AAPS PharmSciTech, Vol. 12, No. 2, June 2011 (© 2011)
DOI: 10.1208/s12249-011-9628-8

Research Article

A Kinetic Study of the Polymorphic Transformation of Nimodipine and Indomethacin during High Shear Granulation

Zhen Guo,[1] Mingxin Ma,[2] Tianyi Wang,[1] Di Chang,[1] Tongying Jiang,[1] and Siling Wang[1,3]

Received 25 January 2011; accepted 27 April 2011; published online 7 May 2011

Abstract. The objective of the present study was to investigate the mechanism, kinetics, and factors affecting the polymorphic transformation of nimodipine (NMD) and indomethacin (IMC) during high shear granulation. Granules containing active pharmaceutical ingredient, microcrystalline cellulose, and low-substituted hydroxypropylcellulose were prepared with ethanolic hydroxypropylcellulose solution, and the effects of independent process variables including impeller speed and granulating temperature were taken into consideration. Two polymorphs of the model drugs and granules were characterized by X-ray powder diffraction analysis and quantitatively determined by differential scanning calorimetry. A theoretical kinetic method of ten kinetic models was applied to analyze the polymorphic transformation of model drugs. The results obtained revealed that both the transformation of modification I to modification II of NMD and the transformation of the α form to the γ form of IMC followed a two-dimensional nuclei growth mechanism. The activation energy of transformation was calculated to be 7.933 and 56.09 $kJ \cdot mol^{-1}$ from Arrhenius plot, respectively. Both the granulating temperature and the impeller speed affected the transformation rate of the drugs and, in particular, the high shear stress significantly accelerated the transformation process. By analyzing the growth mechanisms of granules in high-shear mixer, it was concluded that the polymorphic transformation of NMD and IMC took place in accordance with granule growth in a high-shear mixer.

KEY WORDS: differential scanning calorimetry; granule growth mechanism; high shear granulation; polymorphic transformation kinetic; X-ray powder diffraction.

INTRODUCTION

Drug polymorphism has been the subject of intensive research for many years. The polymorphs of a compound are chemically identical, but they differ in terms of their physical properties, such as density, crystal form, spectrum, melting point, and solubility. However, drug polymorphism may not only cause analytical problems, it may also affect the chemical stability of the drug itself as well as the physical stability of the different dosage forms (1). Furthermore, the crystal structure has a very important effect on the dissolution behavior and therapeutic effectiveness of drugs and their dosage forms.

Nimodipine belongs to the class of pharmacological agents known as calcium channel blockers. It exists into two polymorphic forms known as modification I (Mod. I) and modification II (Mod. II). Mod. II is the stable form, and it is reported that Mod. I can be transformed to Mod. II when suspended in solvents with stirring (2). Indomethacin is a non-steroidal anti-inflammatory drug, and it exists in three true polymorphic forms (α, γ, and δ) and an amorphous form (3,4). It also forms solvates with *tert*-butyl alcohol and methanolate (5). Researchers have revealed that the α form could transform into the γ form when dissolved in ethanol (6).

It is well known that solid-state phase transformation can occur in formulations due to processing (e.g., granulation, drying, milling, and compression) or drug–excipient interactions. Such phase transformation could affect the properties (e.g., dissolution, bioavailability, and stability) of the final products (7,8). Therefore, polymorphic forms of the active pharmaceutical ingredient (API) are directly related to the control and optimization of process parameters for many pharmaceutical manufacturing techniques. High shear granulation is widely used in the pharmaceutical industry and has many advantages over other techniques. A great many papers focusing on the effect of the process parameters on granule properties have been published. The most investigated effects are the mixer load, impeller speed, mixing time (9,10), temperature of the heating jacket (11,12), chopper action (9,10), binder content (9,10), binder viscosity (13), and physical properties of the materials (14). Unfortunately, there is little literature on the occurrence of polymorphic transformation during the high shear granulation process. Therefore, a better understanding of the mechanism, effects, and

[1] School of Pharmacy, Shenyang Pharmaceutical University, No.103 Wenhua Road No. 32 P.O. Box Shenyang 110016, People's Republic of China.
[2] Shenyang Xingqi Pharmaceutical Co. Ltd., Shenyang 110024, People's Republic of China.
[3] To whom correspondence should be addressed. (e-mail: silingwang@syphu.edu.cn)

kinetics of transformation are essential for the quality control of final products.

The particular aim of the present study was to investigate the mechanism, kinetics, and factors affecting the polymorphic transformation of nimodipine (NMD) and indomethacin (IMC) during the high shear wet granulation process; the effects of independent process variables including impeller speed and granulating temperature will be taken into consideration. In addition, a lot of work will be conducted on the granule growth mechanisms that accompany the polymorphic transformation in order to discuss the relationship between the two aspects in a high-shear mixer.

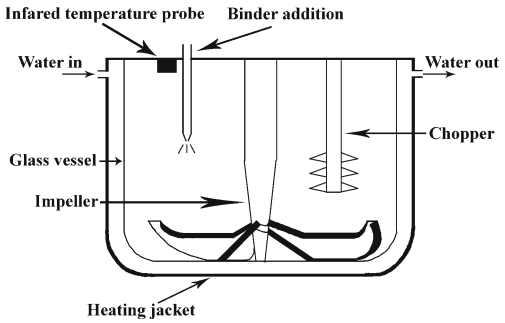

Fig. 1. Schematic representation of the high-shear mixer

MATERIALS AND METHODS

Materials

The APIs used in this study were nimodipine (Shanxi Yabao Pharmaceutical Co. Ltd., China) and indomethacin (Shijiazhuang Pharmaceutical Group Co. Ltd., China). The commercial polymorphic form of nimodipine is Mod. I with a reported melting endotherm at 124°C and a heat of fusion of 40.3 $kJ \cdot mol^{-1}$ (2). The Mod. II of NMD was prepared by dissolving 10 g Mod. I in 200 mL ethanol at 60°C with agitation until the solid had completely dissolved. Then, Mod. II of NMD was allowed to re-crystallize while the solvent was evaporated under vacuum at room temperature.

The commercial polymorphic form of indomethacin is the γ form. It has a melting point of 162°C and a heat of fusion of 37.9 $kJ \cdot mol^{-1}$ (15). The α form of IMC was prepared by dissolving 10 g of the γ form of IMC in 10 mL ethanol at 80°C, removing the undissolved drug by filtration, and adding 20 mL distilled water at room temperature to the IMC-saturated ethanol solution at 80°C. The precipitated crystals were removed by filtration using a glass funnel and then dried overnight in a P_2O_5 desiccator under vacuum at room temperature (6).

The excipients used were microcrystalline cellulose (MCC Avicel® PH101, FMC Corporation, USA) as a diluent with a bulk density of 320 $kg \cdot m^{-3}$, a particle density of 1,611 $kg \cdot m^{-3}$, and a mean particle size of 50 μm and low-substituted hydroxypropylcellulose (L-HPC® (LH31)), Shin-Etsu Chemical Co. Ltd., Japan) as a disintegrant. A 5% (*w*/*w*) ethanolic hydroxypropylcellulose (HPC-L®, Nippon Soda Co. Ltd., Japan) solution was used as a liquid binder with a viscosity of 0.047 Pa·s at 25°C. All other materials were of analytical reagent grade.

Preparation of Granules

Granules were produced in a laboratory-scale high-shear mixer (MicroGral®, Collette-NV, Belgium) equipped with a transparent 1-L glass vessel surrounded with a heating jacket (shown in Fig. 1). Water at a certain temperature flowed through the interlayer to keep a constant granulating temperature. The vertical impeller consisted of three stainless steel blades of 60 mm length, and the vertical chopper consisted of two stainless steel blades of 15 mm length. Granules were prepared with the same composition, containing 10% API (Mod. I of NMD or the α form of IMC), 85% MCC, and 5% L-HPC. A batch of 100 g powder was loaded into the bowl and premixed for 5 min at an impeller speed of 200 rpm and a chopper speed of 1,000 rpm, and then preheated before binder addition. Granulation was then started by the addition of binder which was poured at the middle point between the center and the tip of the impeller at an impeller speed listed in Table I. The chopper speed was four times faster than the impeller speed in order to maintain the same tip velocity. A stop watch was started immediately after addition of the binder, and the kneading time was considered to be the time after all the binder has been added.

Experimental Design

During the preliminary trials, the conditions at which the granulating process resulted in granules with a suitable size were determined. In all experiments, the liquid binder-to-solid ratio (L/S, *w*/*w*) was 0.800 for NMD and 1.000 for IMC, respectively, and the kneading time had to be kept less than 30 min in order to prevent uncontrolled growth. Batches of granules were produced at different impeller speeds ranging from 300 to 700 rpm and a temperature ranging from 25°C to 40°C. A new batch of powder and binder was used to produce a number of samples at each kneading time, which ranged from 2 to 30 min. Twelve batches were prepared, and the batches were stopped at 2, 5, 10, 15, 20, and 30 min after binder addition. Granules were sampled at prescribed inter-

Table I. Granulation Process Parameter Settings

	Process parameters			
Trial number	Impeller speed (rpm)	Temperature (°C)	L/S ratio for NMD (*w*/*w*)	L/S ratio for IMC (*w*/*w*)
1	300	25	0.800	1.000
2	300	30		
3	300	35		
4	300	40		
5	500	25		
6	500	30		
7	500	35		
8	500	40		
9	700	25		
10	700	30		
11	700	35		
12	700	40		

L/S liquid binder-to-solid ratio, *NMD* nimodipine, *IMC* indomethacin

vals and dried under vacuum at room temperature in order to prevent the polymorphic transformation during drying process and then kept in closed containers until their evaluation (6). Each experiment was performed in triplicate. The different settings of the process variables are listed in Table I.

Characterization of Granules

Granule Size Distribution Analysis

The size analysis of granules was carried out with a vibrating instrument (8411 Electric shaker, Hangzhou, China) using a set of nine standard sieve ranges of 76–2000 μm (76, 125, 200, 300, 450, 600, 800, 1,250, and 2,000 μm). The sample size was 100 g, and shaking was carried out for 10 min. The particle size distribution was calculated from the ratio of the residual weight of the granules on each sieve to the granule weight before sieving. A particle size distribution curve was drawn and the median diameter (hereafter, 50% particle diameter) was calculated.

X-ray Powder Diffraction Analysis

X-ray powder diffraction (XRPD) was performed with a Rigaku Geigerflex X-ray diffractometer (model 4037V1, Tokyo, Japan), which was equipped with a Cu-Kα source (λ=1.5406 Å) operating at a tube load of 30 kV and 20 mA. The divergence slit size was 1 mm, the receiving slit, 1 mm, and the detector slit, 0.1 mm. A powder bed of 1 mm thickness was prepared using 70 to 90 mg of samples on the glass holder. Each sample was scanned between 5° and 60° (2θ) with a step size of 0.02°.

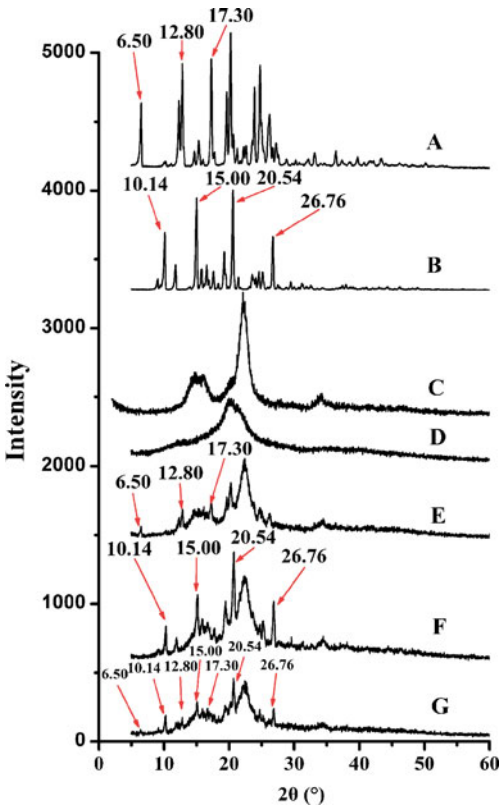

Fig. 2. XRPD results of NMD solid forms: *A* pure Mod. I, *B* pure Mod. II, *C* MCC, *D* L-HPC, *E* granules with pure Mod. I, *F* granules with pure Mod. II, *G* granules with Mod. I and II

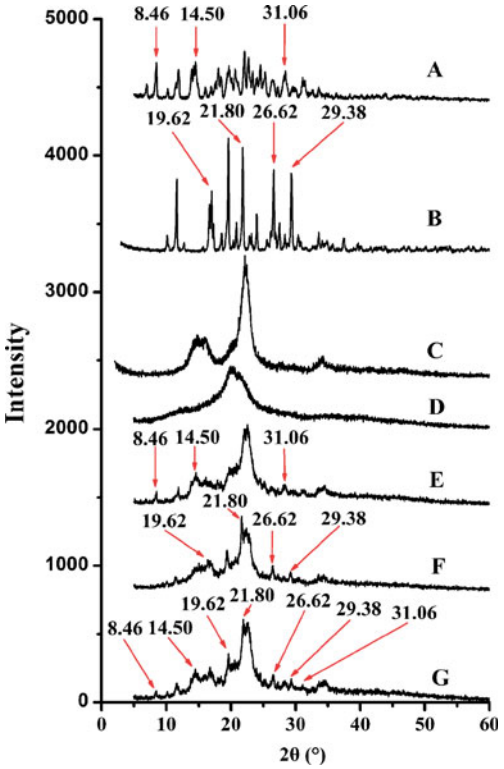

Fig. 3. XRPD results IMC solid forms: *A* pure α form, *B* pure γ form, *C* MCC, *D* L-HPC, *E* granules with pure α form, *F* granules with pure γ form, *G* granules with α and γ forms

Differential Scanning Calorimetry

Samples of 5 mg were carefully weighed into aluminum pans, and the pans were sealed with a pinhole on the top. The

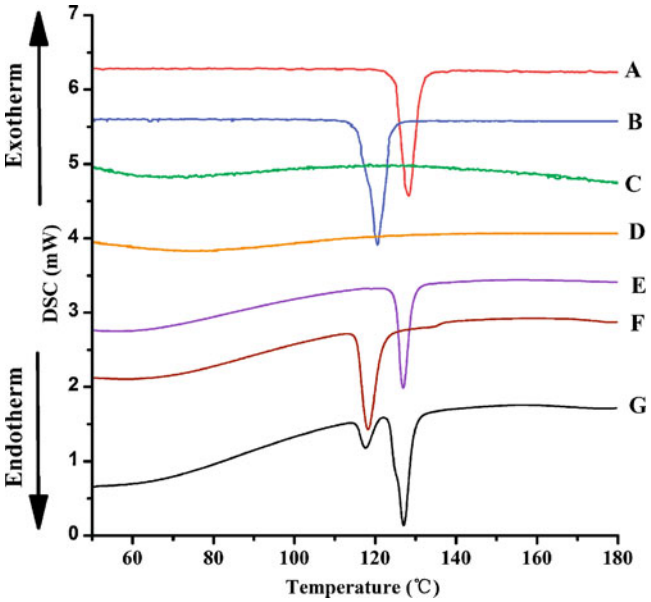

Fig. 4. DSC curve of IMC solid forms: *A* pure Mod. I, *B* pure Mod. II, *C* MCC, *D* L-HPC, *E* granules with pure Mod. I, *F* granules with pure Mod. II, *G* granules with Mod. I and II

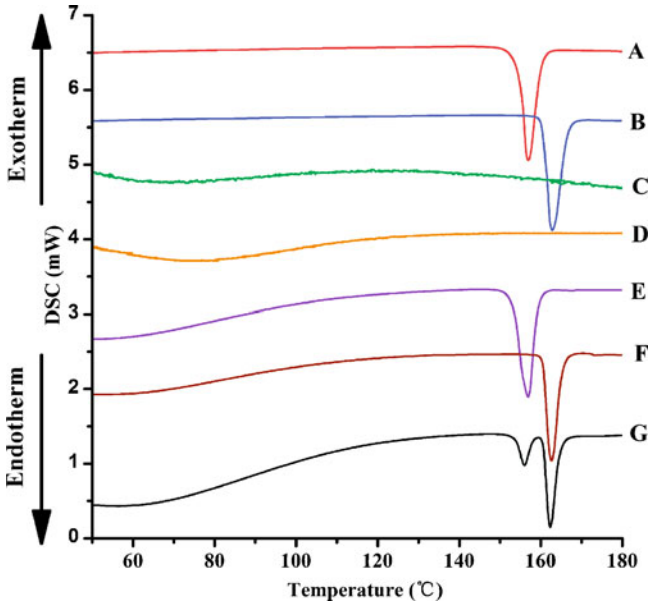

Fig. 5. DSC curve of NMD solid forms: *A* pure α form, *B* pure γ form, *C* MCC, *D* L-HPC, *E* granules with pure α form, *F* granules with pure γ form, *G* granules with α and γ form

amount of crystalline drug in the mixture was determined using a DSC-60 differential scanning calorimeter (DSC; Shimadzu Co., Japan) at a scan rate of 10°C·min^{-1} from 50°C to 180°C under a flow of dry N_2 gas (30 mL·min^{-1}). The content of each drug form was determined by measuring the heats of fusion of the polymorphs (15). The drug crystallinity, which was presented as the percentage of crystalline IMC remaining in the mixtures, was estimated using following equation (16):

$$C_x = \frac{A}{W_t \times S} \times 100\% \quad (1)$$

Where *C* is the drug crystallinity while the symbol x is used to define the polymorphic forms, e.g., Mod. I and Mod. II for nimodipine, and the α form and γ form for indomethacin. *A* is area under the melting endotherm, W_t is the amount of API in the mixture as measured by high-performance liquid chromatography (HPLC), and *S* is the slope of DSC calibration curve (also the heat of fusion). Each sample was performed in triplicate, and all data were evaluated statistically at 0.95 confidence interval.

High-Performance Liquid Chromatography Analysis

In order to reduce the potential errors from inhomogeneous agglomerating during the granulation process, the amount of drugs in the mixtures analyzed by DSC was measured by HPLC even though only a very small amount of sample was used (5 mg). The sample pan was cut open immediately after the DSC study, and the drug in the mixture was extracted with 10 mL mobile phase. After dilution, each sample was analyzed using a Hitachi 7100 HPLC system (Hitachi, Japan) with a Luna C18 column (20×4.6 mm, Merch, Phenomenex, CA, USA). The flow rate was 1 mL·min^{-1}, and the injection volume was 20 μL. The mobile phase was methanol, acetonitrile, and water (35:38:27, *v*/*v*/*v*), and the UV detector was set as 237 nm for NMD (17). For IMC, the mobile phase consisted of 0.1 mol·L^{-1} aqueous acetic acid and acetonitrile (50:50, *v*/*v*), and the wavelength was 228 nm (16).

RESULTS

Physicochemical Properties of Drugs and Granules

Figure 2 shows the X-ray powder diffraction profiles of the polymorphic forms of NMD and granulating excipients. The main XRPD peaks of Mod. I (Fig. 2a) were at 2θ=6.50°, 12.80°, and 17.30°, and those of the Mod. II (Fig. 2b) were at 2θ=10.14°, 15.00°, 20.54°, and 26.76°, as reported previously (18,19). The XRPD profile of the granules with pure Mod. I (Fig. 2e) showed peaks at 6.50°, 12.80°, and 17.30°; granules with pure Mod. II (Fig. 2f) showed peaks at 10.14°, 15.00°, 20.54°, and 26.76°, and granules with Mod. I and II (Fig. 2g) showed peaks at 6.50°, 10.14°, 12.80°, 15.00°, 17.30°, 20.54° and 26.76°, which were distinct from the excipients of MCC (Fig. 2c) and L-HPC (Fig. 2d). The results suggested that polymorphic drugs could be prepared by XRPD in the mixed pharmaceutical preparations.

Similar results are seen in Fig. 3a–g for IMC. The sharp XRPD peaks of the α form occurred at 2θ=8.46°, 14.50°, and 31.06°, and those of the γ form were at 2θ=19.62°, 21.80°, 26.62°, and 29.38° (15,20). These results demonstrated that polymorphic transformation of NMD and IMC occurred during the granulation process.

The DSC curves for polymorphs of NMD and IMC obtained using the previously reported preparation methods are shown in Figs. 4 and 5. The samples used for the XRPD were also used for the DSC analysis. The melting points and enthalpies of fusion of NMD and IMC are shown in Table II,

Table II. Physical Properties of Different Modifications of NMD and IMC (n=3, means±SD)

	Nimodipine		Indomethacin	
	Modification I	Modification II	α Form	γ Form
DSC onset temperature	124±1	116±1	152±1	159±1
Enthalpy of fusion (kJ·mol^{-1})	40.3±1.1	47.3±0.8	34.7±1.2	37.9±1.1
Stability	Metastable[a]	Stable[a]	Metastable[b]	Stable[b]

NMD nimodipine, *IMC* indomethacin, *SD* standard deviation, *DSC* differential scanning calorimetry
[a] Reported by reference (2)
[b] Reported by reference (21)

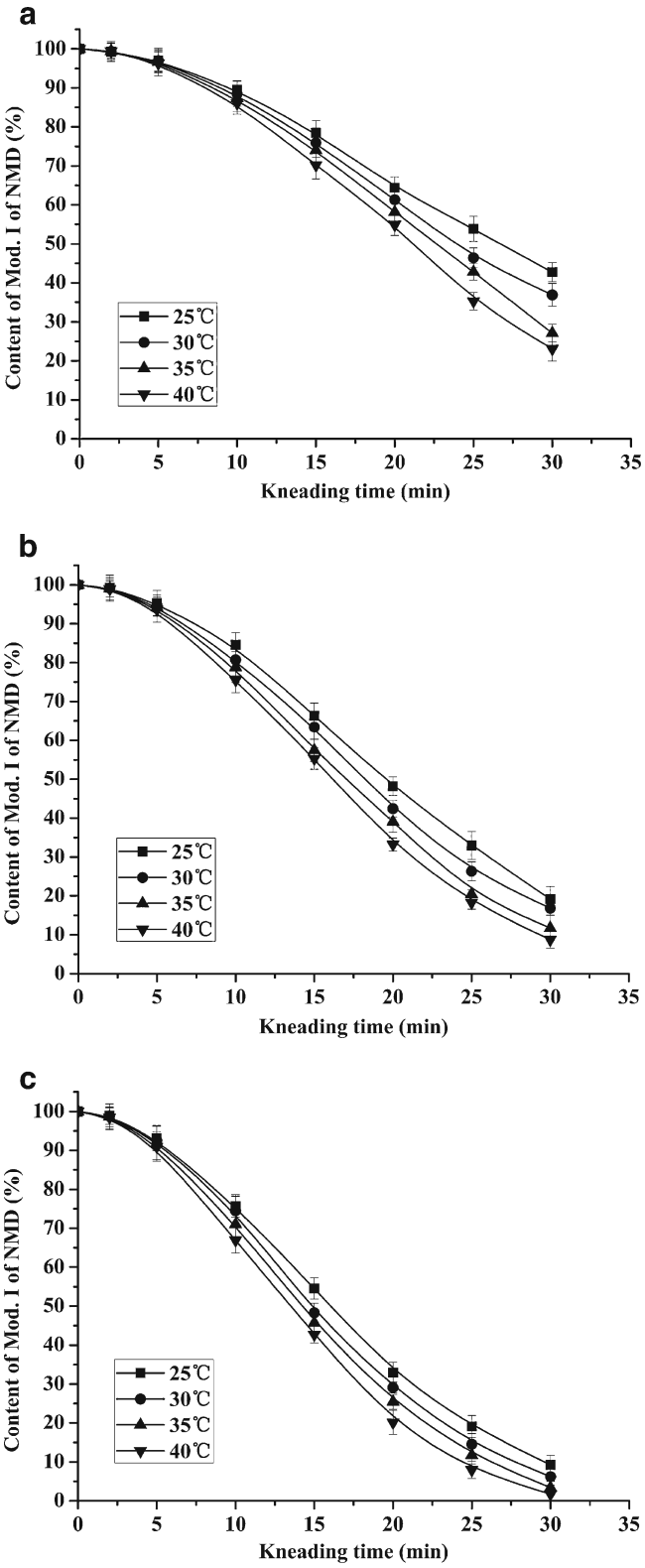

Fig. 6. Content of Mod. I of NMD during granulation process at various temperatures under different impeller speed, **a** 300, **b** 500, **c** 700 rpm. *Error bars* represent standard deviations (n=3)

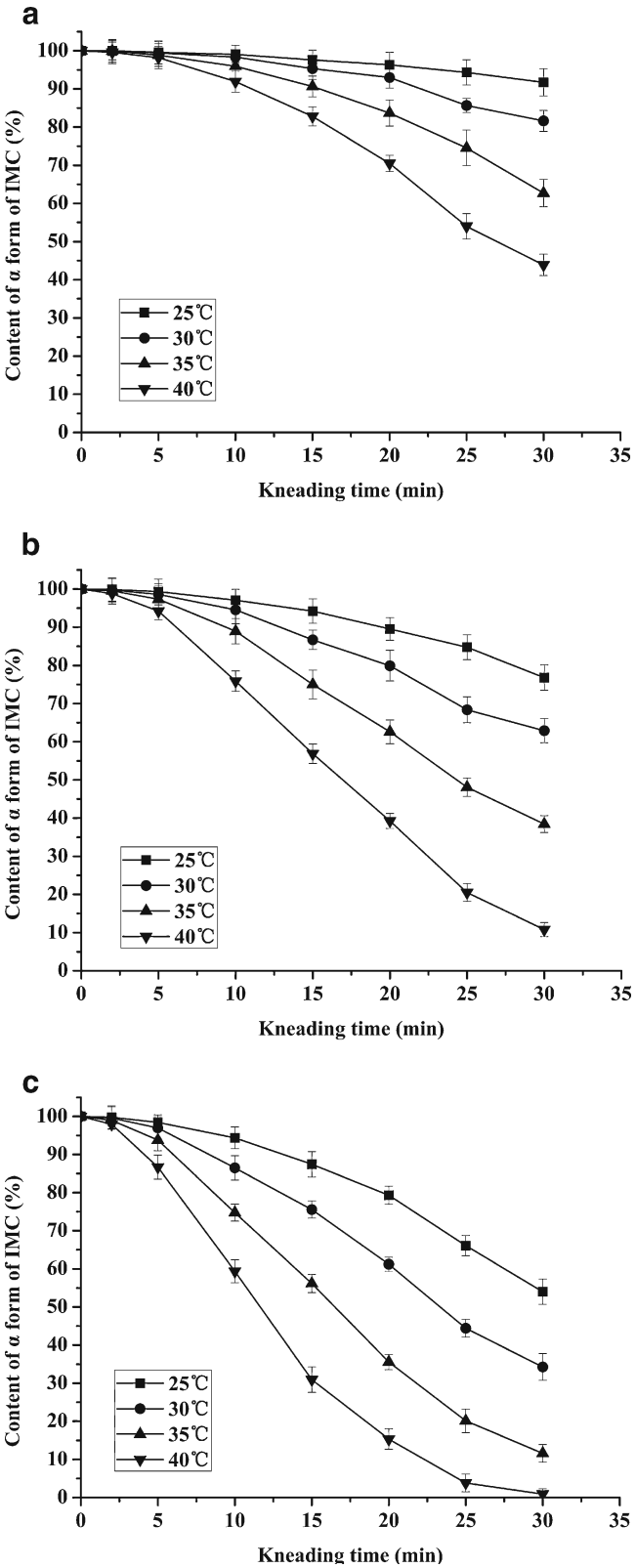

Fig. 7. Content of α form of IMC during granulation process at various temperatures under different impeller speed, **a** 300, **b** 500, **c** 700 rpm. *Error bars* represent standard deviations (n=3)

Table III. Kinetic Equations for the Most Common Mechanisms

Symbol	$g(x)$	m	Mechanism
R_1	x	1.24	Zero-order mechanism (Polany–Wigner equation)
R_2	$2[1-(1-x)^{1/2}]$	1.11	One-half order mechanism
R_3	$3[1-(1-x)^{1/3}]$	1.17	Two-thirds order mechanism
F_1	$-\ln(1-x)$	1.00	First-order mechanism
A_2	$[-\ln(1-x)]^{1/2}$	2.00	Two-dimensional growth of nuclei (Avrami equation)
A_3	$[-\ln(1-x)]^{1/3}$	3.00	Three-dimensional growth of nuclei (Avrami equation)
D_1	x^2	0.62	One-dimensional diffusion
D_2	$(1-x)\ln(1-x)+x$	0.57	Two-dimensional diffusion
D_3	$[1-(1-x)^{1/3}]^2$	0.54	Three-dimensional diffusion (Jander equation)
D_4	$(1-2x/3)-(1-x)^{2/3}$	0.57	Three-dimensional diffusion (Ginstiling–Brounshtein equation)

and these were similar to the reported values (2,21). The peaks of mixed polymorphic forms were completely separated from each other so that they could be quantitatively determined by DSC. The results indicate that Mod. II of NMD and the α form of IMC prepared in the present study were sufficiently pure for granulating and transformation kinetic studies.

Transformation Kinetics

Figures 6 and 7 show the transformation process of Mod. I to II of NMD and the α form to the γ form of IMC at 25°C, 30°C, 35°C, and 40°C under different impeller speeds. In order to analyze kinetically the calorimetric data for the polymorphic transitions, the theoretical kinetic method proposed by Hancock and Sharp was applied (22). In this method, when the range of x is limited to values from 0.15 to 0.50, the reaction mechanism is indicated by the value of m, the Hancock–Sharp constant, calculated as the slope of the following equation:

$$\ln[-\ln(1-x)] = \ln B + m \ln t (0.15 \le x \le 0.50) \qquad (2)$$

Where B is a constant, x is the content of drug transformed, and t is the granulating time. Table III lists the different theoretical equations of the solid-state kinetic model corresponding to the different values of m (23,24). The m values obtained from the Hancock–Sharp plots (ln [−ln (1-x)] *versus* ln$t$ plots) for NMD and IMC at 25°C, 30°C, 35°C, and 40°C under different impeller speeds are listed in Table IV. For NMD, the m values ranged from 1.92 to 2.04, and for IMC, it ranged from 1.94 to 2.06. It appears that both the transformation mechanisms of NMD and IMC involved the two-dimensional growth of nuclei (Avrami equation) which is similar to the reported results (6,24).

Effects of Granulating Temperature on Polymorphic Transformation

Figures 8 and 9 illustrate the plots of the kinetic model function $g(x)$ *versus* the granulating time of NMD and IMC,

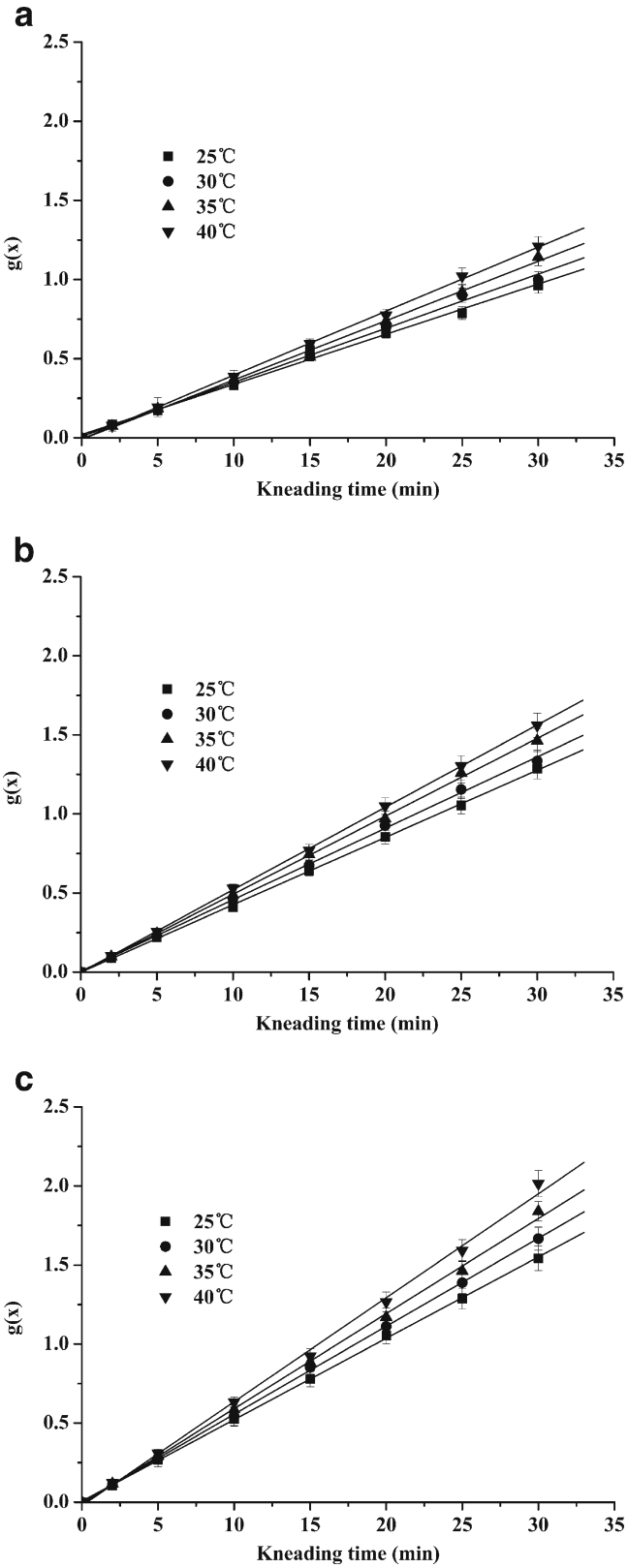

Fig. 8. Dependence of Mechanism function $g(x)$ on time for NMD at various temperatures under different impeller speed, **a** 300, **b** 500, **c** 700 rpm. *Error bars* represent standard deviations (n=3).

Table IV. Kinetic and Thermodynamic Parameters for the Transformation of NMD and IMC (n=3, means±SD)

		Nimodipine			Indomethacin		
Impeller speed (rpm)	Temperature (°C)	m	E_a (kJ·mol^{-1})	lg$A$	m	E_a (kJ·mol^{-1})	lg$A$
300	25	1.94	8.231±0.611	0.7311±0.0476	2.01	56.52±0.83	7.887±0.116
	30	1.99			2.03		
	35	2.04			1.98		
	40	2.01			1.96		
500	25	2.01	7.944±0.762	0.8743±0.0698	1.94	55.68±0.98	8.069±0.142
	30	2.04			1.95		
	35	1.92			1.96		
	40	1.98			2.02		
700	25	2.00	7.625±0.425	0.9178±0.0771	1.98	56.08±0.72	8.204±0.107
	30	2.02			1.99		
	35	1.95			2.06		
	40	2.02			1.94		

NMD nimodipine, *IMC* indomethacin

respectively. The rate constant of transformation (the slope of the linear regression line) increased with the granulating temperature. The plots of lg$k$ *versus* 1/T×10^3 are shown in Fig. 10 for NMD and IMC according to the Arrhenius equation:

$$\lg k = -\frac{E_a}{2.303R} \cdot \frac{1}{T} + \lg A \quad (3)$$

Where k is the rate constant, E_a is the activation energy, T is the absolute temperature, R is the gas constant, and A is a constant. The activation energies can be calculated from the slope, and these are listed in Table IV. The average activation energy of polymorphic transformation was 7.933 kJ·mol^{-1} for NMD and 56.09 kJ·mol^{-1} for IMC transformation, which is in accordance with the results obtained by other methods (2,6,25). The effect of temperature on IMC was more significant than that on NMD because of the high activation energy.

Effects of Impeller Speed on Polymorphic Transformation

As shown in Figs. 7 and 9, the transformation rate constant indicated a dependence on the impeller speed, and it increased significantly as the impeller speed increased. In the Arrhenius plot, the constant lg$C$ was determined by the impeller speed. Previous studies have reported that the process in which one form of NMD or IMC was completely transformed into another would require at least 10 h under storage conditions or immersed in the solvent (2,6). In the present study, the transformation process was completed within 30 min at 40°C under an impeller speed of 700 rpm. This may be due to the high shear stress produced by the impeller. Bauner-Brandl reported that mechanical stress, such as grinding and trituration, could induce a polymorphic transformation from a metastable form to a stable form (26). During the high shear granulation process, increasing the impeller speed means that more liquid is squeezed on to the granule surface, which increases the collision probability between the particles of API, excipients powders, and liquid droplets. As a result of this, not only the growth rate of granules but the rate of polymorphic transformation as well was accelerated by the higher shear stress (shown in Fig. 11).

Activation energy of polymorphic transformation is one of the inherent properties of crystals which is determined by the crystal structures of substances (25) and isolated from the external factors such as temperature (in a narrow range) and impeller speed. If the activation energy of an API was determined, the transformation rate could be calculated as a function of impeller speed at a certain temperature. Therefore, the transformation process of API in high-shear mixer could be predicted before granulation in order to better control the quality of the final products.

DISCUSSION

In a previous study, the transformation of drugs was described as a nuclei-induced process. Keneniwa showed that the dissolution rate of the γ form and the crystallization rate of the γ form of IMC in ethanol exhibited pseudo-equilibrium (6). The presence of 1% of the γ form could play an important role in the crystallization as a seed and accelerates the transformation process. However, during the granulating process, the amount of ethanol was not enough to dissolve all the API and, therefore, the transformation process could not be explained by the above hypothesis.

Former researchers described that the high shear granulation process could be divided into three phases, namely, nucleation, growth, and breakage (27,28). As shown in Fig. 11, the three phases could be easily identified by analyzing the change in mean granule size. In the nucleation phase (about the early 5 min of kneading duration), the primary nuclei were formed due to layering, and the liquid binder was embedded by the powder. As a result, the liquid was unable to make full contact with the drug so that the growth rate of granules and the drug transformation rate were low, which could be reflected by the slope of curves during the early 5 min in Figs. 6, 7, and 11 (29). The primary nuclei then break into secondary nuclei because of the action of the impeller and chopper. These small nuclei started to grow and coalescence rapidly when the solid mass was

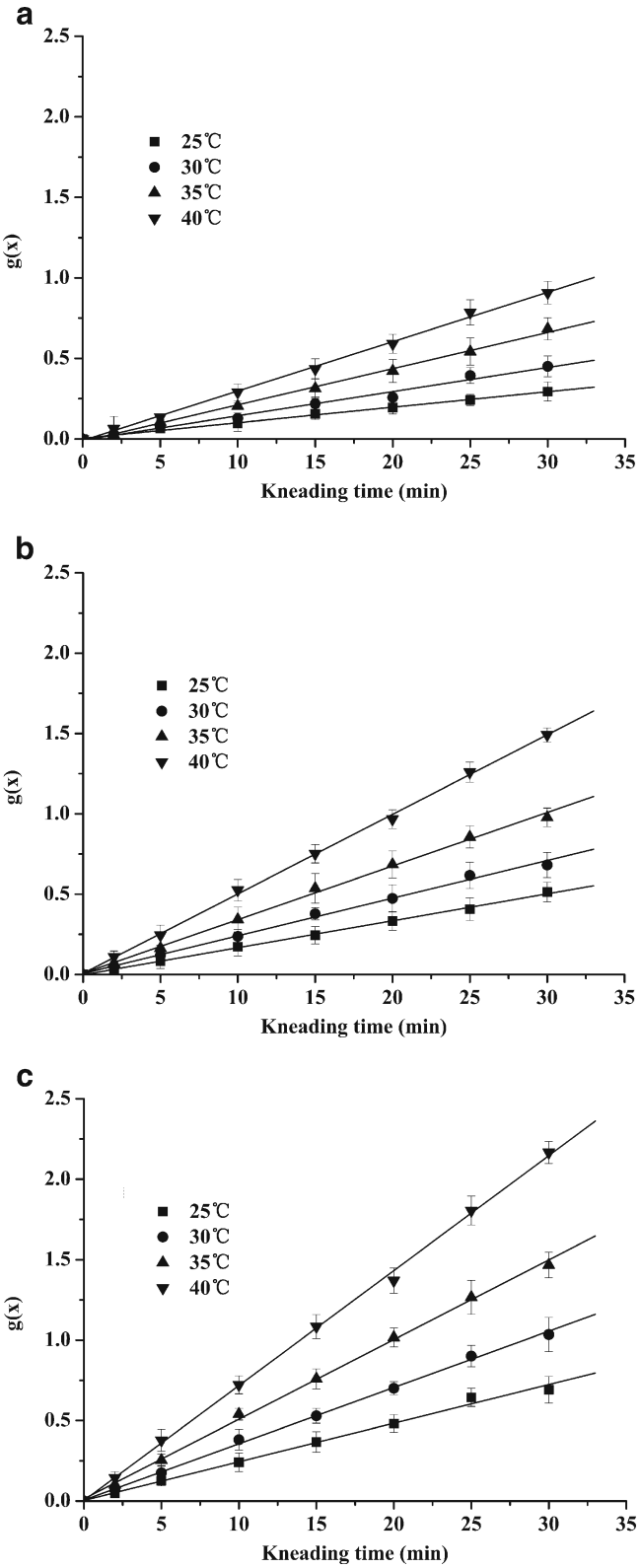

Fig. 9. Dependence of Mechanism function *g(x)* on time for IMC at various temperatures under different impeller speed: **a** 300, **b** 500, **c** 700 rpm. *Error bars* represent standard deviations ($n=3$)

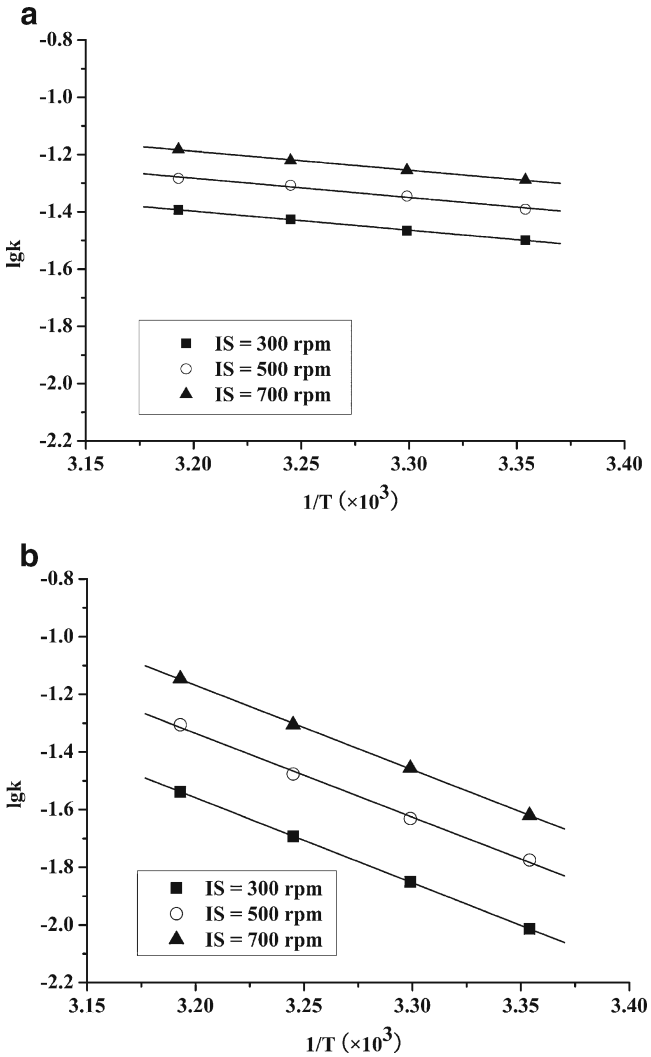

Fig. 10. Arrhenius plot for transformation under different impeller speeds: **a** Mod. I to II of NMD; **b** α form to γ form of IMC

sufficiently wetted, accompanied by a high drug transformation rate owing to the complete blending of drug and liquid binder, which was in accordance with the granulating time of between 5 to 20 min in Fig. 11. The granule growth stopped when no more liquid was applied after the kneading time of about 20 min (varying with impeller speed); meanwhile, the transformation rate also decreased during the last phase of high shear granulation.

By analyzing the function equations of the transformation mechanism listed in Table III, only the curve of two-dimensional nuclei growth equation displayed a similar shape to the granule growth curve with three phases as seen in the comparison of Figs. 6 and 8 with Fig. 11. From these findings, we can conclude that the polymorphic transformation of NMD and IMC during high shear granulation is depended on the granule growth process. For the high shear granulation process with potential probability of polymorphic transformation in industrial practice, granulating process parameters could be controlled and optimized in terms of the analysis of the polymorphic transformation kinetics.

CONCLUSIONS

The polymorphic transformation of NMD and IMC during high shear granulation has been investigated in the present

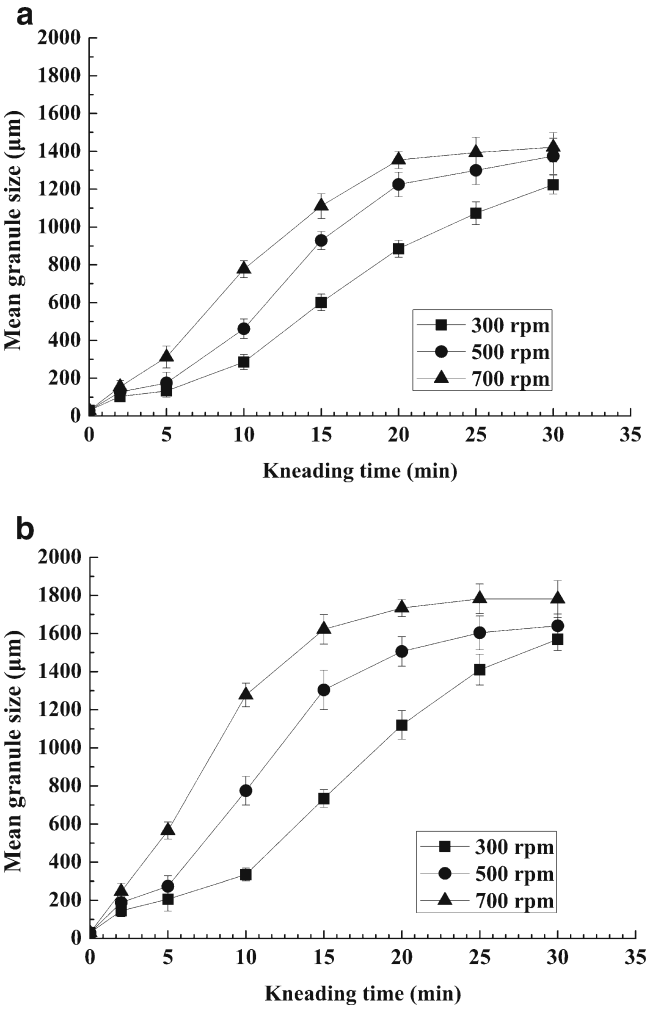

Fig. 11. Change of mean granule size during granulation process: **a** NMD; **b** IMC. *Error bars* represent standard deviations (n=3)

research. The results reported here demonstrate that Mod. I of NMD and α form of IMC would easily transform to Mod. II and γ form, respectively, which are thermodynamically stable modifications when agglomerating with ethanol solution. Both of the polymorphic transformation processes took place via an Avrami two-dimensional nuclei growth mechanism, and the activation energy was calculated to be 7.933 and 56.09 kJ·mol^{-1}, respectively. The transformation rate of the two substances was in proportion to the impeller speed as well as the granulating temperature; in particular, high shear stress could significantly accelerate the transformation process, and the effect of temperature was dependent on the activation energy. Combining with the result of granule growth mechanism, it is concluded that the polymorphic transformations of NMD and IMC are in accordance with the granule growth behavior in a high-shear mixer.

ACKNOWLEDGMENT

The authors would like to thank Collette N.V, Belgium, for supplying the MicroGral® high-shear mixers and for their logistic and technical support. This work was supported by the National Basic Research Program of China (973 Program; No.2009CB930300) and Major National Platform for Innovative Pharmaceuticals (No. 2009ZX09301-012).

REFERENCES

1. Haleblian J, McCrone W. Pharmaceutical applications of polymorphism. J Pharm Sci. 1969;58:911–29.
2. Grunenberg A, Keil B, Henck JO. Polymorphism in binary mixture, as exemplified by nimodipine. Int J Pharm. 1995;118:11–21.
3. Yamamoto H. 1-Acyl-indoles. II. A new syntheses of 1-(*p*-chlorobenzoyl)-5-methoxy-3-indolylacetic acid and its polymorphism. Chem Pharm Bull. 1968;16:17–9.
4. Joshi V. Physical transformations in solvated pharmaceuticals. Ph.D. Dissertation, Purdue University, West Lafayette, IN; 1998.
5. Wu T, Yu L. Origin of enhanced crystal growth kinetics near T_g probed with indomethacin polymorphs. J Phys Chem B. 2006;110:15694–9.
6. Kaneniwa N, Otsuka M, Hayashi T. Physicochemical characterization of indomethacin polymorphs and the transformation kinetics in ethanol. Chem Pharm Bull. 1985;33:3447–55.
7. Morris KR, Griesser UJ, Eckhardt CJ, Stowell JG. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv Drug Deliv Rev. 2001;48:91–114.
8. Zhang GG, Law D, Schmitt EA, Qiu YH. Phase transformation considerations during process development and manufacture of solid oral dosage forms. Adv Drug Deliv Rev. 2004;56:371–90.
9. Schæfer T, Holm P, Kristensen G. Melt pelletization in a high shear mixer. I. Effects of process variables and binder. Acta Pharm Nord. 1992;4:133–40.
10. Wang S, Ye G, Heng PWS, Ma M. Investigation of high shear wet granulation processes using different parameters and formulation. Chem Pharm Bull. 2008;56:22–7.
11. Schæfer T, Mathiesen C. Melt pelletization in a high shear mixer. VII. Effects of product temperature. Int J Pharm. 1996;134:105–17.
12. Voinovich D, Campsi B, Moneghini M, Vincenzi C, Phan-Tan-Luu R. Screening of high shear mixer melt granulation process variables using an asymmetrical factorial design. Int J Pharm. 1999;190:73–81.
13. Keningley ST, Knight PC, Marson AD. An investigation into the effects of binder viscosity on agglomeration behaviour. Powder Technol. 1997;91:95–103.
14. Schaefer T, Holm P, Kristensen G. Melt pelletization in a high shear mixer. III. Effects of lactose quality. Acta Pharm Nord. 1992;4:245–52.
15. Pan X, Julian T, Augsburger L. Increasing the dissolution rate of a low-solubility drug through a crystalline-amorphous transition: a case study with indomethacin. Drug Dev Ind Pharm. 2008;34:221–31.
16. Pan X, Julian T, Augsburger L. Quantitative measurement of indomethacin crystallinity in indomethacin-silica gel binary system using differential scanning calorimetry and X-ray powder diffractometry. AAPS Pharm Sci Tech. 2006;7:E72–8.
17. He Z, Zhong D, Chen X, Liu X, Tang X, Zhao L. Development of a dissolution medium for nimodipine tablets based on bioavailability evaluation. Eur J Pharm Sci. 2004;21:487–91.
18. Barmpalexis P, Kachrimanis K, Georgarakis E. Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic programming. Eur J Pharm Biopharm. 2011;77:122–31.
19. Murali Mohan Babu GV, Prasad CHDS, Ramana Murthy KV. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine. Int J Pharm. 2002;234:1–17.
20. Otsuka M, Kato F, Matsuda Y, Ozaki Y. Comparative determination of polymorphs of indomethacin in powders and tablets by chemometrical near-infrared spectroscopy and X-ray powder diffractometry. AAPS Pharm Sci Tech. 2003;4:1–12.
21. Aceves-Hernadez JM, Nicolás-Vázquez I, Aceves FJ, Hinojosa-Torres J, Paz M, Castaño VM. Indomethacin polymorphs: experimental and conformational analysis. J Pharm Sci. 2009;98:2448–63.

22. Hancock JD, Sharp JH. Method of comparing solid-state kinetic data and its application to the decomposition of kaolinite, brucite, and $BaCO_3$. J Am Ceram Soc. 1972;55:74–7.
23. Criado JM, Morales J, Rives V. Computer kinetic analysis of simultaneously obtained TG and DTG curves. J Thermal Anal. 1978;14:221–8.
24. Hirayama F, Wang Z, Uekama K. Effect of 2-hydroxypropyl-β-cyclodextrin on crystallization and polymorphic transition of nifedipine in solid state. Pharm Res. 1994;11:1766–70.
25. Grunenberg A, Henck JO, Siesler HW. Theoretical derivation and practical application of energy/temperature diagrams as an instrument in preformulation studies of polymorphic drug substances. Int J Pharm. 1996;129:147–58.
26. Bauer-Brandl A. Polymorphic transitions of cimetidine during manufacture of solid dosage forms. Int J Pharm. 1996;140:195–206.
27. Iveson SM, Litster JD. Growth regime map for liquid-bounded granules. AICHE J. 1998;44:1510–8.
28. Tu W, Ingram A, Seville J, Hsiau S. Exploring the regime map for high-shear mixer granulation. Chem Eng J. 2009;145:505–13.
29. Vonk P, Guillaume CPF, Ramaker JS, Vromans H, Kossen NWF. Growth mechanisms of high-shear pelletization. Int J Pharm. 1997;157:93–102.