Effect of screw profile and processing conditions on physical transformation and chemical degradation of gabapentin during twin-screw melt granulation

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A B S T R A C T
Twin-screw melt granulation (TSMG) was applied to process a powder blend consisting of 80% gabapentin (GABA) and 20% hydroxypropyl cellulose. The effect of screw profile and processing conditions on the process-induced transformation and chemical degradation of gabapentin was studied. When a neutral kneading block was used, gabapentin underwent polymorphic transformation. A forward kneading block in combination with processing under torque conditions was required to minimize chemical degradation and to inhibit polymorphic transformation of gabapentin. Both the size of the extruded granules and gabapentin degradant level correlated positively with the specific rate, the ratio between feed rate and screws speed. At higher specific rate, the barrel was filled to a greater extent. The material packing and compressive forces were enhanced, as proven by the increased rupturing of CAMES® sensor beads and GABA crystal size reduction. This resulted in more interaction between the powder particles and facilitated granule growth. Simultaneously, this also resulted in higher degradant level. To attain adequate tabletability, the specific rate must reach a threshold value. The development of an optimum TSMG process requires balancing processing parameters based on the physical and chemical stability of GABA as well as its tabletability.

1. Introduction

In pharmaceutical manufacturing, powder blends are commonly granulated in order to prevent material segregation, improve flow properties, and improve tabletability. Melt granulation is a water and solvent-free process where a molten binder at an elevated temperature enables granulation under shear followed by solidification when cooled to room temperature (Royce et al., 1996). Even though less commonly used than other granulation technologies, melt granulation offers unique advantages. In comparison to high-shear wet granulation and fluid-bed granulation, one major advantage of melt granulation is that solvent mediated chemical degradation (e.g., hydrolysis) and solid state changes (e.g., salt disproportionation) are avoided since no water or solvent is used (Kowalski et al., 2009) (Nie et al., 2017). Another major advantage of melt granulation is that the tabletability of granules is generally improved, which is in contrast to the usual deterioration in tabletability of granules prepared by dry granulation or high-shear wet granulation (Batra et al., 2017) (Shi et al., 2011; Sun and Kleinebudde, 2016).

Traditionally, melt granulation process is carried out in jacketed batch mixers, such as high-shear and fluid-bed granulators. During batch melt granulation, only low melting point binders, e.g., PEG 8000 and waxes, can be used because of the low mixing intensity and efficiency. At the same time, potential thermal degradation of drugs by the exposure to an elevated temperature during twin-screw extrusion is a major drawback, especially if the drug is thermal labile (Haser and Zhang, 2018). These low melting point binders, however, exhibit a limited ability to improve granule tabletability. Some thermoplastic binders, such as hydroxypropyl cellulose (HPC), can profoundly improve granule tabletability when coated on particle surfaces; however, they cannot be used in batch melt granulation because very high temperatures are required for successful granulation in the batch mode (Batra et al., 2017). However, they can be used in twin-screw melt granulation (TSMG) because, in addition to heating by the barrel, frictional and viscous heat dissipation occurs at the particle-particle or particle-screw/barrel contact surfaces driven by the rotating screws (Kittikunakorn et al., 2018). Consequently, the elevated temperature from frictional and viscous heat dissipation happens at local contact points instead of the whole powder bed. This makes it possible to...
granulate powders without exposing bulk powder to an excessively high temperature. In addition, the short residence time (usually < 30 s) during TSMG further reduces any possible thermal degradation (Mu and Thompson, 2012). One commercial product that involves TSMG in its manufacturing is Eucreas™ where TSMG of metformin-hydroxypropyl cellulose (HPC) granule was used for making immediate-release tablets (Lakshman et al., 2011). In this case, TSMG was used because it is more effective than wet granulation and roller compaction in improving the flowability and tabletability of metformin.

As an inherently continuous process, TSMG can be readily integrated into the continuous manufacturing of pharmaceutical dosage forms. With the recent surge of interest in continuous manufacturing (Lee, 2017), TSMG has attracted much attention. The commercial successes discussed earlier highlight the potential of TSMG in pharmaceutical manufacturing. However, clearer understanding of TSMG through systematic studies is needed for the pharmaceutical industry to fully embrace this granulation process (Monteyne et al., 2016b).

Despite the clear advantages TSMG offers, one major concern that slows its adoption by the pharmaceutical industry is the potential chemical and physical instability of drug substances during TSMG. Chemical stability of drug substance has not been extensively studied in the context of TSMG. Polymorphic changes during TSMG have been reported but have not been systematically correlated with processing conditions (Monteyne et al., 2016a). Hence, there is a need for systematic understanding of the level of risks in chemical degradation and solid form change to facilitate a broader adoption of TSMG by the pharmaceutical industry.

During TSMG, drug substance could undergo process-induced form transformation via kinetic trapping and relaxation mechanisms (Morris et al., 2001). A metastable form of drug becomes stable inside the barrel under the conditions induced by the mechanical and thermal stresses. Upon exiting the extruder barrel, this metastable form should “relax” to a stable form at ambient conditions, thermodynamically speaking. However, the time course of this relaxation depends on the characteristics of the process at the molecular level. If the cooling of the granules is fast, drug might be kinetically trapped as metastable form following TSMG. Processing-induced transformations of drug crystals during pharmaceutical manufacturing are well known but difficult to predict or control.

This study is aimed at mechanistically understanding the effect of screw profile and processing conditions on polymorph transformation and chemical degradation during TSMG, using gabapentin (GABA)-hydroxypropyl cellulose (HPC) as a model formulation (Fig. 1). GABA is used here because it undergoes both chemical degradation (Fig. S1) and solid form changes at elevated temperatures (Hsu et al., 2010; Zong et al., 2011). The selection of HPC as a thermoplastic binder is based on its effectiveness in improving tabletability (Picker-Freyer and Dürig, 2007). HPC is an amorphous thermoplastic polymer with a glass transition temperature of about 20 °C (Rials and Glasser, 1988).

2. Materials and methods

2.1. Materials

Gabapentin (GABA, Form II) was purchased from Shenzhen Nexconn Pharmatechs (Shenzhen, China). GABA has water solubility of 100 mg/mL at 25 °C and a melting point of 174 °C. Hydroxypropyl cellulose (HPC, Klucel® EXF) was a gift from Ashland Inc. (Wilmington, DE). All other chemicals were of ACS grade or higher. Calibrated Microencapsulated Sensor (CAMES) beads (Mach 1 Inc., King of Prussia, PA) were used to measure the mechanical stress inflicted onto formulation during melt granulation. The CAMES beads in the size range of 54–63 μm and rupture shear stress of 330 kPa were used in this work. A powder consisting of 80% (w/w) GABA and 20% (w/w) HPC was prepared by mixing with 25 rpm for 10 min using a Turbula® Shaker-Mixer (Glen Mills, Clifton, NJ).

2.2. Twin-screw melt granulation

All extrusion experiments were performed on a co-rotating twin screw extruder (Nano-16, American Leistritz Extruder Corp., Somerville, NJ), where tri-lobal screw elements were used. A twin-screw volumetric feeder (Brabender Technologie, Ontario, Canada) was used to control the powder feed rate. The barrel was divided into four zones. The feeding zone was maintained at room temperature with water circulation. The barrel temperatures at zones 1, 2, and 3 were set at 70 °C, 110 °C and 110 °C, respectively. The barrel temperature was selected based on the soften temperature of HPC at 100–120 °C. The extruder was operated without a die using screw designs detailed in Fig. 2. The feed rate and screw speed were systematically varied as needed (Table 1). Both barrel temperature and torque were monitored throughout the study. Each sample was collected when steady torque and barrel temperature were attained (usually around 5 min after parameters were adjusted). As granules were exiting the barrel, their temperature was measured using a visual infrared thermometer (Fluke®, VT04A, FLUKE, Everett, WA) that blends a visual image with infrared heat map overlay. The distance between the thermometer and granules was kept at 5 cm.

2.3. Granule size distribution

Granule size distribution was characterized using a Dynamic Image Analyzer (Retsch Camsizer® P4, V.4.2.1., Haan, Germany). Approximately 10 g of granules was poured into the feeder of the instrument. Images of the falling granule were captured by a camera (CCD-Basic and CCD-Zoom) with an image rate of 100% (60 images per second). The covered area of the image at which the measurement was included was 2%. The feeder control level for advancing the material from the funnel to the shaft prior to image acquisition and feeder start value for the measurement were set at 65 and 55, respectively.
2.4. Tabletability of melt-extruded granules

The size of granules collected following granulated in twin screw extruder were reduced with a co-mill (Quadro comil, U5-0516, Ontario, Canada). A screen with round holes (0.032 in.) and an impellers speed of 1000 rpm were used for all formulations. Granules between 250μm to 850μm (60–20 mesh) were collected and mixed with 0.5% magnesium stearate in a Turbula® Shaker-Mixer (Glen Mills, Clifton, NJ) at 25rpm for 3min. The tablets (350 ± 5mg) were compressed with a manual tablet compression machine (MTCM-I, Globe pharma, NJ, USA) using flat-faced, round (11mm diameter) tooling. Tablethardness, thickness, and diameter were recorded, and the tensile strength (MPa) of the tablets from each formulation was calculated using the equation:

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TS = \frac{2F}{\pi DH}
\]

(1)

where F, D and H denote the tablet hardness (N), tablet diameter (mm) and tablet thickness (mm), respectively. The compression force ranged from 3 to 12 kN. A total of 5 tablets were prepared and tested under each set of conditions.

2.5. HPLC analysis of GABA and its degradant

GABA granules were stored in a desiccator at ambient conditions prior to analysis. GABA and GABA-L contents were analyzed with a Thermo Scientific Dionex Ultimate 3000 HPLC system (Thermo Scientific, Sunnyvale, CA, USA). An Ultimate 3000 autosampler was utilized to inject 20-μl samples. The HPLC system also included dual Ultimate pumps and an Ultimate RS variable wavelength detector operating at 210nm. The mobile phase consisted of 60% (v/v) water, 30% (v/v) methanol and 10% (v/v) acetonitrile. An isocratic flow at 0.8mL/min was used. Injections were passed through an Inertsil® ODS-2, C18 reverse phase column, 4.6 × 150 mm, with 5μm packing, (GL Sciences Inc., Japan) kept at room temperature. The retention times of GABA and GABA-L were approximately 3.2min and 12.8min, respectively. The standard and sample solutions were diluted using highly purified water to achieve GABA concentrations in the linear range of the calibration curve (0–10mg/mL). Diluted solutions were sonicated and filtered through a 0.45μm Nylon membrane prior to HPLC analysis. Chromeleon Version 6.80 software (Thermo Scientific, Sunnyvale, CA, USA) was used to process all chromatography data. The LOD and LOQ of GABA-L were 0.03 and 0.08μg/mL, respectively.

2.6. Particle size of gabapentin in melt-extruded granules

To determine the particle size of GABA in the TSMG granules, granules were dispersed in acetone, which does not dissolve GABA but readily dissolves HPC. GABA particles were then analyzed on a laser
diffraction sizer (Sympatec Helos, Sympatec GmbH, Germany), equipped with a dispersing cuvette and an R3 lens. A background measurement was taken with the blank acetone medium in the cuvette. Each GABA dispersion in acetone was added to the cuvette drop-wise until the light obscuration was in the range of 10–25%. Light diffraction data was then collected for 100 ms.

2.7. FT-IR analysis

FT-IR analysis was performed to determine the polymorphic form of GABA in the physical mixture and granules using a Thermo Nicolet iS50 spectrometer (ThermoFisher Scientific, Waltham, MA) equipped with an attenuated total reflection accessory. Each sample was placed on the germanium crystal surface compressed using the built-in pressure tower to achieve uniform contact between the solid and the crystal. The samples were analyzed at room temperature with the following settings: 4000–600 cm⁻¹, 64 scans, and a resolution of 4 cm⁻¹. The peak positions were determined using OMNIC software peak picking function (ThermoFisher Scientific, Waltham, MA).

2.8. Powder X-ray diffraction (PXRD)

The polymorphic form of GABA in the physical mixture and granules was determined by using a Rigaku Miniflex 600 (Rigaku Americas, The Woodlands, Texas, USA) instrument equipped with a Cu-Kα radiation source generated at 40 kV and 15 mA. Samples were scanned in continuous mode with a step size of 0.025° over a 2θ range of 5° to 45° at a rate of 2.5° min⁻¹. Data was analyzed by MDI Jade 9 software.

3. Results and discussion

The effect of screw profile, specifically the geometry of kneading block, on process-induced transformation of GABA was investigated initially. Upon the selection of an optimal screw profile, the effects of processing conditions, including screw speed and feed rate, on GABA granule size, polymorphic form, chemical stability, crystal defect, and tabletability were studied.

3.1. Effect of screw profile (kneading block)

All four known GABA polymorphs have extensive networks of hydrogen bonding between NH₃⁺ and COO⁻ groups of neighboring zwitterionic GABA in crystals. Form I is a monohydrate and forms II through IV are anhydrous. GABA Form II used in this study is the most stable form at ambient condition. GABA Form II is known to undergo a form change and chemical degradation simultaneously under heating (Hsu et al., 2010). Since GABA was subjected to elevated thermal and mechanical stresses during TSMG, it was pertinent to assess potential processing-induced physical and chemical changes of GABA.

To study the effect of screw profile, we focused on the kneading-block screw geometry, since kneading blocks impose the most intense mixing, thermal stresses, and mechanical stresses on the materials. At kneading blocks, pressure traps are formed to squeeze, shear, and elongate the powder blend, leading to powder agglomeration (Thiele, 2018). It was observed in our previous study that granulation, chemical degradation, and size reduction of drug crystals for GABA-HPC formulations took place predominately at the kneading block.
Fig. 2 illustrates two screw profiles. The processing parameters for these two runs (runs 1 and 2) can be found in Table 1. Both screw profiles consist of forward-conveying and kneading elements. The design of the screw profile was based on the results from our prior study (Kittikunakorn et al., 2019) and it was intended to minimize GABA degradation. Large-pitch conveying elements were used in this study since small-pitch conveying element resulted in higher degree of fill and greater GABA degradation in our prior study. Kneading elements were positioned at zone 3 so that granules exit the barrel immediately following the granules formation. The only difference between these two screw profiles is the geometry of the kneading elements (60° neutral KB7-3-15-60-N for profile A vs. 30° forward KB7-3-15-30 for profile B). These two types of kneading elements have different stacking angles between adjacent discs. A 60° stacking angle functions as a neutral element which conveys material neither forward nor reverse, while a 30° stacking angle indicates a forward conveying element. Therefore, a 60° kneading block provides more dispersive and distributive mixing than a 30° kneading block. As shown in Table 1, the extrusion torques were 650 and 1300 G·m for screw profiles containing 30° and 60° kneading blocks, respectively. Correspondingly, higher thermal and mechanical stresses were anticipated with a 60° kneading block.

GABA polymorphs differ in the region of 1700–1500 cm⁻¹ in their FT-IR spectra. The peak at 1615 cm⁻¹ is the characteristic band of C=O stretching vibration of COO⁻ group and the peak at 1546 cm⁻¹ is from N–H scissoring vibration of NH₃⁺ group. In the spectrum for the melt-extruded GABA granules using 60° kneading block (Fig. 3A), C=O peak shifted to a higher wave number (from 1615 to 1620 cm⁻¹), N–H peak shifted to a lower wave number (from 1546 to 1522 cm⁻¹), and a new strong peak appeared at 1571 cm⁻¹. These FTIR peaks correspond to the characteristic peaks of GABA form IV. Thus, conversion of Form II to Form IV took place during TSMG when a 60° kneading block was used. The results from FT-IR analysis were supported with those from XRPD analysis (Fig. 3B). With 60° kneading blocks, the characteristic diffraction peak of Form II at 7.3° 2θ angle was absent in the XRPD pattern of melt-extruded granules, while the characteristic diffraction peak of Form IV at 6.3° was observed (Hsu et al., 2010). In comparison, these changes were absent in FT-IR spectra and XRPD patterns of granules prepared using the 30° kneading blocks. We attributed the solid form change associated with the use of 60° kneading blocks to the higher thermal and mechanical stresses arising from higher frictional and viscous heat dissipation. Based on these findings, the screw profile 30° containing kneading blocks (Fig. 2b) was used for the remainder of the study (runs 3 through 16, Table 1).

GABA form IV becomes stable inside the barrel under the conditions induced by the mechanical and thermal stresses. Upon exiting the extruder barrel, form IV should “relax” to form II at ambient conditions, thermodynamically speaking. However, the cooling of the granules was so fast that GABA was kinetically trapped as metastable form IV following TSMG.

(Kitikunakorn et al., 2019).
3.2. Effect of processing condition on the physicochemical properties of GABA granules

The effects of processing condition on the granule attributes, such as size, shape, and strength have been studied (Liu et al., 2018; Monteyne et al., 2016b). However, the effect of processing conditions on the chemical stability and polymorphic transformation has not been systematically investigated.

To evaluate the effect of processing conditions on the properties of GABA granules, twin-screw melt granulation was carried out using screw profile B (Fig. 2). The highest torque used in this part of the study was 750 G·m because > 0.4% GABA-L impurity content accepted by USP and process-induced transformation were observed when the torque exceeded 1200 G·m.

One of our objectives is to identify a correlation between physicochemical properties of GABA granules and processing parameters. A twin-screw process can be defined using machine parameters and system parameters. Machine parameters, e.g., feed rate, screw speed, and screw profiles, can be controlled directly. System parameters, such as specific mechanical energy, shear rate, and specific rate, are functions of both the machine parameters and material properties. System parameters are machine independent. Certain system parameters should be kept the same during process scale-up in order to achieve the same quality attributes (Haser et al., 2018).

3.2.1. Effect of screw speed and feed rate on GABA granule size

Full factorial designs of experiment were performed by three feed rates (5, 7.5 and 10 g/min) and four screw speeds (100, 150, 200 and 300 rpm) as shown in (Table 1). When other things are equal, granule size increased with an increase in feed rate or a decrease in screw speed (Fig. 4). This may be explained by considering the specific rate, the ratio between feed rate and screw speed. As a very useful system parameter to describe twin-screw extrusion, specific rate indicates the degree of the available barrel volume filled by the powder. It strongly influences compressive/shear stresses applied to the formulation. At a higher specific rate, the material packing and compressive forces between the screws were higher. As a result, the more extensive interactions between the powder particles, or the yet developed granules, led to greater extend of granule growth. A sigmoidal correlation between the granule size and the specific rate is observed in this work (Fig. 5). Similar effects of screw speed and feed rate were reported for metformin-HPC granules prepared using TSMG (Lakshman et al., 2011).
3.2.2. Effect of screw speed and feed rate on both polymorphic form stability and disorder of GABA crystals

When compared to the physical mixture, no changes in GABA solid form were detected in TSMG granules prepared using different feed rates and screw speeds by both FT-IR and XRPD techniques. Representative FT-IR spectra and XRPD profiles of granules prepared at the lowest and highest specific rates are shown in Figs. S2 and S3, respectively.

As the result of thermal and mechanical stresses during TSMG, amorphous GABA and disordered GABA crystal lattice in GABA granules may have a significantly negative impact on the physical and chemical stability of GABA (Adrjanowicz et al., 2011) (Fukuoka et al., 1986). Greater molecular mobility in amorphous materials and disordered crystals allows for greater and faster chemical degradation (Makoto and Nobuyoshi, 1990).

3.2.3. Effect of screw speed and feed rate on GABA chemical stability

GABA undergoes intramolecular cyclization to form beta-lactam (GABA-L) at elevated temperatures (Fig. S1). GABA-L is a genotoxic impurity with a USP specification of less or equal to 0.4%. The thermal stress during melt granulation could lead to GABA degradation. Even though heat did conduct from the barrel to granules, the primary source of thermal stress in TSMG is from the dispersive and distributive mixing of the rotating screws, which generates thermal stress via viscous and frictional heat dissipation. As a result, the temperature of GABA granules ranged from 120 to 130°C, 10 to 20°C higher than the barrel temperature of 110°C.

GABA-L content in the melt-extruded granules was affected by both machine parameters, i.e., screw speed and feed rate, and was higher at a higher feed rate and lower screw speed (Fig. 6). Another process parameter, specific mechanical energy (SME), may be potentially used to correlate with GABA-L level. SME represents the amount of power generated by the motor that input into each kg of the material.

Fig. 7. Relation between GABA-L content of melt-extruded GABA granules and system parameters of melt extrusion. (A) Specific mechanical energy, and (B) specific rate. Data presented is the average of three samples.
processed. SME can be calculated using Eq. (2).

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SME = \frac{KW \text{ (motor rating)} \times \text{Torque} \times \frac{\text{RPM running}}{\text{RPM max}}} {\text{Feed Rate} \left( \frac{\text{kg}}{\text{hr}} \right)} \times 0.97 \text{ (gear efficiency)}
\]

For amorphous solid dispersions, higher levels of degradation generally correlate with higher SME, as in the meloxicam and copovidone formulation (Haser et al., 2017). However, there was no clear correlation between GABA-L level and SME (Fig. 7A). Instead, a positive roughly linear correlation between GABA-L level and specific rate is observed (Fig. 7B). This correlation may be explained in the same way as the observed correlation between granule size and specific rate (Fig. 5). In Fig. S4, GABA-L level was plotted as a function of granule size to further illustrate that the same mixing mechanisms contributed to both the granule growth and GABA degradation. Heating of the formulation is required for both granule growth and GABA degradation. Both frictional heat dissipation and heat conducted from the barrel contributed to the heating of the formulation. At a higher specific rate, the degree of fill was higher. As a result, the heat transfer from the barrel to the formulation became more efficient. Our hypothesis is that heat conducted from the barrel played a very significant role in the current melt granulation process.

Particle sizes of GABA crystals in the melt-extruded granules may be used to probe the mechanical stresses during TSMG, as higher mechanical stresses likely cause more GABA crystal fracture and size reduction. Particle size distribution profiles of extracted GABA crystals in melt-extruded granules prepared at the lowest (5 g/min and 300 rpm) specific rates were the same as GABA drug substance (Fig. 8), indicating minimal mechanical stress during TSMG. In contrast, D_{50} of GABA dropped from 64 μm to 18 μm at the highest specific rate at 10 g/min and 100 rpm (Fig. 8), which clearly indicated that GABA was subjected to higher mechanical stress. Following a significant drop initially, GABA D_{50} did not significantly decrease once the specific rate reached 0.03 g/min/rpm (Fig. 9). This implies that the critical brittle-ductile transition size of GABA is 10–20 μm under the conditions employed in this work (Kendall, 1978). At or below the critical size, reduction of GABA by crack propagation is impossible.

The effect of specific rate on the mechanical stress during TSMG was confirmed using CAMES beads. CAMES beads are microcapsules consisting of a cross-linked polymeric shells with dye-containing cores manufactured using a coacervation process. Calibrated shear stress.
levels of CAMES beads are provided by the manufacturer. When mechanical stresses during TSMG exceed the strength of the shell, CAMES beads rupture to release the encapsulated AUTOMATE blue 8A dye. CAMES beads have been used to measure stress distribution during twin-screw polymer compounding (Balakrishnan et al., 2017). CAMES beads (54–63 μm in diameter, 330 kPa strength) were incorporated into GABA-HPC blend at 1% level. Once the extrusion reached a steady state, the extruder was stopped, and the screws were pulled out immediately. GABA granules were sampled at different axial positions and the concentration of the released dye in GABA granules was measured using LC-MS. As mentioned before, GABA degradation occurred predominantly over the kneading blocks. CAMES beads rupture continuously along the axial direction of the screw under both the lowest (5 g/min and 300 rpm) and highest (10 g/min and 100 rpm) specific rates. 80% of beads rupture even prior to entering the kneading block at the highest specific rate, while a maximum of 40% of beads ruptured at the lowest specific rate (Fig. 10). Thus, mechanical stresses are on average greater at higher specific rate. However, the impurity profile (Fig. 10A) increased exponentially as compared to the linear increase of the percentage of rupture for CAMES sensor (Fig. 10B). It was hypothesized that the degradation of GABA might not occur until the shear stress reached a threshold.

3.2.4. Effect of processing condition on the tabletability of GABA granules

The primary motivation of GABA TSMG is to improve its tabletability since GABA exhibits poor tabletability and is a high dose drug (Jagdale et al., 2010). We had previously shown that the surface of TSMG GABA-HPC granules is enriched by HPC (Kittikunakorn et al., 2019). This spatial arrangement of HPC is expected to significantly improve tabletability of GABA granules as surface modification is extremely effective in improving powder compaction properties (Shi and Sun, 2010).

The tabletability, i.e., tablet tensile strength as a function of compression pressure, of the TSMG granulates (20–60 mesh) prepared at the highest specific rate is significantly higher than those of the physical mixture and the granule prepared at the lowest specific rate (Fig. 11A). Tablets with tensile strength of equal to or > 2 MPa are considered to have sufficient mechanical strength (Osei-Yeboah and Sun, 2015). By this measure, the tabletability of GABA granules processed at the lowest specific rate (5 g/min and 300 rpm) physical blend is deficient, since
tensile strength barely reached 1 MPa at the highest pressure of 120 MPa used in this study (Fig. 11A). Granules prepared at the highest specific rate (10 g/min and 100 rpm) could reach 2 MPa tensile strength even at 60 MPa. The significantly improved tabletability of the granules prepared at the highest specific rate is attributed to the efficient spreading and coating of HPC on the GABA surface, which was inadequate at the lowest specific rate. In Fig. 11B, when plotted against specific rate, the tensile strength of tablets at 100 MPa compaction pressure for all granules jumped to above 2 MPa when the specific rate reached 0.03 g/min/rpm. This corresponds to change in GABA crystal spreading (Fig. 9). Therefore, the smaller GABA size likely also contributed to the improved tabletability at the highest specific rate. With further increase in the specific rate, the tensile strength of tablets distributed in a range of 2.2 to 3.3 MPa. Therefore, the tabletability enhancement was robust once the threshold specific rate was reached.

4. Conclusions

Process-induced transformation and chemical degradation of gabapentin during TSMG have been investigated using a formulation containing 20% HPC Klucel EXF. The 60° neutral kneading block led to significantly higher thermal and mechanical stresses, which caused more significant GABA conversion from form II to form IV. The usage of a 30° forward kneading block in combination with a low extrusion torque was required in order to prepare GABA granules with no polymorphic transformation and good chemical stabilities (GABA-I level below 0.15%). Under these machine parameters, a higher specific rate was found to lead to larger extruded granules, smaller GABA crystals, and higher tabletability, but also higher degradant content in GABA granules. This was attributed to the higher mechanical stresses at higher specific rate, which was proven using CAMES sensors. Thus a successful TSMG process requires a balance between achieving sufficient granule growth to improve tabletability, process-induced form change, and chemical degradation of GABA.

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Appendix A. Supplementary data

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