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# The Prediction of the Dissolution Rate Constant by Mixing Rules: The Study of Acetaminophen Batches

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**The purpose of this article is to promote two simple and scalable methods to accelerate the formulation development of formulated granules using acetaminophen as a model system. In method I, formulated granules made from the batch of small particle–sized acetaminophen (1) by ball milling the batch of large particle–sized acetaminophen (2), and the mixture of the two batches at equal weights (mix) gave the dissolution rate constants ($k$) of $k_1$ = 0.43 0.15 minutes $^{1}$, $k_2$ = 0.18 0.01 minutes $^{1}$, and $k_{mix}$ = 0.30 0.03 minutes $^{1}$ for 75 wt percent formulation; $k_1$ = 0.75 0.01 minutes $^{1}$, $k_2$ = 0.18 0.01 minutes $^{1}$, and $k_{mix}$ = 0.34 0.03 minutes $^{1}$ for 62 wt percent formulation; and $k_1$ = 0.28 0.01 minutes $^{1}$, $k_2$ = 0.16 0.01 minutes $^{1}$, and $k_{mix}$ = 0.22 0.02 minutes $^{1}$ for 30 wt percent formulation. In method II, the mixture of the formulated granules produced by mixing the formulated granules from the two batches at equal weights gave dissolution rate constants of $k_{mix}$ = 0.30 0.03 minutes $^{1}$, 0.30 0.02 minutes $^{1}$, and 0.22 0.01 minutes $^{1}$ for 75 wt percent, 62 wt percent, and 30 wt percent formulations, respectively. After fitting the three data points of $k_1$, $k_2$, and $k_{mix}$ to the 10 mixing rules in materials science—series mixing rule, Hashin and Shtrikman upper bound, logarithmic mixing, Looyenga mixing rule, effective media approximation (EMA), three-point lower bound, Torquato approximation, three-point upper bound, Maxwell mixing rule, and parallel mixing rule—we found that the selection of the best suited mixing rules based on $k_1$, $k_2$, and $k_{mix}$ was solely dependent on the formulations under a given operating condition and regardless of whether the system was a powder mixture or a granular mixture. The values of $k_1$, $k_2$, and $k_{mix}$ in both the 75 wt percent and 30 wt percent formulations were enveloped by the parallel mixing rule and Maxwell mixing rule, whereas the values of $k_1$, $k_2$, and $k_{mix}$ for the 62 wt percent formulation were encompassed by the logarithmic mixing rule, Hashin and Shtrikman upper bound, and the series mixing rule. Apparently, the best suited mixing rules could be used to predict the right proportions of either the powder mixture (Method I) or the granular mixture (Method II) for obtaining any other desired dissolution rate constant, $k_{mix}$, whose value fell in between the values of $k_1$ and $k_2$.**

**Keywords** mixing rules; dissolution rate constant; acetaminophen

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## INTRODUCTION

The conventional formulation development (Figure 1) begins when a large amount of active pharmaceutical ingredient (API) with a defined solid form is available. A typical development cycle is carried out repeatedly until the bulk specification, such as the particle size range, the formulation about the choice of the excipients and the drug load, the process critical control points like the end point in the wet granulation and the specified dissolution rate constant $k$, of the formulated granules are all set. Therefore, the conventional method consumes many API batches of various particle size distributions.

Recently, however, we have successfully demonstrated that the large number of trials in the conventional method (Figure 1) can actually be reduced into two main trials by the cross-performance method (Figure 2; Lee & Hsu, 2007). As a

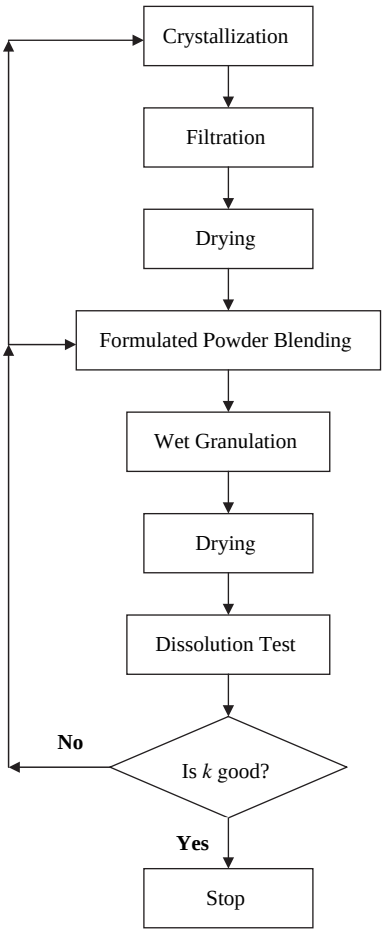


FIGURE 1. Conventional process flow diagram of formulation development.

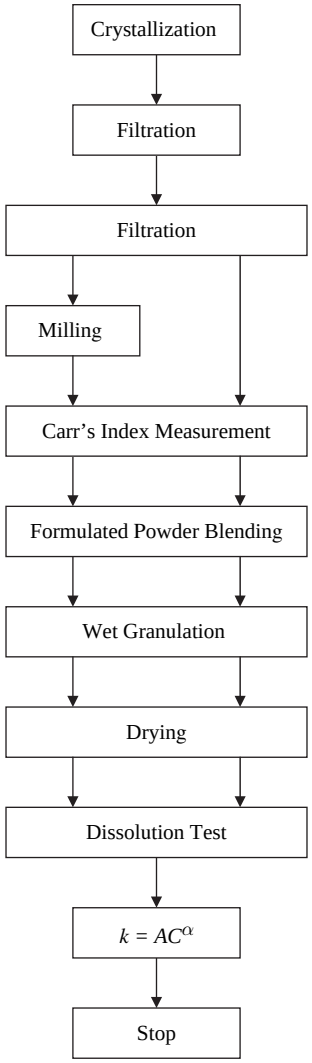


FIGURE 2. A cross-performance method relating Carr's index with dissolution rate in formulation development.

result, only two key API batches having extreme particle size range, one small and one large, giving distinctive Carr's indices, *C*, after blending with a given formulation, were required to determine the corresponding upper and lower bound of the dissolution rate constant, *k*. The two pairs of values of *C* and *k* would then give a linear relationship of $ln\ k = \alpha\ ln\ C + ln\ A$ (or, exponentially, by a power law of $k = AC^{\alpha}$) where *A* was the exponential factor and $\alpha$ was the power index. With this specific linear relationship at hand, the dissolution rate constants of granules, *k*, prepared from other new batches of API with various particle size distribution for the same formulation could be predicted (a) by the Carr's index, *C*, measured from only a few grams of the dry blended formulated API, and (b) without the need of doing any wet granulation, drying, and dissolution test.

Obviously, the contrast between the conventional method (Figure 1) and the cross-performance method (Figure 2) is remarkable. The conventional method is onerous, labor intensive, and consumes a lot of material, whereas the cross-performance method is efficient, economical, and predictive. And yet, the formulation development would have been accelerated even more if the desired dissolution rate constant, *k*, of the formulated granules could be obtained from crystallizing only one API batch with a fixed particle size range (Bryn, Morris, & Comella, 2005).

Therefore, the aim of this paper is to promote two novel and simple scalable methods towards this goal:

In method I (Figure 3), the formulation development began with a single API batch having large-sized particles. One half of this batch was ball milled into bulk powders of small-sized particles. If the weight fraction of small particles, $\phi_1$, was defined as

$$\phi_1 = \frac{w_1}{w_1 + w_2} \tag{1}$$

where $w_1$ and $w_2$ were the weight of the small particles and the weight of the large particles respectively, the small particles

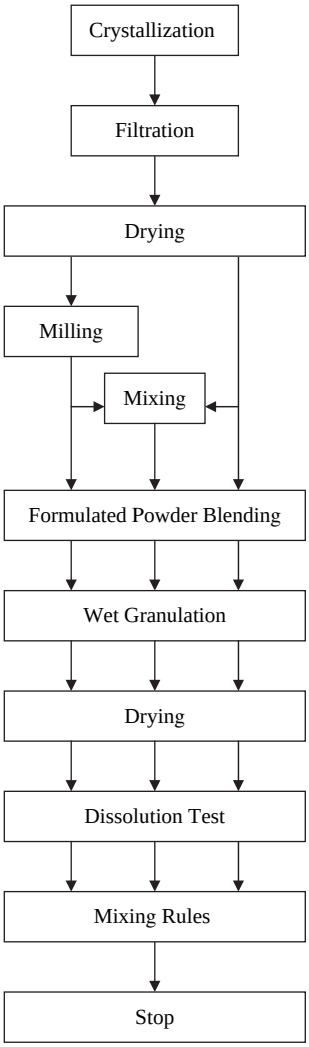


FIGURE 3. Method I of achieving the desired dissolution rate by mixing the API of a large-sized distribution and the API of a small-sized distribution.

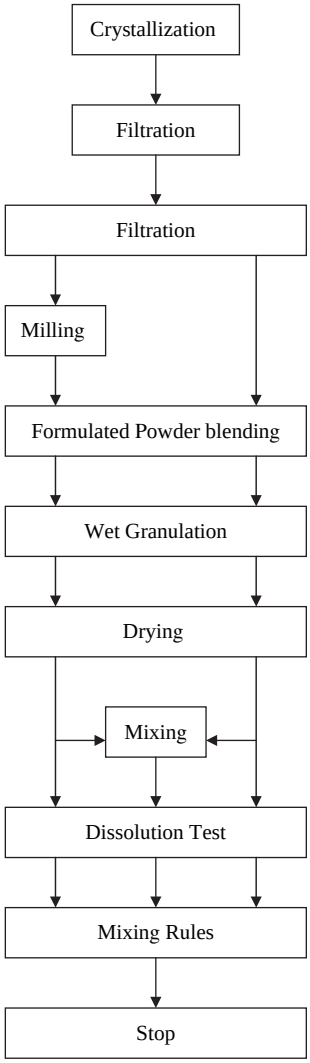


FIGURE 4. Method II of achieving the desired dissolution rate by mixing granules made from the API of a large-sized distribution and granules made from the API of a small-sized distribution.

and the large particles were then blended at equal weights to give a mixed batch of $\phi_1 = 0.5$. The three dissolution rate constants of $k_1$, $k_2$, and $k_{mix}$, of the granules made from the small particles, the large particles, and the mixed powder batch of $\phi_1 = 0.5$, respectively, were then measured experimentally and fitted to the mixing rules. Once the best suited mixing rule whose locus was in the proximity of $k_{mix}$ was identified, granules of some other desired dissolution rate constants, *k*s, could be easily made in the wet granulation step by simply blending the existing small particle–sized batch and large particle–sized batch at the deduced $\phi_1$ according to the mixing rules.

In method II (Figure 4), the formulation development also began with a single API batch having large-sized particles, and one-half of this batch was ball milled into bulk powders of small-sized particles. If the weight fraction of granules made from the small-sized particles (small-sized particle granules) was assumed to be $\phi_1$, Equation 1 can be reused. Except, this time $w_1$ and $w_2$ would have to be the weight of the granules made from the small-sized particles and the weight of the granules made from the large-sized particles (large-sized particle granules), respectively. The mixed granules of $\phi_1 = 0.5$ could then be prepared by blending equal weights of the small-sized particle granules and the large-sized particle granules. The three dissolution rate constants, $k_1$, $k_2$, and $k_{mix}$, of the small-sized particle granules, the large-sized particle granules and the mixed granules of $\phi_1 = 0.5$ respectively were then measured experimentally and fitted to the mixing rules. Once the best suited mixing rule whose locus was in the proximity of $k_{mix}$, was established, granules of some other dissolution rate constants, *k*s, could be easily made by simply blending the small-sized particle granules with the large-sized particle granules at the deduced $\phi_1$ according to the mixing rules.

The 10 mixing rules selected in material science are commonly used in dielectric constant, conductivity, elastic modulus, fluid permeability, and diffusion-controlled trapping constant for random heterogeneous composites. However, to the best of our knowledge, this is the very first time for these mixing rules to be applied to the dissolution rate constant, *k*. The 10 mixing rules are summarized in Table 1 and arranged from the lowest to the highest bound. They were: series mixing rule (Randall, Miyazaki, More, Bhalla, & Newnham, 1992), Hashin and Shtrikman upper bound (Hashin, & Shtrikman, 1963; Torquato, 1991), logarithmic mixing (Randall et al., 1992; Torquato, 1991), Looyenga mixing rule (Looyenga, 1965), effective media approximation (EMA; Simpson, 1974), three-point lower bound (Torquato, 1991), Torquato approximation (Torquato, 1991), three-point upper bound (Torquato, 1991), Maxwell mixing rule (Maxwell, 1904), and the parallel mixing rule (Randall et al., 1992).

Assuming dissolution is directly proportional to the permeability of water in the microstructures of the mixture, which is directional along a concentration gradient, the geometry of the mixture enters into the calculation. If the API is one phase and all the other excipients are considered the other phase, two extreme situations are shown in Figures 5A and 5B. When the mass transfer direction of water is parallel to the structure, the purely additive parallel mixing rule applies (Table 1). But when the structure is in series, water must be transferred perpendicularly to the layers (Table 1). This leads to a reciprocal series mixing rule which is concaved down. But the more commonly encountered microstructures involve a dispersion of two continuous phases with random orientations possessing some parallel regions and some series domains (Figure 5C). The dissolution property of such a mixture can be depicted by some other mixing rules in Table 1 that are also curved and enveloped by the highest bound of the parallel mixing rule and the lowest bound of series mixing rule at the same time.

Acetaminophen, an analgesic API, was chosen for this study because of (a) its low cost and high commercial values, (b) our experiences in engineering the acetaminophen crystals (Lee, Hung, & Kuo, 2006; Lee, Kuo, & Chen, 2006), and (c) the many studies about acetaminophen granulation mechanism

TABLE 1
Mixing Rules

| Mixing Rules Relationships | Structure-Dissolution Performance |
|---|---|
| Series mixing rule | $1/k_{mix} = \phi_1/k_1 + \phi_2/k_2$ |
| Hashin and Shtrikman upper bound | $k_{mix} = k_2[(1+2\phi_1\beta_{12})/(1-\phi_1\beta_{12})]$ |
| Logarithmic mixing rule | $\text{In}\, k_{mix} = \phi_1 \text{In} k_1 + \phi_2 \text{In} k_2$ |
| Looyenga mixing rule | $k_{mix} = [(k_2^{1/3} - k_1^{1/3})\phi_2 + k_1^{1/3}]^3$ |
| Effective media approximation (EMA) | $k_{mix} = [\beta + (\beta^2 + 8k_1k_2)^{1/2}]/4$ |
| Three-point lower bound | $k_{mix}/k_1 = \{1+[(d-1)(1+\phi_2)-\varsigma_2]\beta_{21}+(d-1)\{[(d-1)\phi_2-\varsigma_2]\beta_{21}^2\}/$ $\{1-[\phi_2+\varsigma_2)-(d-1)\beta_{21}+\{[\phi_2-(d-1)\phi_1]\varsigma_2-(d-1)\phi_2\}\beta_{21}^2\}$ |
| Torquato approximation | $k_{mix}/k_1 = (1+2\phi_2\beta_{21}-2\phi_1\varsigma_2\beta_{21}^2)/(1-\phi_2\beta_{21}-2\phi_1\varsigma_2\beta_{21}^2)$ |
| Three-point upper bound | $k_{mix}/k_1 = \{1+[(d-1)(\phi_1+\varsigma_1)-1]\beta_{12}+(d-1)\{[(d-1)\phi_1-\phi_2]\varsigma_1-\phi_1\}\beta_{12}^2\}/$ $\{1-[1+\phi_1-(d-1)\varsigma_1]\beta_{12}+[\phi_1-(d-1)\varsigma_1]\beta_{12}^2\}$ |
| Maxwell mixing rule | $k_{mix} = k_1 + [3\varepsilon_1\phi_2(k_2-k_1)]/[\phi_1(k_2-k_1)+3k_1]$ |
| Parallel mixing rule | $k_{mix} = \phi_1k_1 + \phi_2k_2$ |

Let 1 = acetaminophen of small particle–sized distribution, 2 = acetaminophen of large particle–sized distribution, mix = effective value of the mixture, $k$ = dissolution constant, $\phi$ = volume fraction (= weight fraction if 1 and 2 are the same substances), $\beta = k_2(3\phi_2-1) + k_1(2-3\phi_2)$, $\beta_{12} = (k_1-k_2)/(k_1+2k_2)$, $\beta_{21} = (k_2-k_1)/(k_2+2k_1)$, d = 3 (three-dimensional), and for isotropically dispersed identical hard spheres $\zeta_2$ = 0, 0.02, 0.041, 0.060, 0.077, 0.094, 0.110, and 0.134 when $\phi_2$ = 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.55, and 0.6, respectively. $\zeta_1 = 1-\zeta_2$

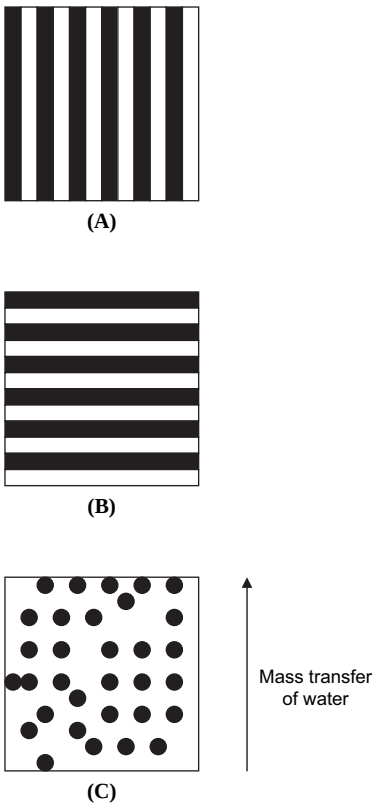


FIGURE 5. Dissolution versus phase distribution (idealized) of acetaminophen (black region) and the excipients (white domain). (A) Parallel dissolution. (B) Series dissolution. (C) Dissolution of a dispersed phase when the two phases have markedly dissimilar dissolution performances.

(Van den Dries & Vromans, 2003) and dissolution rate (Cao, Choi, Cui, & Lee, 2005; Keleb, Vermeire, Vervaet, & Remon, 2004; Railkar & Schwartz, 2001).

## MATERIALS AND METHODS

### Chemicals

The large-sized acetaminophen powders ($CH_3CONHC_6H_4OH$, M.W. = 151.17 g/mol, 100%, Lot: 0540385) were purchased from Lu'An, Anqiu, China (Lu'An acetaminophen powders). The small particle–sized acetaminophen powders were produced from ball milling the large particle–sized Lu'An acetaminophen powders as described in the experimental section (ball milled acetaminophen powders). 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 (PVP, Kollidon® 30; $[C_6H_9NO]_{450}$, M.W. = 50000 g/mol, m.p. = 150°C, Lot G42116 PT0; Wade & Weller, 1994) received from O-BASF, New Jersey, USA was used as a binder and a disintegrant. 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, Catalog number: QGARDOOR1, Lot: F4JN45093) from Millipore, Massachusetts, USA, was used as the solvent in wet granulation and dissolution.

### Analytical Instrumentations

*Differential Scanning Calorimetry (DSC)*

DSC was used to verify that the polymorphism and the crystallinity of acetaminophen powders remained unchanged before and after ball milling. 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, USA) with a temperature scanning rate of 10°C/minute 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, CT, U.S.A.).

*Dry Sieve Analysis*

Particle size distributions of ball milled acetaminophen and Lu'An acetaminophen were determined through a stack of metal sieve plates from the largest aperture to the finest in the order of 500 μm, 350 μm (Der Shuenn, Taiwan), 250 μm, 150 μm, 75 μm, and 45 μm (Cole-Palmer, Illinois, USA). 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 that passed through the 500-μm sieve plate 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 about the effect of loading, shaker speed, and time on the data obtained for the particle size distribution. The weight of the powders retained on the surface of each sieve plate was divided by the total sample weight of the powders to obtain the corresponding weight percent oversize for each sieve fraction.

*Optical Microscopy*

The optical microscope (Olympus SZII, Tokyo, Japan) with a charge couple device camera (SONY, model: SSC-DC50A, Tokyo, Japan) was used to characterize the crystal habits of the ball-milled acetaminophen powders and the Lu'An acetaminophen powders. All optical micrographs were taken by dispersing the bulk powders in a mineral oil at 25°C.

*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, USA). About 1 g of sample was predried 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 μmHg and kept at 115°C. When the vacuum value was reached, the sample was aerated back to atmosphere and the analysis begun. Nitrogen gas was used as the analysis adsorptive gas and the bath temperature was 77.35 K. The drying temperature of 115°C did not introduce any artifacts in the porosity measurements because of the high melting point of PVP at 150°C and the unchanged dissolution performance of the 115°C treated formulated granules.

*Scanning Electron Microscopy (SEM)*

SEM (Hitachi S-3500N, Tokyo, Japan) was used to observe the morphology of the cross section of the formulated granules. Both secondary electron imaging and backscattered electron imaging were used for the SEM detector and the magnification was 15- to 300,000-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, five to six granules were chosen randomly from granules that passed through the 1.19-mm sieve screen and were 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 (Product number 16073, TED Pella Inc., California, USA) and then sputter-coated with gold (HITACHI E-1010 ION SPOTTER, Tokyo, Japan), having a thickness of about 6 nm. The discharge current used was about 0 to 30 mA and the vacuum was around 10 Pa.

*Ultraviolet (UV) and Visible Spectrophotometry*

The withdrawals from the dissolution apparatus at fixed times were filtered, diluted 50 times, and assayed through UV absorbance determination at 243 nm using a UV and visible (UV/Vis) spectrophotometer (Lambda 25, Perkin Elmer, Norwalk, Connecticut, USA.). 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 five standard acetaminophen solutions each with a known concentration of acetaminophen.

## Experimental

*Preparation of Ball-Milled Acetaminophen Powders*

Fifty g of Lu'An acetaminophen powders (large particle–sized acetaminophen powders) were milled in a ball miller (MUBM-236-RTD, Shin Kwan Machinery, Taiwan, R.O.C.) each time with a ceramic-ball-to-powder mass ratio of 12:1 to produce the ball-milled acetaminophen powders (small-sized acetaminophen powders). The volume of the ball jar was 1.5 liters and the ball milling process took 120 minutes to finish with a rotating speed of 335 to 345 rpm.

*Powder Mixing*

The ball-milled acetaminophen powders were mixed with the Lu'An acetaminophen powders at different weight fractions, $\phi_1$ of 1.0, 0.8, 0.6, 0.5, 0.4, 0.2, and 0. Each corresponding mixture with a total weight of 150 g was prepared in a ball milling jar with the ceramic balls removed. The mixing time was set to 120 minutes and a rotating speed of 335 to 345 rpm.

*Formulated Powder Blending*

The formulations used for wet granulation are listed in Table 2. MCC was a filler and PVP was a binder and a disintegrant. Small particle–sized acetaminophen powders or large particle–sized acetaminophen powders or the acetaminophen powder mixtures were dry blended with MCC and PVP for 3 minutes in an 8-L sized planetary mixer (Tian Shuai Food Machine Co. Ltd., Taiwan) with a rotational speed of 135 rpm. Formulations composing 75 wt percent, 62 wt percent and

TABLE 2
Formulation Compositions of Acetaminophen at 75 Wt Percent, 62 Wt Percent, and 30 Wt Percent

| 75 wt % Formulation | | |
|---|---|---|
| Ingredient | Weight (g) | Composition (wt %) |
| Acetaminophen | 181 | 75 |
| Microcrystalline cellulose | 56 | 23 |
| Polyvinylpyrrolidone | 4.8 | 2 |
| **62 wt % formulation** | | |
| Ingredient | Weight (g) | Composition (wt %) |
| Acetaminophen | 150 | 62 |
| Microcrystalline cellulose | 87 | 36 |
| Polyvinylpyrrolidone | 4.8 | 2 |
| **30 wt % formulation** | | |
| Ingredient | Weight (g) | Composition (wt %) |
| Acetaminophen | 72.5 | 30 |
| Microcrystalline cellulose | 164.5 | 68 |
| Polyvinylpyrrolidone | 4.8 | 2 |

30 wt percent of acetaminophen were abbreviated as 75 wt %, 62 wt % and 30 wt % formulations, respectively.

*Wet Granulation*

The ultrapure water was introduced into the powder mixture at the third minute of dry blending by a peristaltic pump (Micropump, Concord Corporation, California, USA) with a water flow rate of 7 ml/minute. The agglomerates started to become pasty (end point) after the addition of about 114 to 161 g of ultrapure water for a total wet mixing time of 19 to 23 minutes, depending on the weight fraction of the ball-milled acetaminophen powders for 75 wt percent, 62 wt percent, and 30 wt percent formulations (Table 2). Wet granulation was stopped at the end point.

*Drying*

The wet granules were then oven dried at 50°C 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 g 75 wt percent formulation, 0.806 g 62 wt percent formulation, and 1.667 g 30 wt percent formulation for an equivalent of 500 mg acetaminophen in the dissolution study.

*Granule Mixing*

Granules prepared by mixing granules made from ball milled acetaminophen powders (small-particle granules) with granules made from Lu'An acetaminophen powders (large-particle granules) were set at different weight fractions, $\phi_1$ of 1.0, 0.8, 0.6, 0.5, 0.4, 0.2, and 0. Each corresponding mixture of granules with a total weight of 0.667 g, 0.806 g and 1.667 g were hand shaken in a scintillating vial for 75, 62, 30 wt percent formulation respectively.

*Dissolution*

A dissolution test station (SR6, Hanson Research Corporation, Chatsworth, California, USA) Type II (paddle method) at a 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 of the formulated granules was carried out on an equivalent of 500 mg acetaminophen. 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 ± 0.2°C, respectively (Sorasuchart, Wardrop, & Ayres, 1999). Samples of 4 to 5 ml were withdrawn at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 40 minutes, 60 minutes and 90 minutes by a plastic syringe near the stirring paddle. Each sample was filtered by a 0.22-μm syringe filter (Millex-GV, Millipore, Massachusetts, USA), 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. The dissolution test for each sample for a given formulation was repeated at least three times to obtain the mean, the standard deviation and the error bar.

## RESULTS AND DISCUSSION

DSC use test scans in Figure 6 indicate that the ball-milled acetaminophen powders (small-sized particles) and the Lu'An acetaminophen powders (large-sized particles) were both Form I crystals with a melting point of about 171°C (Lee, Kuo, et al., 2006). Obviously, the ball milling process did not alter the polymorphism of acetaminophen (Braga, & Grepioni, 2005). The sieve fractions in Figure 7 show that the ball-milled acetaminophen powders had a bimodal size distribution peaked at the size cut of > 75 μm and > 500 μm, and the Lu'An acetaminophen powders had a relatively wide particle size distribution, mainly centered at the size cut of > 75 μm. Optical micrographs in Figure 8 further reveal that the ball-milled acetaminophen powders in Figure 7 were lumpy and were actually aggregates of > 500 μm composed of a large number of small primary particles of about 70 μm or less being held together by cohesive electrostatic forces (Ebube et al., 1997). As for the Lu'An acetaminophen powders, SEM showed that they were actually crystals with definitive geometrical shapes of about 75 to 150 μm on the average.

The dissolution profiles of 75 wt percent, 62 wt percent, and 30 wt percent formulated granules of mixed acetaminophen powders having various weight fractions, $\phi_1$, of the ball-milled acetaminophen powders are illustrated in Figure 9. On the other hand, the dissolution profiles of the mixed granules having various weight fractions, $\phi_1$, of granules made from the ball milled acetaminophen powders with 75 wt percent, 62 wt percent, and 30 wt percent formulations are illustrated in Figure 10. All dissolution profiles followed first-order kinetics

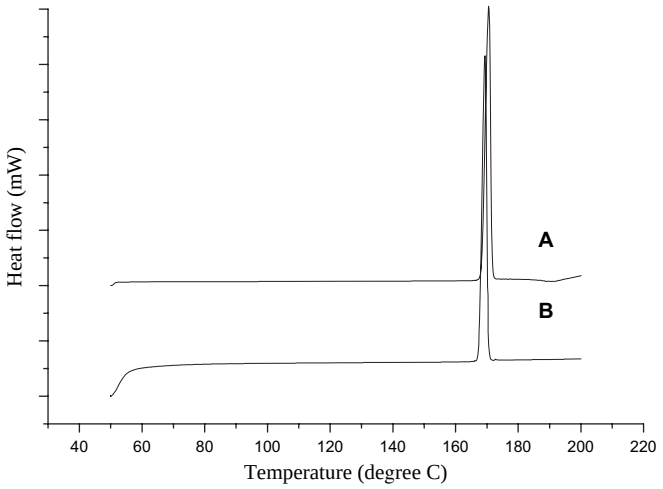


FIGURE 6. DSC trials of (A) the ball-milled acetaminophen powders and (B) the Lu'An acetaminophen powders

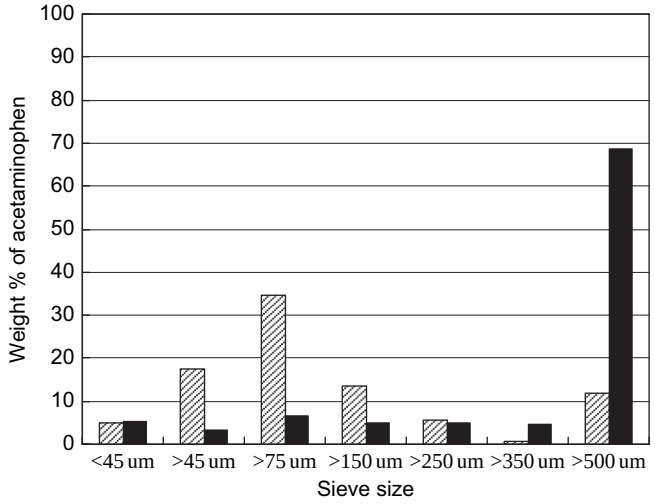


FIGURE 7. Particle size distributions of (A) the ball-milled acetaminophen powders (black bar) and (B) the Lu'An acetaminophen powders (shaded bar), by the sieving method.

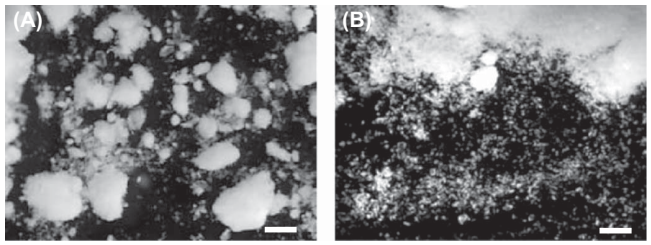


FIGURE 8. Optical micrographs of (A) the ball-milled acetaminophen powders and (B) the Lu'An acetaminophen powders (scale bar = 1000 μm).

whose release rate, *dc/dt*, at any point was proportional to the remaining concentration of acetaminophen, *c* (Jørgensen, & Christensen, 1996):[1]

$$\frac{dc}{dt} = -kc \qquad (2)$$

where *k* was the first-order dissolution rate constant and $k = k_1$ when $\phi_1 = 1$, $k = k_2$ when $\phi_1 = 0$, and $k = k_{mix}$ for all other $\phi_1$s according to Table 1. The difference between 0.5 g/900 ml and the amount of acetaminophen dissolved at any time point, *W*, in Figures 9 and 10 was determined as *c* divided by 900 ml. Using the acetaminophen contents from $t = 0$ minutes to 50% drug release time, $t_{50}$, 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, Venkataram, & Delwar Hussain, 2001). The 50% drug release times, $t_{50}$s, and dissolution rate constants, *k*s, derived from

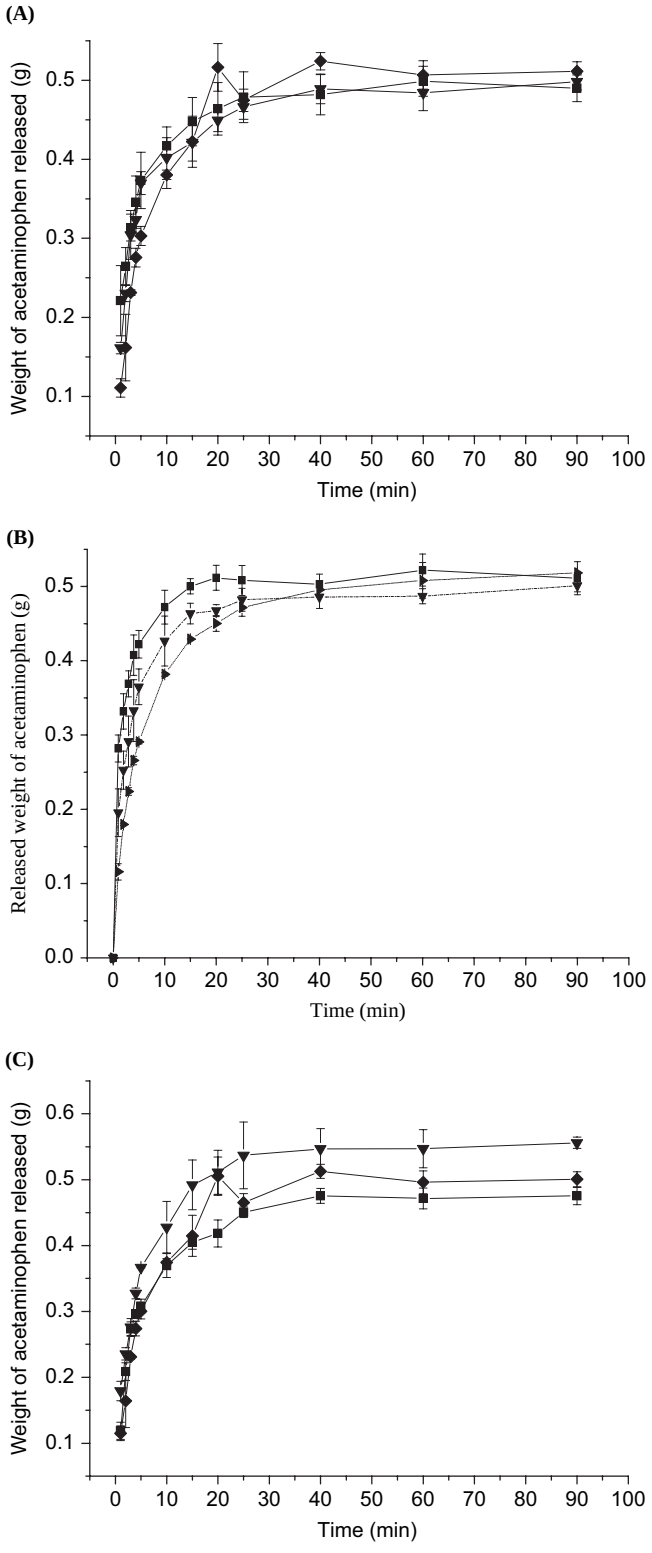


FIGURE 9. Dissolution profiles of (A) 75 wt percent, (B) 62 wt percent, and (C) 30 wt percent formulated granules containing mixed acetaminophen powders of different weight fractions, $\phi_1$, of the ball-milled acetaminophen powders: ■:1.0, ▼:0.5 and ♦:0.

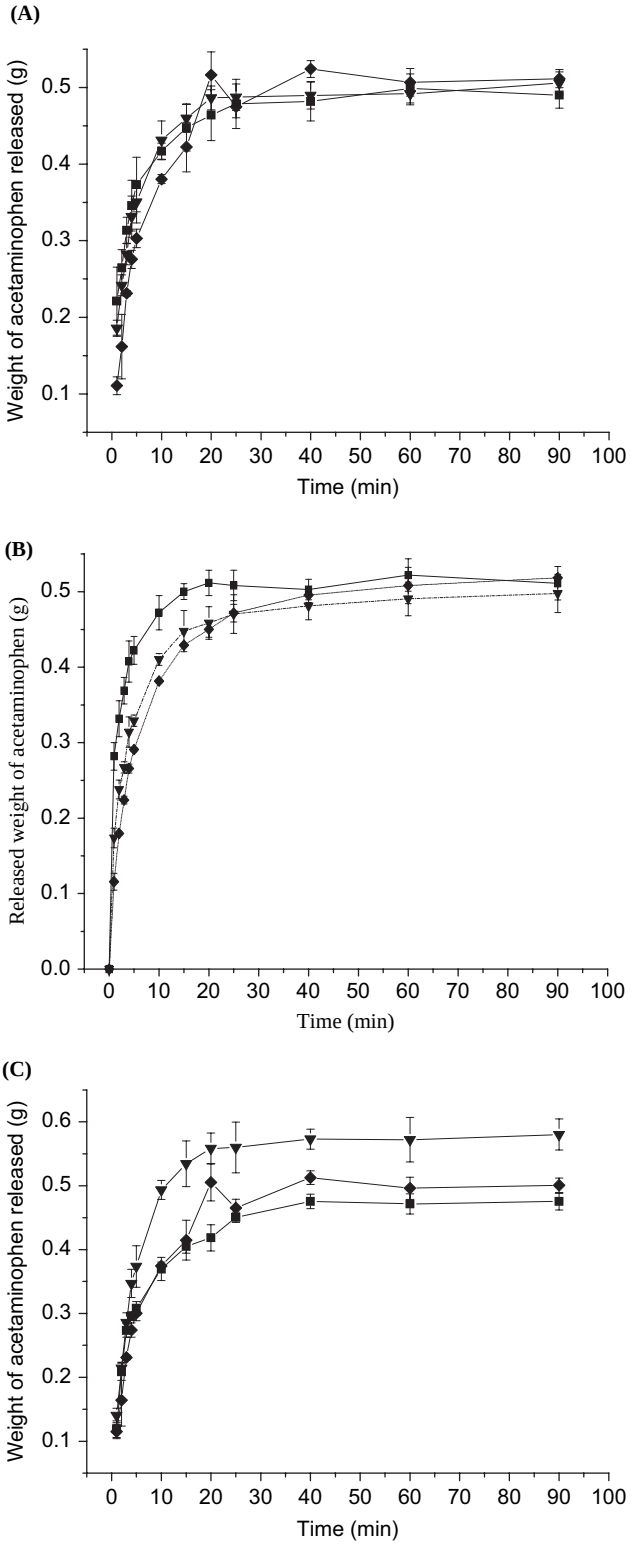


FIGURE 10. Dissolution profiles of (A) 75 wt percent, (B) 62 wt percent, and (C) 30 wt percent formulated granules containing mixed granules of different weight fractions, $\phi_1$, of the granules made from the ball-milled acetaminophen powders: ■ = 1.0, ▼ = 0.5, and ♦ = 0.

Figures 9 and 10 based on Equations 1 and 2 for 75 wt percent, 62 wt percent, and 30 wt percent formulated granules were summarized in Tables 3 and 4, respectively.

The dissolution profiles in Figures 9 and 10 and the dissolution rate constants at $\phi_1$ = 1.0, 0.5, and 0 in Tables 3 and 4 are the experimental data that are required to be determined for each new trial. Intriguingly, the similar values of $t_{50}$ and $k$ at $\phi_1$ = 0.5 in Tables 3 and 4 of 75 wt percent, 62 wt percent, and 30 wt percent formulations showed that methods I and II gave very close results in the dissolution performance of acetaminophen. This fact suggests that the simple mixing of the small particle–sized acetaminophen and the large particle–sized acetaminophen in the planetary mixer might not completely delump the aggregates of the small particle–sized acetaminophen, so that it did not really matter whether the formulated granules were made by premixing the two different sized acetaminophen powders or simply made by mixing the formulated small-sized particle granules and the formulated large-sized particle granules. Apparently, the values of $k_1$ appeared to be more sensitive to the formulations than the value of $k_2$ because the microstructures of the granules made from the small particle–size acetaminophen were more prone to the interplay between the two granule growth mechanisms of agglomeration and layer by layer (Lee & Hsu, 2007) than the microstructures of the granules made from the large particle–size acetaminophen. Therefore, the 62 wt percent formulation gave the optimal results as a whole.

After fitting the three data points of $k_1$, $k_2$, and $k_{mix}$ to the 10 mixing rules in material science (Figures 11 and 12), we found that the selection of the best suited mixing rules based on $k_1$, $k_2$, and $k_{mix}$ was solely dependent on the formulations under a given operating condition and was regardless of whether the system was granules made from a mixture of two different particle sized acetaminophen or was a mixture of two kinds of granules—one kind of granules made from the small particle–sized acetaminophen and the other kind from the large particle–sized acetaminophen. The values of $k_1$, $k_2$, and $k_{mix}$ in both cases of the 75 wt percent and 30 wt percent formulations were enveloped by the parallel mixing rule and Maxwell mixing rule (Figures 11A, 11C, 12A, and 12C), whereas the values of $k_1$, $k_2$, and $k_{mix}$ for the 62 wt percent formulation were encompassed by the logarithmic mixing rule, Hashin and Shtrikman upper bound, and the series mixing rule (Figures 11B and 12B).

But to further demonstrate the feasibility of both methods I and II, typical dissolution profiles (Figures 13 and 14) and dissolution rate constants (Tables 5 and 6) of granules of mixed acetaminophen powders and mixed granules at some other weight fractions of the ball-milled acetaminophen powders at $\phi_1$ = 0.8, 0.6, 0.4, and 0.2 for the 62 wt percent formulations were experimentally determined and then calculated from Equations 1 and 2. Since the determination of the dissolution performance was onerous, only the optimal formulation of 62 wt percent was chosen for a detailed illustration.

TABLE 3
$t_{50}$ and $k_{mix}$ of Mixed Acetaminophen Powders at Different Weight Fractions of 1.0, 0.5, and 0 of Ball-Milled Acetaminophen With 75 Wt Percent, 62 Wt Percent, and 30 Wt Percent Formulations

| Weight Fraction of Ball-Milled Acetaminophen, $\phi_1$ | $t_{50}$, Mixed Acetaminophen (min) | $k$, Mixed Acetaminophen ($min^{-1}$) |
|---|---|---|
| 75 wt % formulation | | |
| 1.0 | 1.65 ± 0.46 | $k_1$ = 0.43 ± 0.15 |
| 0.5 | 2.27 ± 0.22 | $k_{mix}$ = 0.30 ± 0.03 |
| 0 | 3.69 ± 0.22 | $k_2$ = 0.18 ± 0.01 |
| 62 wt % formulation | | |
| 1.0 | 0.93 ± 0.01 | $k_1$ = 0.75 ± 0.01 |
| 0.5 | 1.96 ± 0.24 | $k_{mix}$ = 0.34 ± 0.03 |
| 0 | 3.84 ± 0.23 | $k_2$ = 0.18 ± 0.01 |
| 30 wt % formulation | | |
| 1.0 | 2.45 ± 0.16 | $k_1$ = 0.28 ± 0.01 |
| 0.5 | 3.04 ± 0.21 | $k_{mix}$ = 0.22 ± 0.02 |
| 0 | 3.59 ± 0.20 | $k_2$ = 0.16 ± 0.01 |

1 = small particle–sized acetaminophen by ball milling the Lu'An batch. 2 = large particle–sized acetaminophen purchased from Lu'An.

TABLE 4
$t_{50}$ and $k_{mix}$ of Mixed Formulated Granules at Different Weight Fractions of 1.0, 0.5, and 0 of Granules Made From Ball-Milled Acetaminophen With 75 Wt Percent, 62 Wt Percent, and 30 Wt Percent Formulations

| Weight Fraction of Granules Made from Ball-Milled Acetaminophen, $\phi_1$ | $t_{50}$, Mixed Acetaminophen (min) | $k$, Mixed Acetaminophen ($min^{-1}$) |
|---|---|---|
| 75 wt % formulation | | |
| 1.0 | 1.65 ± 0.46 | $k_1$ = 0.43 ± 0.15 |
| 0.5 | 2.27 ± 0.22 | $k_{mix}$ = 0.30 ± 0.03 |
| 0 | 3.69 ± 0.22 | $k_2$ = 0.18 ± 0.01 |
| 62 wt % formulation | | |
| 1.0 | 0.93 ± 0.01 | $k_1$ = 0.75 ± 0.01 |
| 0.5 | 2.37 ± 0.17 | $k_{mix}$ = 0.30 ± 0.02 |
| 0 | 3.84 ± 0.23 | $k_2$ = 0.18 ± 0.01 |
| 30 wt % formulation | | |
| 1.0 | 2.45 ± 0.16 | $k_1$ = 0.28 ± 0.01 |
| 0.5 | 3.07 ± 0.17 | $k_{mix}$ = 0.22 ± 0.01 |
| 0 | 3.09 ± 0.20 | $k_2$ = 0.16 ± 0.01 |

1 = small particle–sized acetaminophen by ball milling the Lu'An batch. 2 = large particle–sized acetaminophen purchased from Lu'An.

Substituting the vales of $k_1$ = 0.75 ± 0.01 $minutes^{-1}$ and $k_2$ = 0.18 ± 0.01 $minutes^{-1}$ of 62 wt percent formulation into the 10 mixing rules in Table 1 and feeding them with $\phi_1$ = 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1 to calculate the corresponding $k_{mix}$ values, the loci of all 10 mixing rules could then be mapped out, as illustrated in Figures 15 and 16. To verify the validity and the reliability of methods I and II, we experimentally produced four test points of $k_{mix}$ = 0.51 ± 0.03 $minutes^{-1}$, 0.39 ± 0.01 $minutes^{-1}$, 0.27 ± 0.01 $minutes^{-1}$, and 0.21 ± 0.01 $minutes^{-1}$ at $\phi_1$ = 0.8, 0.6, 0.4, and 0.2, respectively for method I and four test points of $k_{mix}$ = 0.53 ± 0.11 $minutes^{-1}$, 0.39 ± 0.19 $minutes^{-1}$, 0.26 ± 0.02 $minutes^{-1}$, and 0.20 ± 0.05 $minutes^{-1}$ at $\phi_1$ = 0.8, 0.6, 0.4, and 0.2 respectively for method II (Tables 5 and 6). All these test points along with the original

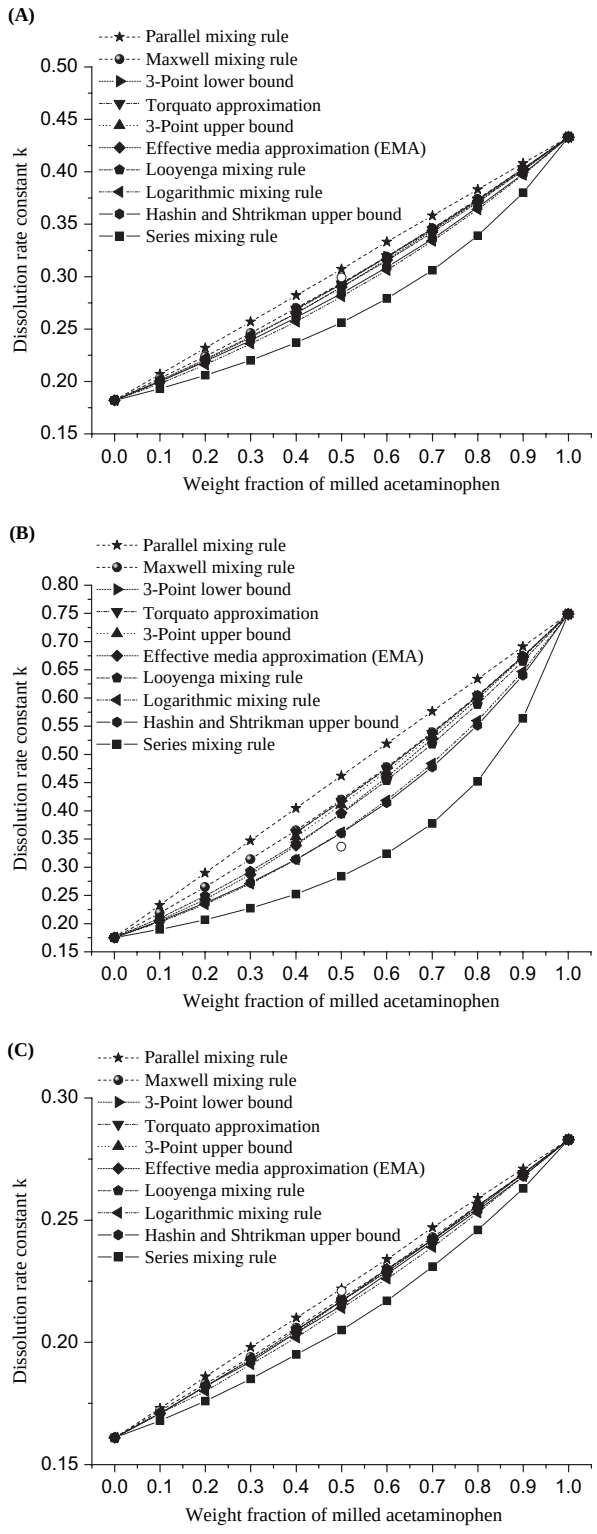


FIGURE 11. The fitting of 10 mixing rules to the three experimentally determined dissolution constants (open circles) of (A) 75 wt percent, (B) 62 wt percent, and (C) 30 wt percent formulated granules made from the mixed acetaminophen powders of three different weight fractions, $\phi_1$, of the ball-milled acetaminophen powders of 1.0, 0.5 and 0.

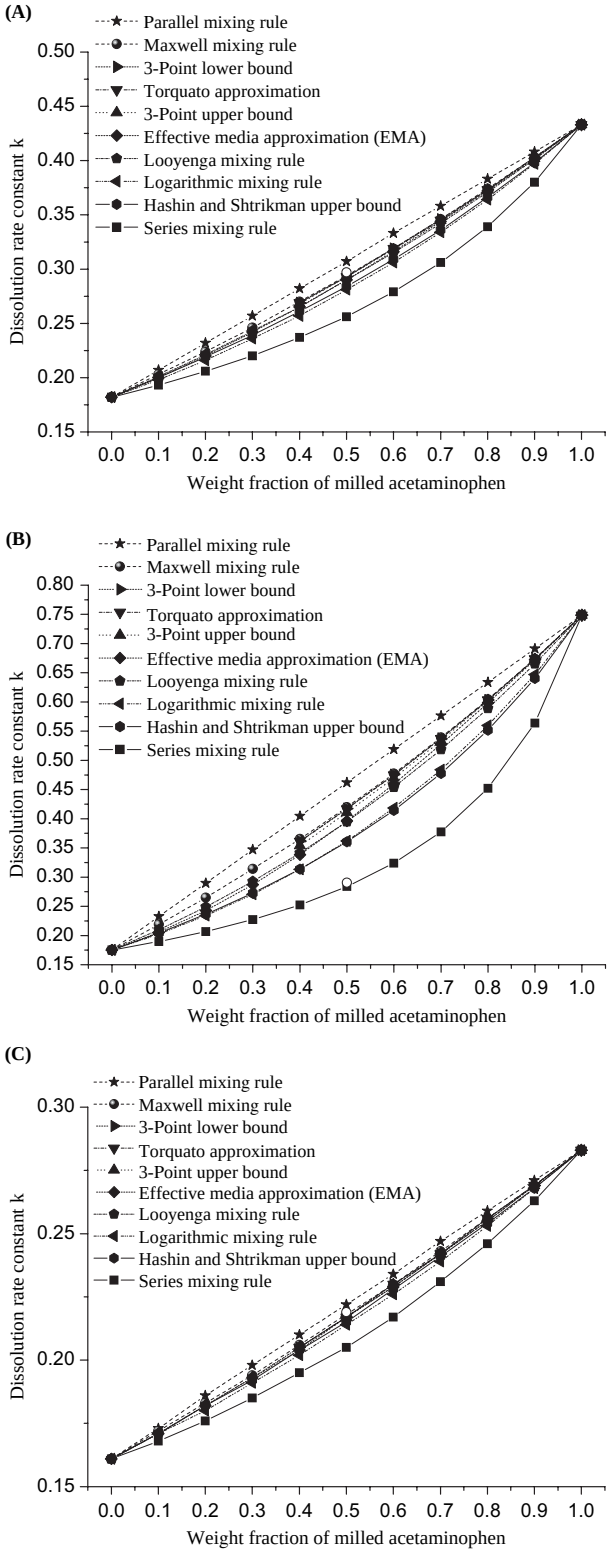


FIGURE 12. The fitting of three mixing rules to the three experimentally determined dissolution constants (open circles) of (A) 75 wt percent, (B) 62 wt percent and (C) 30 wt percent formulated mixed granules made from three different weight fractions, $\phi_1$, of granules of ball-milled acetaminophen of 1.0, 0.5 and 0.

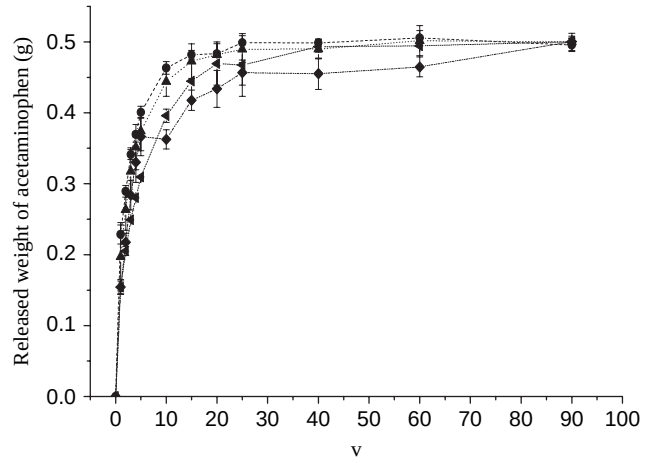


FIGURE 13. Dissolution profiles of 62 wt percent formulated granules containing mixed acetaminophen powders of different weight fractions, $\phi_1$, of the ball-milled acetaminophen powders: ● = 0.8, ▲ = 0.6, ◀ = 0.4, and ▶ = 0.2.

TABLE 5
$t_{50}$ and $k_{mix}$ of Mixed Acetaminophen Powders at Different Weight Fractions of 1.0, 0.8, 0.6, 0.5, 0.4, 0.2, and 0 of Ball-Milled Acetaminophen with a 62 Wt Percent Formulation

| Weight Fraction of Ball-Milled Acetaminophen, $\phi_1$ | $t_{50}$, Mixed Acetaminophen (min) | $k_{mix}$, Mixed Acetaminophen ($min^{-1}$) |
|---|---|---|
| 1.0 | 0.93 ± 0.01 | $k_1$ = 0.75 ± 0.01 |
| 0.8 | 1.40 ± 0.18 | 0.51 ± 0.03 |
| 0.6 | 1.81 ± 0.48 | 0.39 ± 0.01 |
| 0.5 | 1.96 ± 0.24 | 0.34 ± 0.03 |
| 0.4 | 2.27 ± 0.19 | 0.27 ± 0.01 |
| 0.2 | 3.03 ± 0.23 | 0.21 ± 0.01 |
| 0 | 3.84 ± 0.23 | $k_2$ = 0.18 ± 0.01 |

1 = small particle–sized acetaminophen by ball milling the Lu'An batch. 2 = large particle–sized acetaminophen purchased from Lu'An.

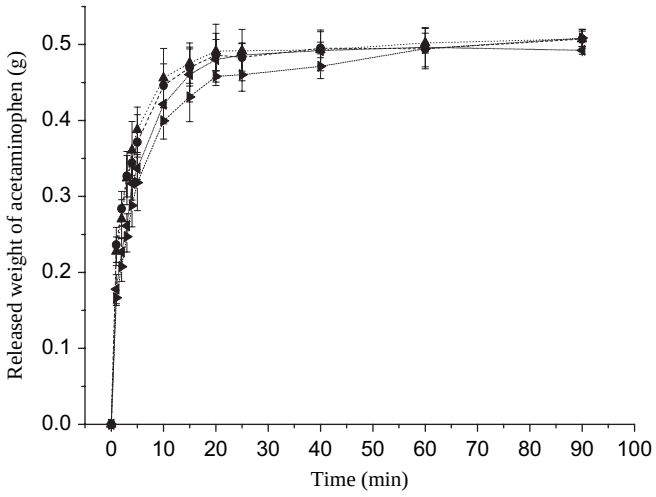


FIGURE 14. Dissolution profiles of 62 wt percent formulated granules containing mixed granules of different weight fractions, $\phi_1$, of the granules made from the ball-milled acetaminophen powders: ● = 0.8, ▲ = 0.6, ◀ = 0.4, and ▶ = 0.2.

TABLE 6
$t_{50}$ and $k_{mix}$ of Mixed Formulated Granules at Different Weight Fractions of 1.0, 0.8, 0.6, 0.5, 0.4, 0.2, and 0 of Granules Made from Ball-Milled Acetaminophen with a 62 Wt Percent Formulation

| Weight Fraction of Granules Made from Ball Milled Acetaminophen, $\phi_1$ | $t_{50}$, Mixed Granules (min) | $k_{mix}$, Mixed Granules ($min^{-1}$) |
|---|---|---|
| 1.0 | 0.93 ± 0.01 | $k_1$ = 0.75 ± 0.01 |
| 0.8 | 1.37 ± 0.33 | 0.53 ± 0.11 |
| 0.6 | 1.61 ± 0.53 | 0.39 ± 0.19 |
| 0.5 | 2.37 ± 0.17 | 0.30 ± 0.02 |
| 0.4 | 2.62 ± 0.18 | 0.26 ± 0.02 |
| 0.2 | 3.18 ± 0.66 | 0.20 ± 0.05 |
| 0 | 3.84 ± 0.23 | $k_2$ = 0.18 ± 0.01 |

1: small particle–sized acetaminophen by ball milling the Lu'An batch, 2: large particle–sized acetaminophen purchased from Lu'An.

values of $k_{mix}$ at $\phi_1$ = 0.5 were lying in the crescent area enveloped by the three mixing rules. This meant that the lower and the upper bounds of $\phi_1$ to achieve a desired $k_{mix}$ could now be predicted. For example, if the desired $k_{mix}$ = 0.40, drawing a horizontal line from the y-axis at 0.40 to the right until it intersected with the loci of the logarithmic mixing rule, the Hashin and Shtrikman upper bound, and the series mixing rule in Figures 15 and 16, the intersects gave the lower and upper bounds of $\phi_1$ of 0.59 and 0.74 respectively. This range had significantly narrowed down the possible values of $\phi_1$ that were needed to be tried out experimentally. Moreover, the mixing rules might also be useful in predicting the allowable amount of fines in a typical batch that experienced particle attrition in filtration, drying, and wet granulation (Lee & Lee, 2003).

## CONCLUSION

The promising results of applying the mixing rules to the dissolution rate constant implied that any desired dissolution rate constant, $k$, between the dissolution rate constant of $k_1$

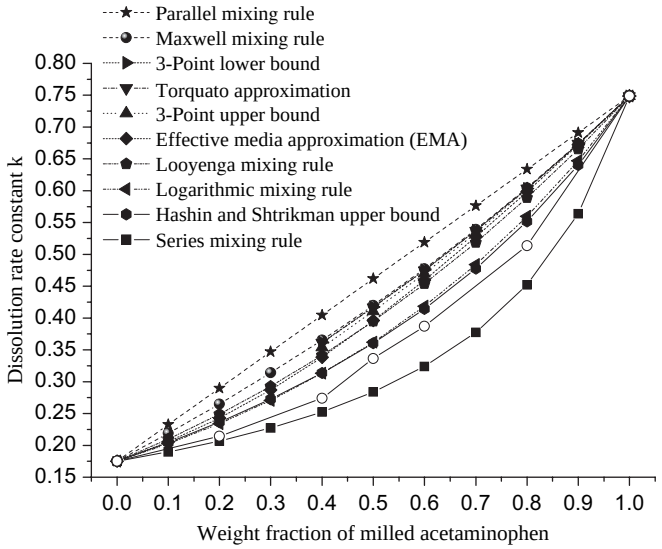


FIGURE 15. The fitting of three mixing rules with the closest loci to the rest of the experimentally determined dissolution constants (open circles) of 62 wt percent formulated granules made from the mixed acetaminophen powders of four different weight fractions, $\phi_1$, of the ball-milled acetaminophen powders of 0.8, 0.6, 0.4, and 0.2.

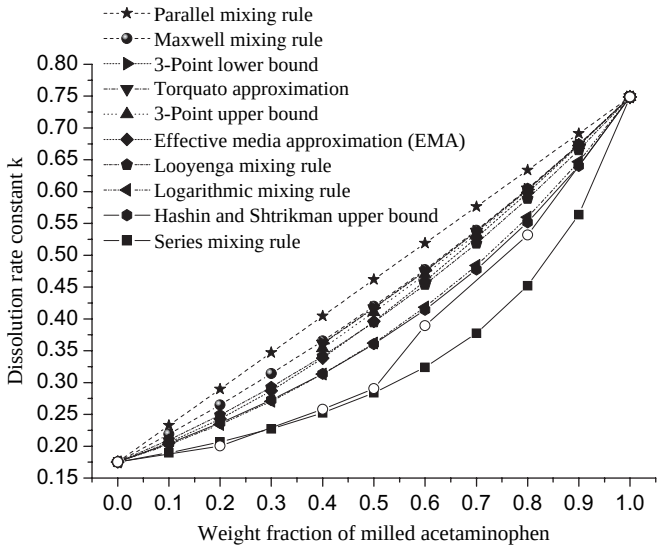


FIGURE 16. The fitting of three mixing rules with the closest loci to the rest of the experimentally determined dissolution constants (open circles) of 62 wt percent formulated granules containing mixed granules of four different weight fractions, $\phi_1$, of the granules made from the ball-milled acetaminophen powders of 0.8, 0.6, 0.4, and 0.2..

from granules made of the small particle–sized API and the dissolution rate constant of $k_2$ from granules composed of the large particle–sized API could be achieved by granules produced from mixing the two kinds of API (method I) or by mixing the granules made from the small particle–sized API with the granules composed of the large particle–sized API (method II) at a certain proportion. Only one large particle–size API batch was needed to be manufactured and the small particle–size API batch could be obtained directly by milling. This should greatly reduce the operation time, labor force, and materials used. To go even one step further, we speculate that methods I and II could be extended to the mechanical properties in tablets and even electric properties in batteries.

## ACKNOWLEDGMENTS

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