules by $\ln k = \alpha \ln C + \ln A$ (or exponentially by a power law of $k = AC^{\alpha}$) where *A* was the exponential factor and α was the power index. *A* and α were dependent on the mass transfer of acetaminophen powders and the rheological properties of the formulated dry blended powders, respectively. The three linear relationships for 75, 62, and 30 wt % formulations were $\ln k = 2.9 \ln C - 12.3$, $\ln k = 2.8 \ln C - 12.5$, and $\ln k = 4.2 \ln C - 18.0$, respectively. The power laws for 75, 62, and 30 wt % formulations were $k = 4.7 \times 10^{-6} C^{2.9}$, $k = 3.9 \times 10^{-6} C^{2.8}$, and $k = 1.5 \times 10^{-8} C^{4.2}$, respectively. The formulation used in our study contained acetaminophen, microcrystalline cellulose, and polyvinylpyrrolidone. The validation of the linearity between *k* and *C* was verified (1) by acetaminophen batches from different processes and sources, (2) by the various formulation compositions of acetaminophen of 75, 62, and 30 wt%, and (3) by the growth mechanisms of wet granulation and the resultant granular structures determined by dry sieve analysis, optical microscopy (OM), mercury intrusion porosimetry (MIP), the Brunauer-Emmett-Teller (BET) method, scanning electron microscopy (SEM), and Fourier transformed infrared (FT-IR) microscopic mapping. In general, granules grown from the small-size ranged acetaminophen powders of a given formulation had a higher *C*. Since the growth mechanism was dominated by agglomeration, the granules were more porous, higher in surface area, more homogenous, and higher in dissolution rate constant, *k*, as opposed to granules grown from the large-size ranged acetaminophen powders of a given formulation having a lower, *C*, whose growth was dominated via consolidation and layer-by-layer mechanism and resulted in a lower dissolution rate constant, *k*.

Keywords cross-performance relationship; power law; Carr's index; dissolution rate constant; FT-IR microscopic mapping; acetaminophen

INTRODUCTION

In the face of increasing molecular complexity of drug molecules and generic competition and growing pressures to reduce drug prices, there is an unprecedented need for a more effective and efficient approach to drug development. Since about 80% of all marketed drug products and more than 95% of the top selling drug products are solid oral dosage forms, (Byrn, Morris, & Comella, 2005) it is important to accelerate the development of solid oral dosage so that their revenue lifecycles can be expanded. One strategy to reduce time to market is by progressing the new chemical entities (NCEs) rapidly from candidacy to Phase I clinical studies. (Byrn et al., 2005).

However, the current development of a simplified formulation begins when a sufficient amount of active pharmaceutical ingredient (API) with a defined solid form is available. A typical development cycle involving a chain of five key steps: crystallization → dry blending → wet granulation → drying → dissolution, is carried out repeatedly until the bulk specification

Address correspondence to Tu Lee, Department of Chemical and Materials Engineering, and Institute of Materials Science and Engineering, National Central University, 300 Jhong-Da Road, Jhong-Li City 320, Taiwan, R.O.C. E-mail: tulee@cc.ncu.edu.tw

such as the particle-size range, the process critical control points like the end-point in the wet granulation and the specified dissolution rate are set. During the same time, a manufacturing process for the formulation is also being identified. However, this working strategy is time-consuming and requires a relatively large amount of expansive API powders. (Kim, Lotz, Lindrud, Girard, Moore, Nagarajan, Alvarez, Lee, Nikfar, Davidovich, Srivastava, & Kiang, 2005)

Although a lot of efforts have been focused on the physics of the granular growth in wet granulation (Goldszal & Bousquet, 2001; Johansen & Schaefer, 2001; Schaefer, 2001) and the granular structure-dissolution performance in dissolution, (Albertini, Cavallari, Passerini, Voinovich, Gonzalez-Rodriguez, Magarotto, & Rodriguez, 2004; Cao, Choi, Cui, & Lee, 2005; Garcia & Ghaly, 1996) a prediction of the dissolution rate of the granules prepared from the bulk of API of a known size-distribution and from a given formulation is still unavailable.

Therefore, the aim of this paper is two-fold: (1) to establish a cross-performance relationship linking the Carr's index, *C*, of the bulk of API of a known size-distribution with a given formulation at the dry blending step (i.e., formulated dry blended powders) to the dissolution rate constant, *k*, of the formulated granules at the dissolution step, so that the number of experiments containing five processing steps of: crystallization → dry blending → wet granulation → drying → dissolution, can be reduced to a minimum, and (2) to elucidate the feasibility of this cross-performance relationship with the granular growth dynamics (Pepin, Blanchon, & Couarraze, 2001; Timmins, Delargy, Minchom, & Howard, 1992) and the resultant granular structures. (Rough, Wilson, & York, 2005; van den Dries, de Vegt, Girard, & Vromans, 2003; van den Dries, & Vromans, 2002) By so doing, the formulation development can be abbreviated significantly and the clinical API batches released earlier.

Acetaminophen, an analgesic API, was chosen for this study because of its low-cost and high commercial values. Moreover, we have experiences in engineering the crystals of acetaminophen (Lee, Kuo, & Chen, 2006) and acetaminophen has already been studied as a model API for the granulation mechanism (van den Vries & Vromans, 2003) and dissolution rate. (Cao et al., 2005; Keleb, Vermeire, Vervaet, & Remon, 2004; Railkar & Schwartz, 2001)

MATERIALS AND METHODS

Chemicals

Acetaminophen for making small-sized distribution of crystals ($CH_3CONHC_6H_4OH$, M.W. = 151.17 g/mol, 98%, Lot: S23272-444) was purchased from Sigma-Aldrich, Steinheim, Germany. Another source of acetaminophen for growing (100%, Batch: 0540385) large-sized distribution of crystals was obtained from Lu'An, Anqiu, China. Microcrystalline cellulose (MCC, PH-101) ($(C_6H_{10}O_5)_{220}$, M.W. = 36000 g/mol, > 80%, Lot: 1512) was purchased from Asahi Kasei, Tokyo, Japan. Polyvinylpyrrolidone (Wade & Weller, 1994) (PVP, Kollidon® 30) ($(C_6H_9NO)_{450}$, M. W. = 50000 g/mol, *m.p.* = 150°C, Lot: G42116PT0) used as a binder and disintegrant was received from O-BASF, New Jersey. Mineral oil (Paraffin oil, Viscosity at 40°C = 68.10 centistokes, Flash point = 110°C, Lot: 903046) purchased from TEDIA (Fairfield, Ohio), was used to disperse the acetaminophen agglomerates for optical microscopy. Hydrochloric acid (HCl, M. W. = 36.46, 37% reagent grade, ACS, ISO, density: ~1.19 g/cm^3, Lot: 60015) obtained from Scharlau Chemie S.A., Barcelona, Spain was used to prepare a pH = 1.4 dissolution medium. The ultrapure water (Milli-Q® ultrapure water purification system, pack name: Q-Gard® 1, Catalogue No.: QGARDOOR1, Lot: F4JN45093) from Millipore, Massachusetts was used as the solvent in re-crystallization, wet granulation, and dissolution.

Analytical Instrumentations

Dry Sieve Analysis

Particle size distributions of acetaminophen bulk powders, microcrystalline cellulose, polyvinylpyrrolidone, and formulated granules were determined through a stack of metal sieve plates from the largest aperture to the finest in the order of 500, 350 (Der Shuenn, Taiwan), 250, 150, 75, and 45 μm (Cole-Palmer, Illinois). To eliminate the unwanted mesh plugging, minimize particle breakage and aggregation on the mesh, a small sample loading of 0.8 to 1.0 g of powders was placed at the center of the 500 μm sieve plate first. Vibration was then generated by holding the 500 μm sieve plate with one hand and tapping the sieve plate sideways with a spatula by another hand until no more powders (or granules) on the 500 μm sieve plate passed through by eye. Particles, which passed through the 500 μm, were collected on the surface of the 350 μm sieve plate. The same shaking method was then repeated successively for other sieve plates with smaller-sized openings. With this method, there was no need to worry the effect of loading, shaker speed, and time on the data obtained for the particle size distribution. The weight of the powders (or granules) retained on the surface of each sieve plate was divided by the total sample weight of the powders (or granules) to obtain the corresponding weight % oversize for each sieve fraction.

Rheological Study (the Carr's Index)

The rheological properties of acetominophen powders, formulated dry blended powders, and formulated granules were characterized through the packing studies of about 1 to 2 g of the sample powders (or granules) by the Carr's index:

$$C = \frac{\rho_t - \rho_p}{\rho_t} \times 100\% \quad (1)$$

where the poured density, ρ_p, was the mass of the sample powders (or granules) divided by the undisturbed volume in a

10 mL graduated cylinder after filling, and the tapped density, ρ_t, was the mass of the sample powders (or granules) per unit volume after tapping a bed of powders (or granules) until no change in the volume was seen. The number of times of tapping was about 200 to 250.

Optical Microscopy

The optical microscope (Olympus SZII, Tokyo, Japan) with a charge couple device (CCD) camera (SONY, model: SSC-DC50A, Tokyo, Japan) was used to characterize the morphology of acetaminophen powders and excipients. All optical micrographs were taken by dispersing the bulk powders in mineral oil at 25ºC.

Brunauer-Emmett-Teller (BET) Surface Area Analysis

The total surface area of formulated granules was measured by a BET surface area analyzer (Micromeritics ASAP 2010, Georgia). About 1 g of sample was pre-dried in a vacuum oven at 115°C (under the melting point of acetaminophen, MCC, and PVP) overnight. Before the analysis began, the sample was de-gased to a vacuum value below 8 μm Hg and kept at 115°C. When the vacuum value was reached then aerated back to atmosphere and started analysis. Nitrogen gas was used as the analysis adsorptive gas and the bath temperature was 77.35 K. The drying temperature of 115ºC did not introduce any artifacts in the porosity measurements because of the high melting point of PVP at 150ºC and the unchanged dissolution performance of the 115ºC treated formulated granules.

Mercury Intrusion Porosimetry

The porosity of the formulated granules was measured by a mercury intrusion method (Micromeritics AutoPore IV 9500, Georgia). The sample weight was about 0.3 to 0.4 g. The intrusion pressure was from 0.10 to 60000.00 psia.

Scanning Electron Microscopy

The scanning electron microscope (SEM) (Hitachi S-3500N, Tokyo, Japan) was used to observe the morphology of the acetaminophen powders, formulated granules, and the cross-section of the formulated granules. Both secondary electron imaging (SEI) and backscattered electron imaging (BEI) were used for the SEM detector and the magnification was 15 to 300000-fold. The operating pressure was 10^{-5} Pa vacuum and the voltage was 15.0 keV. For the acetaminophen powders, a sample weight of 3 to 5 mg was selected arbitrarily from the bulk. For the formulated granules, 5 to 6 granules were chosen randomly from granules, which passed through the 1.19 mm sieve screen and retained on the 500 μm sieve screen. Cross-sectional samples were prepared by cutting the same sieve fraction of granules in half by a razor blade. All samples were mounted on a carbon conductive tape (Prod. No. 16073, TED Pella Inc., California) and then sputter-coated with gold (HITACHI E-1010 ION SPOTTER, Tokyo, Japan) with a thickness of about 6 nm. The discharge current used was about 0 to 30 mA and the vacuum was around 10 Pa.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was used to identify the thermal property of all samples. Thermal analytical data of 3 to 5 mg of samples placed in perforated aluminum sealed 60 μL pans were collected on a Perkin Elmer DSC-7 calorimeter (Perkin Elmer Instruments LLC, Shelton, Connecticut) with a temperature scanning rate of 10°C/min from 50 to 200°C using nitrogen 99.990% as a blanket gas. Calibration of temperature axis was calibrated with indium 99.999 % (Perkin Elmer Instruments LLC, Shelton, Connecticut).

Ultraviolet and Visible Spectrophotometry

The withdrawals from the dissolution apparatus at fixed times was filtered, diluted for 50 times and assayed through ultraviolet absorbance determination at 243 nm using an ultraviolet and visible (UV/Vis) spectrophotometer (Lambda 25, Perkin Elmer, Norwalk, Connecticut). The concentration of acetaminophen at each time point was converted from the absorbance value to the corresponding concentration by a linear calibration line according to Beer's Law established from 5 standard acetaminophen solutions each with a known concentration of acetaminophen. The mean results of triplicate measurements and the standard deviation were then calculated.

Fourier Transform Infrared Microscopy

The homogeneity of acetaminophen inside a granule at the micron level was measured by the FT-IR microscopic mapping technique (Autoimage FT-IR Microscope System, Perkin Elmer, New York) of cross-sectional areas of granules which passed through the 1.19 mm sieve screen and retained on the 500 μm sieve screen. Granules were cross-sectioned by a razor blade. The FT-IR microscopic image was determined by a reflectance mode with an aperture of 50 μm × 50 μm. The scanning type was an attenuated total reflection (ATR) mapping and had a 1 cm^{-1} resolution with a scanning range from 700 to 4000 cm^{-1}. The mapping image of the cross-sectional area revealed the relative IR absorption intensity of acetaminophen and the excipients.

EXPERIMENTAL

Crystallization

To bring out the differences and to envelop the formulation performance, two batches of acetaminophen (the API) were tailor-made. A batch of powders with the large-size ranged was produced by re-crystallization of the acetaminophen batch from Lu'An, and a batch of powders with the

small-size ranged was made by grinding the acetaminophen lot from Sigma-Aldrich. Both batches were subjected to the same wet granulation protocol and the resultant granules were tested for their dissolution performance in a dissolution tester.

Re-Crystallization: The solubility of acetaminophen was determined to be about 15 and 50 mg/ml at 25 and 60ºC, respectively. A total of 0.5 kg of acetaminophen was mixed with 10 kg of ultrapure water (solubility at 60ºC) at 25ºC in a 10 L glass vessel with a set agitation speed of 250 rpm. The water temperature in the vessel jacket was gradually raised to and maintained at 70ºC for 1 hr by a temperature-controlled water bath. The overheating to 70ºC by 10°C was to ensure a complete dissolution of acetaminophen. After the solution was clear, the water bath was turned off and it was cooled down to about 25°C altogether with the glass vessel to induce slow spontaneous nucleation. It took about 14 hrs for re-crystallization to finish. The wet cake was filtered, washed with 1.5 L of cold ultrapure water and oven-dried at 50°C for about 6 hrs until there was no significant weight loss and the final weight was about 255.5 g and the yield was calculated to be 73 wt%.

Grinding: About 200 g of acetaminophen powders were ground by a ceramic pestle and mortar.

Particle size distributions and polymorphism of recrystallized powders, Lu'An powders, Sigma-Aldrich powders, and ground powders were determined by dry sieve analysis and DSC, respectively.

Dry Blending

The formulations used for wet granulation were listed in Table 1. MCC was a filler and PVP was a binder and a disintegrant. Powders of acetaminophen were dry-blended with MCC and PVP for 3 min in a 8-L sized planetary mixer (Tian Shuai Food Machine Co. Ltd., Taiwan) with a rotational speed of 135 rpm. Formulations composing 75, 62, and 30 wt % of acetaminophen were abbreviated as 75, 62, and 30 wt % formulation, respectively.

Wet Granulation

The ultrapure water was introduced into the powder mixture at the 3rd min of dry blending by a peristaltic pump (Micropump, Concord Corporation, California) with a water flow rate of 7 mL/min. If necessary, 2.0 to 3.0 g of granules were sampled for every 3 min from the bowl randomly at three locations and oven dried at 40ºC overnight. The granular size distributions were determined by dry sieve analysis and the packing studies such as the Carr's index in Eq. (2). Three samples were used for calculating the standard deviation of the granular growth curves which were plotted as granular weight % oversize versus time. The agglomerates started to become pasty after the addition of about 112, 147, and 217 g of ultrapure water for a total wet mixing time of about 16, 21, and 31 min for 75, 62, and 30 wt % formulations (Table 1), respectively. Wet granulation was stopped at those end-points.

TABLE 1
75, 62, and 30 wt. % Formulation Compositions of Acetaminophen

Ingredient	Weight (g)	Composition (wt. %)
75 wt. % Formulation		
Acetaminophen	181	75
Microcrystalline Cellulose	56	23
Polyvinylpyrrolidone	4.8	2
62 wt. % Formulation		
Acetaminophen	150	62
Microcrystalline Cellulose	87	36
Polyvinylpyrrolidone	4.8	2
30 wt. % Formulation		
Acetaminophen	72.5	30
Microcrystalline Cellulose	164.5	68
Polyvinylpyrrolidone	4.8	2

Drying

The wet granules were then oven dried at 50ºC until there was no significant weight loss. Granules between the 1.19 mm sieve plate with a diameter of 25 cm (mesh no. 16, Der Shuenn, Taiwan) and the 500 μm sieve plate with a diameter of 11.5 cm (mesh no. 35, Der Shuenn, Taiwan) were used to weigh out 0.667, 0.806, and 1.667 g for 75,, 62, and 30 wt % formulation, respectively in filling the number 00 capsule (Dah Feng Capsule Industry Co. Ltd., Taiwan) for an equivalent of 500 mg acetaminophen in the dissolution study.

Dissolution

A dissolution test station (SR6, Hanson Research Corporation, Chatsworth, California) Type II (paddle method) at rotation speed of 50 rpm was used for in vitro testing of acetaminophen dissolution from the various formulated granules grown from different batches of acetaminophen. Dissolution was carried out on an equivalent of 500 mg acetaminophen filled capsules. Ultrapure water of pH 1.4 with HCl was used as the dissolution medium. The volume and temperature of the dissolution medium were 900 mL and 37.0 ± 0.2ºC, respectively. (Sorasuchart, Wardrop, & Ayres, 1999) Sample of 4 to 5 ml were withdrawn at 1, 2, 3, 4, 5, 10, 15, 20, 25, 40, 60, and 90 min by a plastic syringe near the stirring paddle. Each sample was filtered by a 0.22 μm syringe filter (Millex-GV, Millipore, Massachusetts), diluted 50 times in a volumetric flask with ultrapure water of pH 1.4 and then assayed for the concentration of acetaminophen by a UV/vis spectrometer.

RESULTS AND DISCUSSION

DSC use-test scans in Figure 1 showed that the ground and recrystallized acetaminophen powders and the acetaminophen batches from Sigma-Aldrich and Lu'An were all Form I crystals with a melting point of about 171°C. (Espeau, Ceolin, Tamarit, Perrin, Gauchi, & Leveiller, 2005; Lee, Hung, & Kuo, 2006; Lee et al., 2006). The sieve fractions of the small-size and the large-size ranged acetaminophen powders produced from grinding and re-crystallization, respectively were demonstrated in Figure 2 along with the ones of Lu'An acetaminophen powders, Sigma-Aldrich acetaminophen powders, MCC, and PVP. The ground acetaminophen powders had a bimodal size distribution peaked at 75 and 500 μm and the recrystallized acetaminophen powders had a relatively wide distribution towards the large sizes from 350 to 500 μm. Optical micrographs showed that the ground acetaminophen powders of sieve fractions > 150 μm were spherical and looked like aggregates of smaller particles (Figure 3a) and the recrystallized acetaminophen powders were actually crystals with definitive geometrical shapes (Figure 3b). SEM image (Figure 4) verified that the ground acetaminophen powders of large sizes such as > 500 μm were actually aggregates of primary particles with sizes of about 10 to 70 μm. Aggregates were usually formed when the primary particles were held together by cohesive and electrostatic forces. (Ebube, Hikal, Wyandt, Beer, Miller, & Jones, 1997)

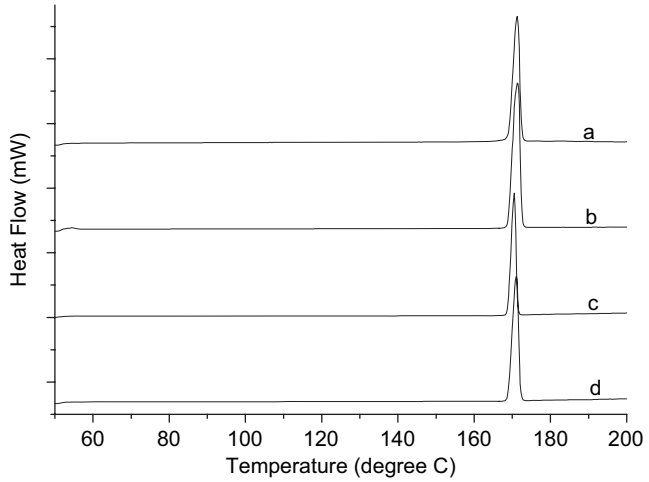

FIGURE 1. DSC scans of (a) recrystallized, (b) Lu'An, (c) Sigma-Aldrich, and (d) ground acetaminophen powders.

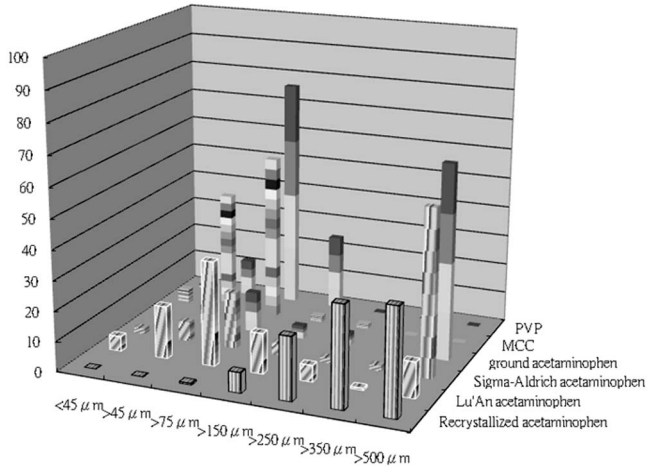

FIGURE 2. Sieve fractions of PVP, MCC, ground (small-size ranged) acetaminophen powders, Sigma-Aldrich acetaminophen powders, Lu'An acetaminophen powders and recrystallized (large-size ranged) acetaminophen powders.

The dissolution profiles of granules of ground, Sigma-Aldrich, Lu'An, and recrystallized acetaminophen powders with 75, 62, and 30 wt. % formulations were illustrated in Figure 5. All dissolution profiles followed the first-order kinetics whose release rate, *dc/dt*, at any point was proportional to the remaining concentration of acetaminophen, *c* (Jorgensen & Christensen, 1996; Lai & Tsiang, 2005)

$$\frac{dc}{dt} = -kc \tag{2}$$

where *k* was the first-order dissolution rate constant. *c* was determined as the difference between 0.5 g/900 mL and the amount of acetaminophen dissolved at any time point, *W*, in Figure 5 divided by 900 mL. Using the acetaminophen contents from t = 0 min to 50% drug release time, (Oyewo & Spring, 1994) t_{50}, a straight line resulted when (*ln* 0.5/900 – *ln W/900*) was plotted against time, *t*. The dissolution rate constant, *k*, was then obtained from the slope of the line. (Habib, Venkatram, & Delawar Hussein, 2001). The dissolution rate constants, *k*, derived from Figure 5 based on Eq. (2) for all kinds of formulated granules were summarized in Table 2.

Since on the one hand, the dissolution performance of granules was dependent on the granular structures which were determined by the granular growth mechanism, and on the other hand, the rheological property of the *formulated dry blended* powders could be revealed by the Carr's index, *C*, we speculated that there could be a link between the dissolution rate constant, *k*, and the Carr's index, *C*. Therefore, the Carr's indices, *C*'s, of the formulated dry blended powders were determined and listed in Table 2 as well. To bring out the link between *k* and *C*, *ln k* was plotted against *ln C* in Figure 6. The correlation coefficient, slope, and *y*-intercept for the 75, 62, and 30 wt. % formulations were {0.98, 2.9, –12.3}, {0.99, 2.8, –12.5}, and {0.98, 4.2, –18.0}, respectively. High correlation coefficient values of ≥ 0.98 indicated a high degree of linearity between *ln k* and *ln C*. Each straight line in Figure 6 could be represented by:

$$\ln k = \alpha \ln C + \ln A \tag{3}$$

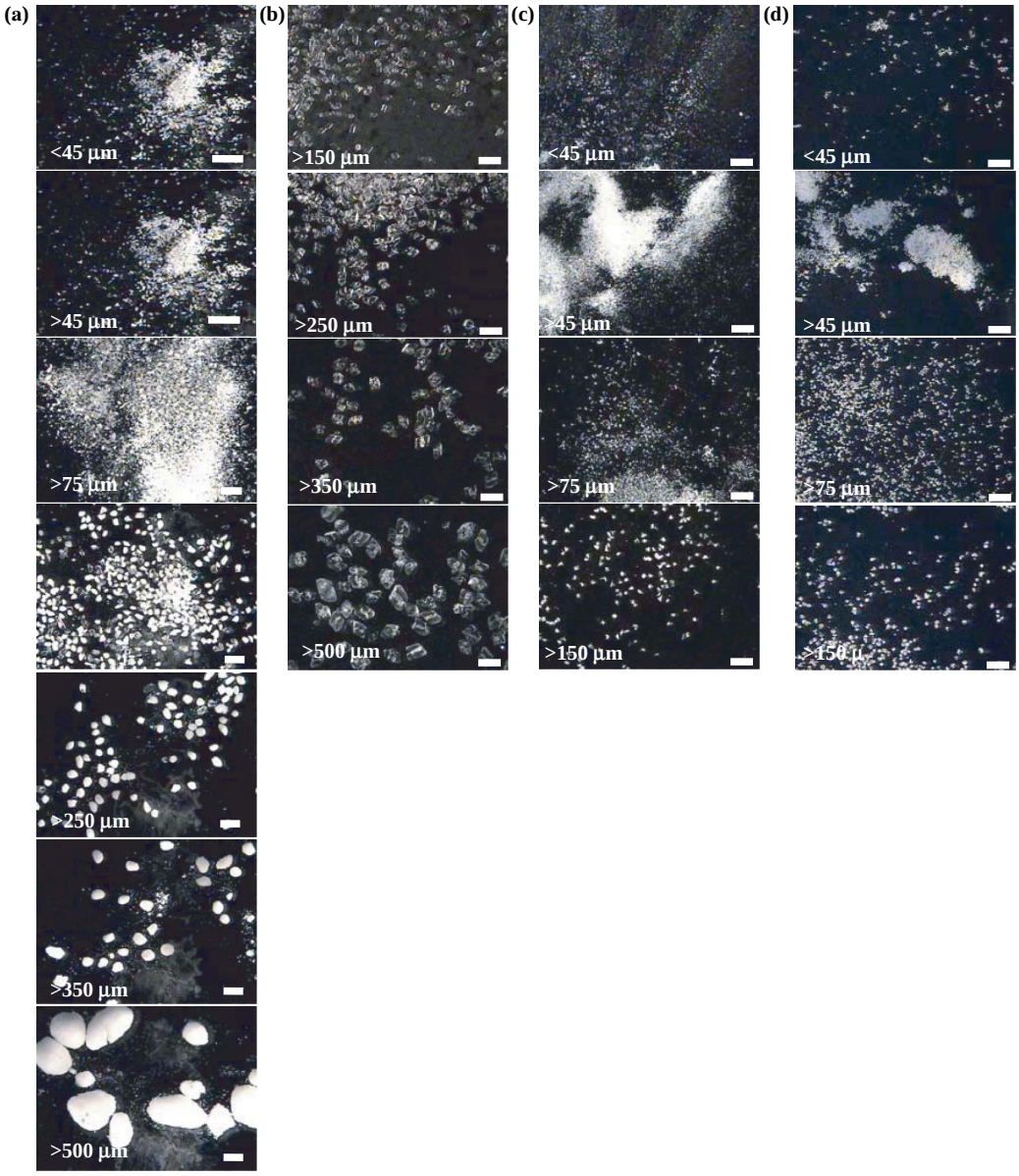

FIGURE 3. Optical micrographs of (a) ground, (b) recrystallized acetaminophen powders, (c) MCC, and (d) PVP (scale bar = 1000 μm).

where α was the slope and *ln A* was the *y*-intercept. Therefore, the three linear operating lines for 75, 62, and 30 wt. % formulations were $ln\ k = 2.9\ ln\ C - 12.3$, $ln\ k = 2.8\ ln\ C - 12.5$, and $ln\ k = 4.2\ ln\ C - 18.0$, respectively. Eq. (3) could further be reduced to a power law:

$$k = AC^a \tag{4}$$

The power laws for 75, 62, and 30 wt. % formulations had become $k = 4.7\times10^{-6}\ C^{2.9}$, $k = 3.9\times10^{-6}\ C^{2.8}$, and $k = 1.5\times10^{-8}\ C^{4.2}$, respectively.

A closer look at Table 2 and its depiction in Figure 6 had revealed several important features that deserved our notice. The linearity of each operating line pointed to the fact that the $k - C$ relationship could be easily established at a given formulation solely based on *two* batches of acetaminophen powders with extreme sizes such as the ground powders and the recrystallized powders. If the formulation remained unchanged, the dissolution rate constant, *k*, of the granules grown from other batches of acetaminophen powders with intermediate size ranges, such as Sigma-Aldrich and Lu'An acetaminophen powders, could be predicted empirically through the operating line by simply measuring the Carr's index, *C*, of only a few

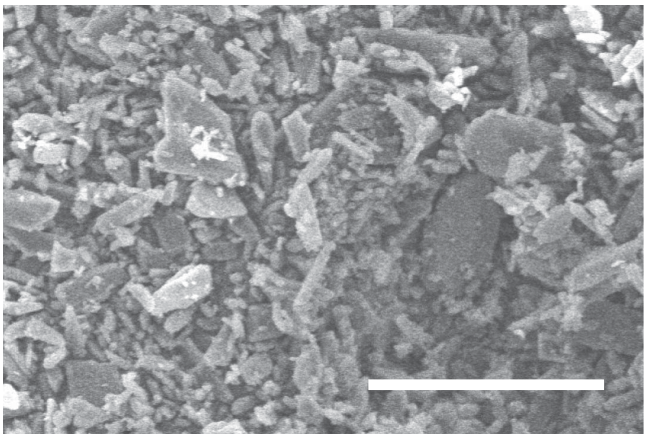

FIGURE 4. SEM image of the surface of a ground acetaminophen powder > 500 μm covered with primary particles of 10 μm to 70 μm (scale bar=100 μm).

grams of the formulated, dry blended acetaminophen powders without the need of performing wet granulation → drying → dissolution. The implementation of this novel approach no doubt would have drastically reduced the workload, materials, and time in the engineering of API crystals and the development of formulations.

As the formulation composition of acetaminophen decreased, the operating line shifted downward as a whole with a more negative y-intercept, *ln A*, regardless of the size-range of acetaminophen being used. This phenomenon was caused by the general decrease in the dissolution rate constant, *k*, resulted from a slower dissolution rate, *dc/dt*, in Eq. (2) originated largely from the lowering of the wt % of the constituents rather than from the local change in granular microstructures such as the porosity, specific surface area, and chemical homogeneity related to the particle size distribution. Since the rate, *dc/dt*, at which a solid substance dissolved in its own solution was proportional to the difference between the concentration of the saturated solution, C_s, and the concentration of that solution, C_b, as: (Habib et al., 2001; Leuenberger & Lanz, 2005)

$$\frac{dc}{dt} = \frac{DS}{hV}(C_s - C_b) \tag{5}$$

according to the film theory, where *D* was the diffusion coefficient of the solute; *S* was the specific surface area; *h* was the thickness of the diffusion layer; and *V* was the volume of the dissolution medium. Apparently, the decrease in the formulation composition of acetaminophen played a key role in the reduction of the specific surface area, *S*, of acetaminophen crystals. And yet, the relative increase of the formulation compositions of the excipients might have also decreased the diffusivity, *D*, of acetaminophen due to the rise of viscosity of the solution at the acetaminophen crystal-solution interface. The lowering of both *S* and *D* in Eq. (5) decreased the dissolution rate, *dc/dt*, and consequently the dissolution rate constant, *k*, in Eq. (2).

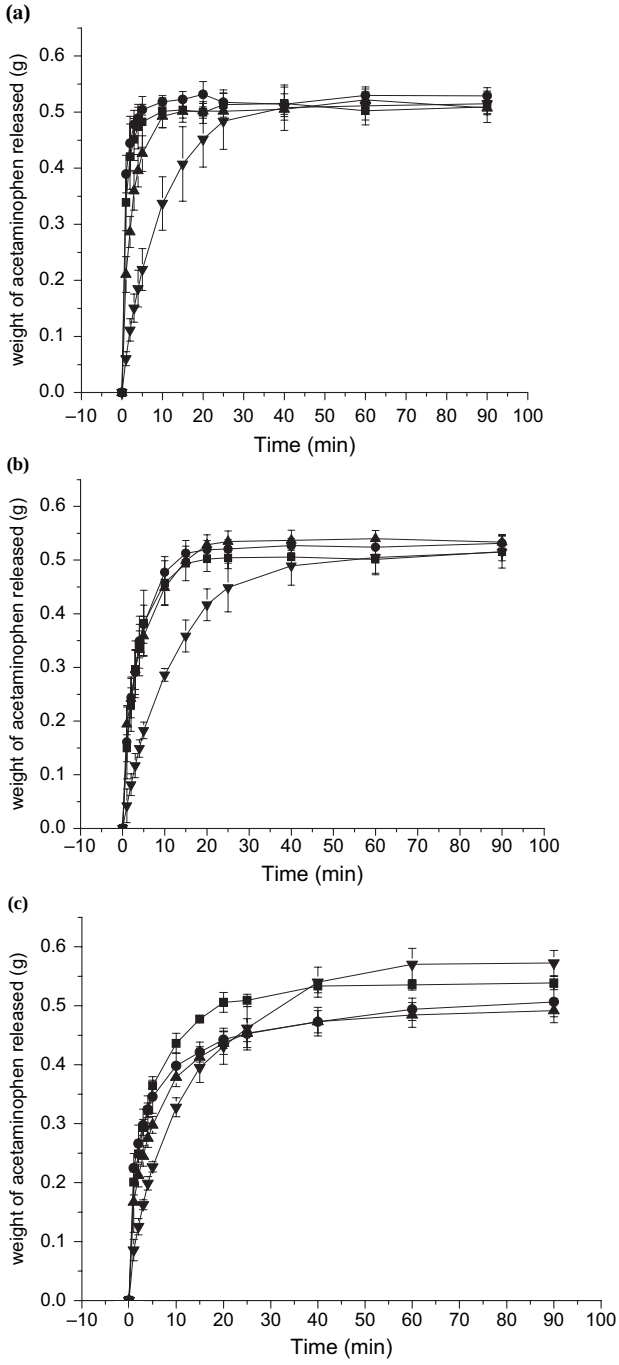

FIGURE 5. Dissolution curves of (a) 75 wt %, (b) 62 wt %, and (c) 30 wt % formulation with various kinds of acetaminophen powders: ■ = ground, ◆ = Sigma-Aldrich, ▲ = Lu'An, and ▼ = recrystallized.

Moreover, as the formulation composition of acetaminophen decreased, the values of the dissolution rate constants, *k*, of different batches of formulated dry blended powders would be less dependent on *S* and *D*, and the values of *k* should

TABLE 2
Carr's Index of Dry Blended Powders, 50% Drug Release Time, and Dissolution Rate of Formulated Granules for 75, 62, and 30 wt. % Formulations of Various Batches of Ground Acetaminophen, Sigma-Aldrich Acetaminophen, Lu'An Acetaminophen, and Recrystallized Acetaminophen

Acetaminophen Batches	Formulation	Carr's Index, ***C***, of Dry Blended Powders (%)	50% Drug Release Time, t_{50}, of Formulated Granules (min)	Dissolution Rate, ***k***, of Formulated Granules (min^{-1})
	75 wt %	66 ± 3.2	0.76	0.80
Ground	62 wt %	61 ± 2.8	1.91	0.36
	30 wt %	56 ± 2.7	2.46	0.27
Sigma-Aldrich	75 wt %	60 ± 3.2	0.72	0.95
	62 wt %	58 ± 1.9	1.89	0.37
	30 wt %	51 ± 1.5	2.94	0.22
Lu'An	75 wt %	56 ± 2.3	1.23	0.59
	62 wt %	60 ± 1.2	2.31	0.28
	30 wt %	49 ± 0.9	3.55	0.19
Recrystallized	75 wt %	31 ± 2.1	6.62	0.10
	62 wt %	34 ± 2.8	8.79	0.07
	30 wt %	42 ± 2.1	7.95	0.09

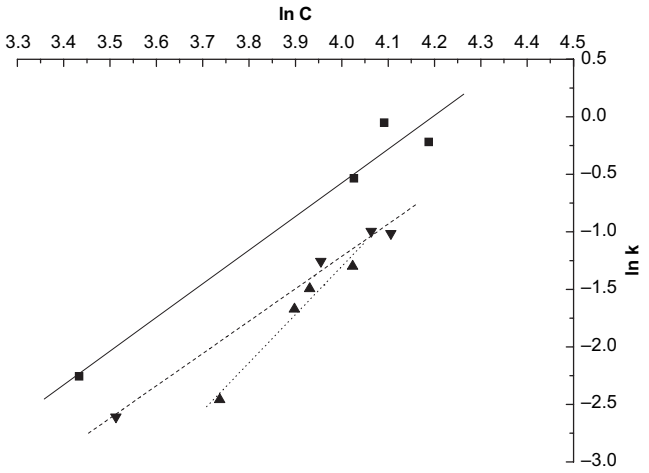

FIGURE 6. The *ln k* versus *ln C* plot of ground, Sigma-Aldrich, Lu'An and recrystallized acetaminophen powders of different formulations: ■ = 75 wt %, ▼ = 62 wt %, and ▲ = 30 wt %. The Carr's indices, *C*, of the formulated blends were used.

be getting closer and closer towards one another. This was verified by the shrinking distance between the two extreme points on the operating line. We believed that when the formulation composition of acetaminophen was small enough, the operating line would eventually be shrunk to a point with only one Carr's index, *C*, and one dissolution rate constant, *k*, regardless of which batches of acetaminophen powders were used.

The other influence of decreasing the formulation composition of acetaminophen was the increase in the slope, α, of the operating line ($\triangle lnk/\triangle lnC$) because the particle size distribution of the formulated dry blended powders would be dominated by the particle size distribution of the excipients and not by the one of acetaminophen. As long as the same kinds of excipient were being used, the difference of the Carr's indices ($\triangle lnC$) among batches of formulated dry blended powders would be diminished.

In general, good flow properties were indicated by the small *C* values after tapping. The empirical constants, *A* and α, in Eqs. (3) and (4) were mainly dependent on the mass transfer of acetaminophen powders and the rheological properties of the formulated dry blended powders respectively. Figure 6 showed that it was possible to meet a desired dissolution rate constant, *k*, with more than one formulation composition, wt. %, and Carr's index, *C*.

The *k* – *C* relationship between the dissolution rate constant of formulated granules and the flow properties of formulated dry blended powders was fundamentally sound and not merely an empirical coincidence. To elucidate this point further, we would consider the *evolution* of two extremes for the 62 wt. % formulation in Figure 6 derived from the small-size ranged, ground acetaminophen powders and the large-size ranged, recrystallized acetaminophen powders by dry sieve analysis.

The particle size distribution at $t = 0$ min was the initial particle size distribution of acetaminophen crystals. The initial particle size distributions of ground and recrystallized acetaminophen crystals were shown in Figure 2 and 7. After dry blending with the powdery excipients with their own particle size distributions (Figure 2) for 3 mins, the particle size distribution of the blend became different from the initial particle size

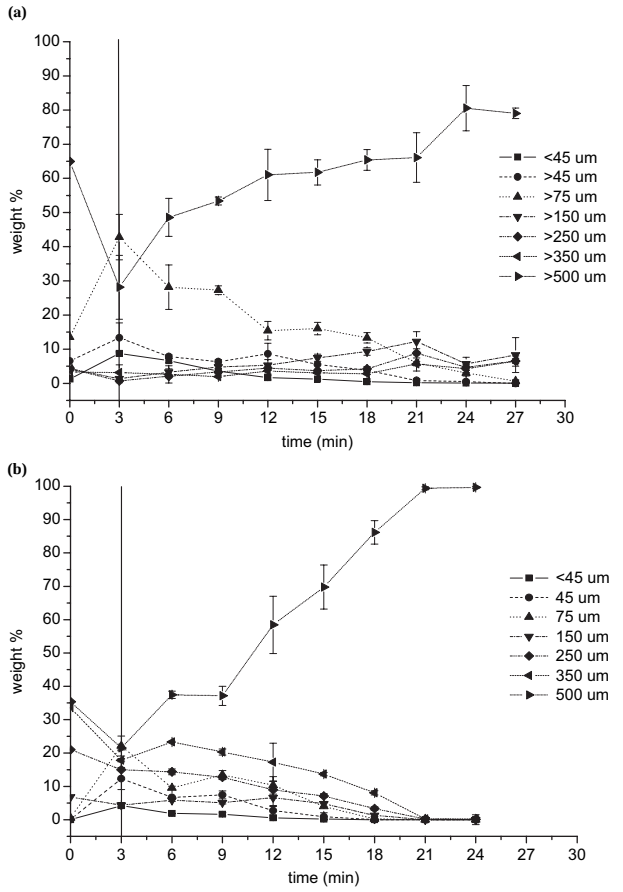

FIGURE 7. Weight fractions of powders and granules of different sizes grown from (a) Blend A, and (b) Blend B as a function of the mixing time.

distribution of acetaminophen crystals (Figure 7). There was a noticeable increase in the weight fraction of > 75-μm powders in both cases due to the major contributions of > 75-μm powders from the excipients.

The particle size distribution of the blend containing ground acetaminophen crystals (Blend A) and the particle size distribution of the blend composing of recrystallized acetaminophen crystals (Blend B) could definitely govern their final corresponding granular structures through different growth history. The sieve fractions of granules derived from Blend A and Blend B were plotted against the mixing time (Figure 7) during the whole process of wet granulation.

For Blend A in Figure 7(a), the weight fraction of > 500-μm granules increased gradually in the expense of > 45-μm and > 75-μm granules and other granule sizes of > 150, > 250, and > 350 μm increased only a little in the first 21 min. This suggested that granules smaller than 150 μm were coalesced through the water bridge and then agglomerated gradually to sizes larger than 150 μm, eventually to > 500 μm or more. The growth was dominated by agglomeration (Figure 8). (Iveson, Lister, Hapgood, & Ennis, 2001) At the end-point of about t = 27 min, there was a little drop in the weight fraction of

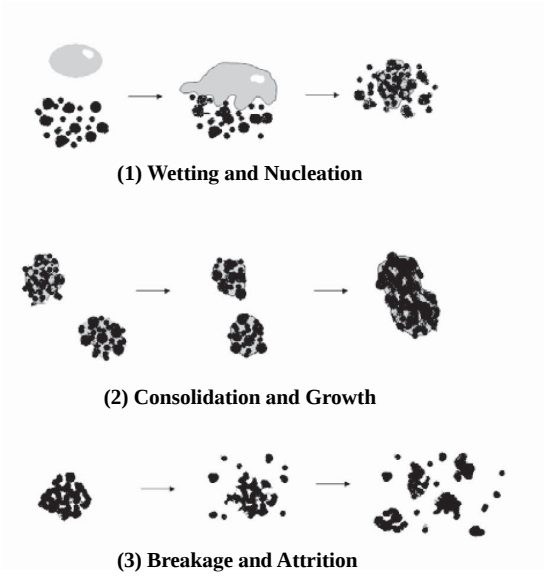

FIGURE 8. The granular growth mechanism by agglomeration.

> 500-μm granules and a small increase in granules of smaller sizes due to the breakage of the large-sized granules. (Albertini et al., 2004). This was the mass conservation phenomenon.

For Blend B in Figure 7(b), the weight fraction of > 500-μm granules increased rapidly in the expense of all sizes especially towards the end of t = 21 min. The large-size ranged acetaminophen powders were coated with the smaller MCC powders being bound with the viscous PVP. Granules were thought to be grown by consolidation and layer-by-layer mechanism (Figure 9). (Vonk, Guillaume, Ramaker, Vromans, & Kossen, 1997) When the nuclei of granulation were consolidated, the inter-pores were being made and filled up with the MCC particles. Eventually, an equilibrium state between breakage and coalescence was reached at the end-point of about t = 21 min.

The agglomeration mechanism for Blend A in the wet granulation process produced granules with more pores, (Johansen & Schaefer, 2001; Schaefer, 2001) larger surface area (Hecq, Deleers, Fanara, Vranckx, & Amighi, 2005) and more homogenously mixed (van den Dries & Vromans, 2003) than granules of Blend B grown from the consolidation and layer-by-layer mechanism when acetaminophen and excipients had unequal particle sizes. Mercury intrusion porosimetry and BET surface area analysis revealed that granules from Blend A gave a porosity of 54.86% and a surface area of 0.87 m^2/g, whereas granules from Blend B had a porosity of 32.80% and a surface area of 0.36 m^2/g.

Moreover, SEM images of the exterior and interior of granules revealed that particles of MCC and PVP were indistinguishable from acetaminophen powders in granules grown from Blend A (Figures 10(a) and (b). However, large acetaminophen crystals were sprinkled with clusters of small MCC and PVP particles in granules grown from Blend B (Figures 10(c) and (d)). This implied that the morphological inhomogeneity

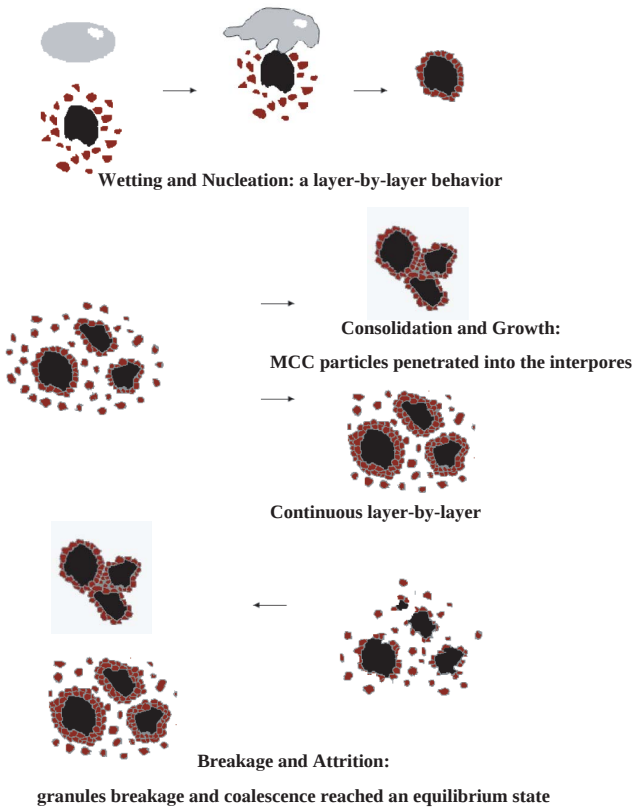

FIGURE 9. The granular growth mechanism by consolidation and layer-by-layer.

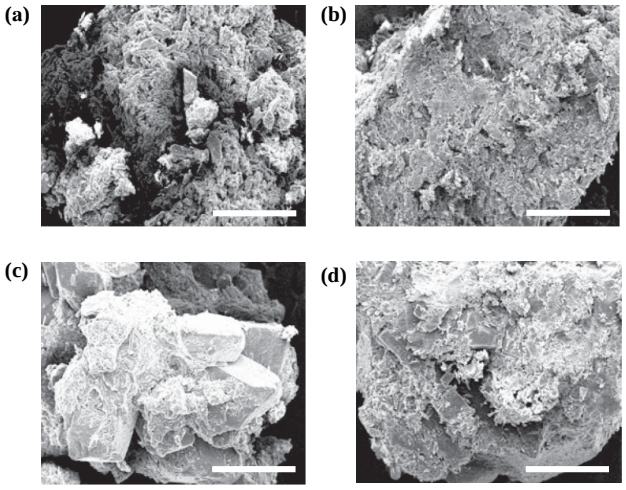

FIGURE 10. SEM images of (a) the exterior, and (b) the cross-section of a > 500-μm granule grown from Blend A, and (c) the exterior, and (d) the cross-section of a > 500-μm granule grown from Blend B (scale bar = 500 μm).

could also bring about the uneven distribution of chemical ingredients. FT-IR microscopic mapping (Chan & Kazarian, 2005; Colley, Kazarian, Weinberg, & Lever, 2004; Fleming, Chan, & Kazarian, 2004; Petibois & Deleris, 2006; Lee & Lin, 2004) (Figure 11) showed that the relative IR absorption intensity of the unique amide functional group of acetaminophen shown by the color scale from dark black to grayish white was very uneven inside the granules grown from Blend A. Since the strongest IR absorption intensity was represented by the grayish white color, the large grayish white areas in Figure 11(b) indicated that the local concentration of acetaminophen was actually very high in some regions of granules grown from Blend A.

The higher dissolution rate constant, k, of 0.36 min^{-1} of granules grown from Blend A than the one of 0.07 min^{-1} of granules derived from Blend B with 62 wt. % formulation (Table 2) clearly indicated that the dissolution performance with the same formulation was not only dependent on the specific surface area of the acetaminophen crystals but also directly proportional to several internal structural parameters of the granules such as porosity, specific surface area, and chemical homogeneity, which were determined by the growth mechanism of a particular blend.

Since the growth mechanism of a blend was governed by its flow property which was also a total manifestation of the overall particle size distribution, the use of the Carr's index, C, of the blend, and not the one of the API or the formulated granules, certainly would allow us to condense all the intertwined structural information of formulated granules originated from the particle size distribution into a single indicator, C. The role of the Carr's index, C, was very much like the one of the dissolution rate constant, k, which was also a reflection of the complicated structural information of formulated granules. Therefore, it was natural to expect an empirical relationship between the dissolution rate constant, k, of formulated granules and the Carr's index, C, of a formulated blend (Figure 6). But when the dissolution rate constant, k, of formulated granules was plotted against the Carr's index of either the API (Figure 12(a)) or the formulated granules (Figure 12(b)), no specific relationship was observed. This was because the Carr's index of the API and the formulated granules were unable to take the contributions of the formulation and the internal structures of granules into account.

CONCLUSIONS

The encouraging result of a linear relationship of the Carr's index, C, of a formulated blend and the dissolution rate constant, k, of formulated granules implied a revolutionary drug product development logics for the five-step process flow of: crystallization → dry blending → wet granulation → drying → dissolution. Only two batches of API with about 100 to 200 g having the extreme particle size range with a given formulation were required for determining the upper and the lower bound of the dissolution rate constant, k, by going through the entire process flow for only twice. Only 1 to 2 g of the dry blended formulation from the two batches of API with the extreme particle size range were needed to determined the Carr's indices,

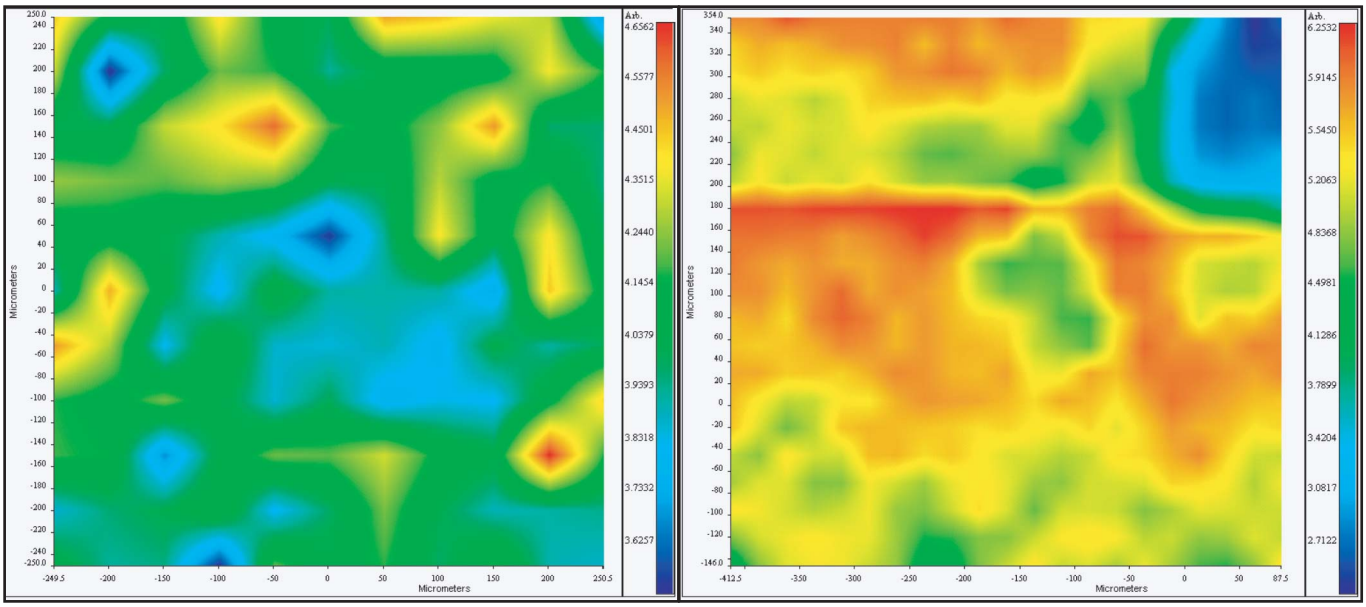

FIGURE 11. FT-IR microscopic mapping images of the cross-sectional area of granules grown from (a) Blend A, and (b) Blend B powders. The imaging area was 1000×1000 μm. The strongest IR absorption intensity of the amide functional group of acetaminophen was represented by grayish white and the weakest by dark black.

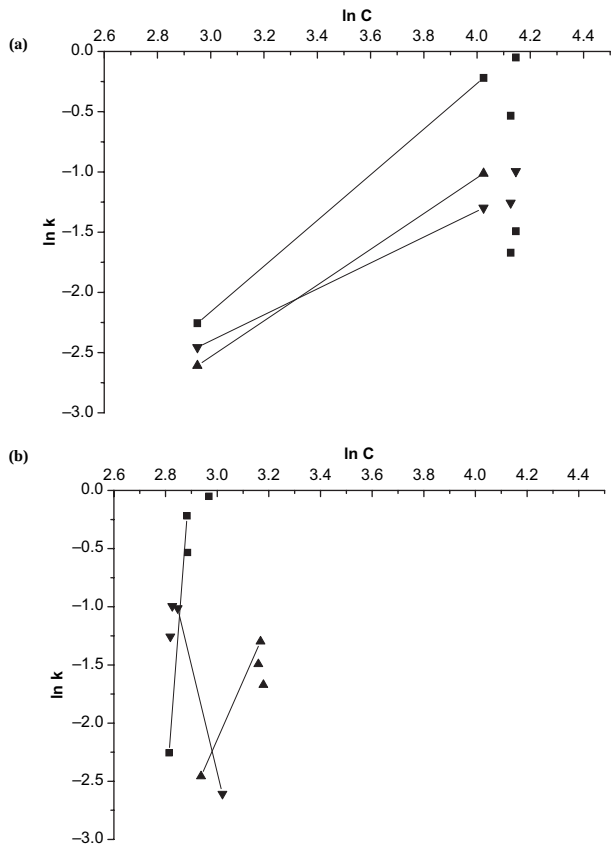

FIGURE 12. The *ln k* versus *ln C* plot of ground, Sigma-Aldrich, Lu'An and recrystallized acetaminophen powders of different formulations: ■ = 75 wt. %, ▼ = 62 wt. %, and ▲ = 30 wt. %. The Carr's indices of (a) acetaminophen bulk powders were used, and (b) formulated granules were used.

C. With the two pairs of upper and lower (*ln C*, *ln k*) values determined, two points could then be located in the *ln C* versus *ln k* domain. A straight line was drawn to connect the two points to find out the empirical relationship of $ln\ k = \alpha\ ln\ C + ln\ A$ for a given formulation.

With this linear relationship at hand, the effect of the particle size distribution of an API falling in between the two extreme particle size ranges on the dissolution rate constant, *k*, of formulated granules could be simply predicted by the Carr's index of only a few grams of formulated dry blended powders in a 10 mL graduated cylinder of less than 5 min. The five-step process flow was shortened to two-step process of: crystallization → dry blending without the need of going through a train of the labor intensive, material- and time-consuming processes of wet granulation, drying, and dissolution every time. Another implication of this novel approach was to provide a rapid way to predict the incorporation effects of the API powders collected at the heels or on the walls of any vessels on the dissolution performance of the rest of the batch. To take even one step further, we speculated that the Carr's index could be related to some other overall performances of powders such as electrical properties in battery and mechanical properties in tablets.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Science Council of Taiwan, R. O. C. (NSC 93–2119-M-008–030 and NSC 94–2119-M-008–001, and NSC 95–2113-M-008–012-MY2). Suggestions from Ms. Jui-Mei Huang for DSC and BET and Ms. Ching-Tien Lin for SEM in the Precision Instrument Center and High Valued Instrument Center at National Central University are gratefully acknowledged. Special assistance in

FT-IR microscopic imaging from Dr. Kelvin Chang at Perkin Elmer (Taiwan) Corporation (Taipei, Taiwan) and Ms. Mei-Ling Cheng working for the Precision Instrument Center at Yuan Ze University are appreciated. Special thanks were also given to Kuan Hui Lee for the assistance in MIP in the Particular Technology Laboratory at the National Taiwan University.

REFERENCES

Albertini, B., Cavallari, C., Passerini, N., Voinovich, D., González-Rodríguez, M. L., Magarotto, L., & Rodriguez, L. (2004). Characterization and taste-masking evaluation of acetaminophen granules: comparison between different preparation methods in a high-shear mixer. *Eur. J. Pharm. Sci., 21*, 295–303.

Byrn, S., Morris, K., & Comella, S. (2005). Reducing time to market with a science-based product management strategy. *Pharmaceutical Technology*, outsourcing resources for the pharmaceutical industry, 46–56.

Cao, Q. R., Choi, Y. W., Cui, J. H., & Lee, B. J. (2005). Formulation, release characteristics, and bioavailability of novel monolithic hydroxypropylmethylcellulose matrix tablets containing acetaminophen. *J. Contr. Release, 108*, 351–361.

Chan, K. L. A., & Kazarian, S. G. (2005). Fourier transform infrared imaging for high-throughput analysis of pharmaceutical formulations. *J. Comb. Chem., 7*, 185–189.

Colley, C. S., Kazarian, S. G., Weinberg, P. D., & Lever, M. J. (2004). Spectroscopic imaging of arteries and atherosclerotic plaques. *Biopolymers, 74*, 328–335.

Ebube, N. K., Hikal, A. H., Wyandt, C. M., Beer, D. C., Miller, L. G., & Jones, A. B. (1997). Effect of drug, formulation and process variables on granulation and compaction characteristics of heterogenous matrices. Part 1: HPMC and HPC systems. *Int. J. Pharm., 156*, 49–57.

Espeau, P., Céolin, R., Tamarit, J. L., Perrin, M. A., Gauchi, J. P., & Leveiller, F. (2005). Polymorphism of paracetamol: Relative stabilities of the monoclinic and orthorhombic phases inferred from topological pressure-temperature and temperature-volume phase diagrams. *J. Pharm. Sci., 94*, 524–539.

Fleming, O. S., Chan, K. L. A., & Kazarian, S. G. (2004). FT-IR imaging and Raman microscopic study of poly(ethylene terephthalate) film processed with supercritical CO_2, *Vib. Spectrosc., 35*, 3–7.

Garcia, A. M., & Ghaly, E. S. (1996). Preliminary spherical agglomerates of water soluble drug using natural polymer and cross-linking technique. *J. Contr. Release, 40*, 179–186.

Goldszal, A., & Bousquet, J. (2001). Wet agglomeration of powders: from physics toward process optimization. *Powder Tech., 117*, 221–231.

Habib, M. J., Venkataram, S., & Delwar Hussain, M. (2001). Fundamentals of solid dispersions. In M. J. Habib (Ed.) *Pharmaceutical solid dispersion technology* (pp. 7–35). Lancaster: Technomic.

Hecq, J., Deleers, M., Fanara, D., Vranckx, H., & Amighi, K. (2005). Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. *Int. J. Pharm., 299*, 167–177.

Iveson, S. M., Lister, J. D., Hapgood, K., & Ennis, B. J. (2001). Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review. *Powder Tech., 117*, 3–39.

Johansen, A., & Schæfer, T. (2001). Effects of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. *Eur. J. Pharm. Sci., 12*, 297–309.

Jørgensen, K., & Christensen, F. N. (1996). Shape modeling of dissolution profiles by non-integer kinetic orders. *Int. J. Pharm., 143*, 223–232.

Keleb, E. I., Vermeire, A., Vervaet C., & Remon, J. P. (2004). Extrusion granulation and high shear granulation of different grades of lactose and high dosed drugs: A comparative study. *Drug Dev. Ind. Pharm., 30*, 679–691.

Kim, S., Lotz, B., Lindrud, M., Girard, K., Moore, T., Nagarajan, K., Alvarez, M., Lee, T., Nikfar, F., Davidovich, M., Srivastava, S., & Kiang, S. (2005). Control of the particle properties of a drug substance by crystallization engineering and the effect on drug product formulation. *Org. Proc. Res. Dev., 9*, 894–901.

Lai, M. K., & Tsiang, R. C. C. (2005). Microencapsulation of acetaminophen into poly(L-lactide) by three different emulsion solvent-evaporation methods. *J. Microencap., 22*, 261–274.

Lee, T. H., & Lin, S. Y. (2004). Microspectroscopic FT-IR mapping system as a tool to assess blend homogeneity of drug excipient mixtures. *Eur. J. Pharm. Sci., 23*, 117–122.

Lee, T., Hung, S. T., & Kuo, C. S. (2006). Polymorph farming of acetaminophen and sulfathiazole on a chip. *Pharm. Res., 23*, 2542–2555.

Lee, T., Kuo, C. S., & Chen, Y. H. (2006). Solubility, polymorphism, crystallinity, and crystal habit of acetaminophen and ibuprofen by initial solvent screening. *Pharm. Tech., 30*, 72–92.

Leuenberger, H. & Lanz, M. (2005). Pharmaceutical powder technology—from art to science; the challenge of the FDA's process analytical technology initiative. *Adv. Powder Tech., 16*, 3–25.

Oyewo, M. N. F., & Spring, M. S. (1994). Studies on paracetamol crystals produced by growth in aqueous solution. *Int. J. Pharm., 112*, 17–28.

Pepin, X., Blanchon, S., & Couarraze, G. (2001). Power consumption profiles in high-shear wet granulation. I: Liquid distribution in relation to powder and binder properties. *J. Pharm. Sci., 90*, 322–331.

Petibois, C., & Déléris, G. (2006). Chemical mapping of tumor progression by FT-IR imaging: Towards molecular histopathology. *Trends Biotechnol., 24*, 455–462.

Railkar, A. M., & Schwartz, J. B. (2001) Use of a moist granulation technique (MGT) to develop controlled-release dosage forms of acetaminophen. *Drug Dev. Ind. Pharm., 27*, 337–343.

Rough, S. L., Wilson, D. I., & York, D. W. (2005). Effect of solids formulation on the manufacture of high shear mixer agglomerates. *Adv. Powder Technol., 16*, 145–169.

Schæfer, T. (2001). Growth mechanisms in melt agglomeration in high shear mixers. *Powder Tech., 117*, 68–82.

Sorasuchart, W., Wardrop, J., & Ayres, J. W. (1999). Drug release from spray layered and coated drug-containing beads: effects of pH and comparison of different dissolution methods. *Drug Dev. Ind. Pharm., 25*, 1093–1098.

Timmins, P., Delargy, A. M., Minchom, C. M., & Howard, J. R. (1992). Influence of some process variables on product properties for a hydrophilic matrix controlled release tablet. *Eur. J. Pharm. Biopharm., 38*, 113–118.

van den Dries, K., de Vegt, O. M., Girard, V., & Vromans, H. (2003). Granule breakage phenomena in a high shear mixer; influence of process and formulation variables, and consequences on granule homogeneity. *Powder Tech., 133*, 228–236.

van den Dries, K., & Vromans, H. (2002). Relationship between inhomogeneity phenomena and granule growth mechanisms in a high shear mixer. *Int. J. Pharm., 247*, 167–177.

van den Dries, K., & Vromans, H. (2003). Experimental and modelistic approach to explain granulate inhomogeneity through preferential growth. *Eur. J. Pharm. Sci., 20*, 409–417.

Vonk, P., Guillaume, C. P. F., Ramaker, J. S., Vromans, H., & Kossen, N. W. F. (1997). Growth mechanisms of high-shear pelletization. *Int. J. Pharm., 157*, 93–102.

Wade, A., & Weller, P. J. (1994). *Handbook of pharmaceutical excipients.* 2nd ed. Washington: American Pharmaceutical Association, pp. 392–399.