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Assessment of amorphization behavior of a drug during co-grinding with an amino acid by discrete element method simulation

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ABSTRACT

The amorphization of indomethacin (IMC) with cystine (Cys2) was studied by discrete element method (DEM) simulations and principal component analysis (PCA). X-ray powder diffraction (XRPD) analysis suggested that the conversion of crystalline IMC to amorphous state was accelerated by co-grinding with Cys2. XRPD spectra about amorphization of IMC with Cys2 were analyzed by PCA. PCA results suggest that IMC/Cys2 system undergoes two-phase amorphization, as indicated by the 2nd PC score, and that the change in phase depends on the total frictional energy calculated by DEM simulations. Electron spin resonance result revealed that the radical from Cys2 may be related to the amorphized progression of IMC.

Introduction

New drug candidates tend to have low solubility, and currently over 75% of drug candidates fall into Class II of the Biopharmaceutics Classification System (BCS) [1]. Low solubility limits the therapeutic efficacy of these drug candidates. Several approaches to addressing this problem have been reported [2,3]. Although salt formation and co-crystallization greatly improve solubility and dissolution profiles, ideal salt candidates are difficult to identify for drug candidates that contain ionic bonds. In contrast, amorphization is theoretically applicable to all drugs, where the dissolution rate of disordered drugs could be enhanced by their increased energy [4]. The amorphous state can be produced in several ways, such as vapor condensation, supercooling liquid, precipitation from solution, and disruption of the crystalline lattice [5]. The high-energy state of a compound is chemically and physically unstable, resulting in re-crystallization or the generation of impurities during storage [6]. These drawbacks are being addressed using amorphous solid dispersion techniques for formulating poorly water-soluble drugs [7]. In an amorphous solid dispersion, solid mixtures of an amorphous drug and a large polymer prevent the precipitation or crystallization of the amorphous drug from a supersaturated state [8]. However, the drug loading ratio into solid dispersions is limited by the high molecular weight of polymers. Hydroscopic polymers absorb water, resulting in re-crystallization and reduction of the glass transition temperature, simultaneously enhancing the solubility and stability of the drug [9]. Several co-amorphous drug–drug and drug-excipient systems have been studied [10,11]. Drug–drug systems could be administered in combination therapy but may not be practical due to the high dose required for one drug. In contrast, drug-excipients may be widely applicable as an alternative to the use of polymers, with drug–amino acid systems being a particularly promising combination [12,13]. Amino acids have a low molecular mass and can increase the drug load in the formulation due to interactions between their functional groups and the drug. Intimate mixing of an amorphous drug and amino acid at the molecular level has been attempted by quench cooling, ball milling, cryo-milling, and spray drying [14,15]. Ball milling is a widely used process for amorphizing drugs by solely using mechanical force [16] in which ball–ball and ball–wall friction provides local intense energy to the raw materials. In planetary ball milling, centrifugal forces are alternately synchronized since the bowl and disc turn in opposite directions and ball–ball and ball–wall frictional energy likely dominates the mechanochemical

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reaction during grinding [17]. The amorphization of drugs by ball milling is complicated by the coupling of mechanical and chemical phenomena at the molecular scale since each molecule is different due to thermal or photochemical reactions [18]. The effect of an amino acid on the amorphization mechanism remains unknown, as most previous studies have focused on the physicochemical properties and improvements in dissolution behavior provided by the amorphous state, not on the amorphization process by ball milling [19].

Balls in a planetary ball mill are moved along the wall by centrifugal force and this force increases as the rotation speed of the mill increases [20]. Friction is produced by differences in speed between a ball and the wall of the vessel and this frictional energy acts on the samples being milled. Increasing revolution speed increases the Coriolis force (rotation bias force) applied to the balls and they detach from the wall [21–23]. Ball behavior during planetary ball milling was previously modeled using DEM and an appropriate geometrical relationship for the motion of a ball in the grinding mill [24,25].

In the present study, we conducted discrete element method (DEM) simulations to investigate the relationship between frictional energy and the amorphization of a drug with an amino acid during ball milling. Indomethacin (IMC) was selected as a model poorly water-soluble drug as it has been widely studied by various amorphization techniques [26,27]. Cystine (Cys2) is an amino acid dimer whose disulfide bond is easily broken and may form reactive radicals when strongly impacted [28,29]. The amorphous state is achieved by ball milling by disrupting the crystalline state of the raw materials but it is difficult to predict the frictional energy during ball milling due to the complex non-linear motion of balls in the closed system [30,31]. Consequently, DEM simulation was performed to estimate the frictional energy as an input parameter during ball milling [32]. Changes in the amorphization of IMC and Cys2 were determined simultaneously by collecting X-ray powder diffraction (XRPD) spectra before and after milling and analyzing by principal component analysis (PCA). The results allowed estimation of the amorphization of IMC with Cys2 during co-grinding from the relationship between the frictional energy and the PCA score. The involvement of radical formation in the amorphization of IMC with Cy22 was investigated by electron spin resonance measurements.

Experimental sections

Preparation of ground samples

Indomethacin (IMC) and cystine (Cys2) were purchased from Nakarai Tesque, Inc. (Japan). The effect of the molar ratio of IMC and Cys2 on amorphization was investigated by using several combinations of the two compounds and measuring their X-ray powder diffraction (XRPD) diffractograms (Supplementary Fig. S1). Most experiments were conducted using a 1:1 molar ratio (1.180 g IMC and 0.794 g Cys2) [33]. IMC and Cys2 were mixed in a mortar before co-grinding and stored in a desiccator at 20%RH (controlled by silica gel) at room temperature. A planetary ball mill, Pulverisette 7 from Fritsch GmbH (Germany), was used for grinding at room temperature. Eight YTZ balls (10 mm diameter) were placed in the 45 mL zirconia vessel and the revolution rate was 1:−2. This ratio provided effective grinding regardless of the rotation speed, based on the calculated critical speed ratio [34]. Grinding time was defined as the total time and was conducted in 10 min intervals to avoid over-heating the milling vessel. The maximum rotation speed was 600 rpm and the maximum grinding time was 10 h. Ground samples were analyzed by XRPD, Fourier transform-infrared spectroscopy (FT-IR), and dissolution tests, as described below.

X-ray powder diffraction (XRPD)

XRPD analyzes were performed on 20.0 mg samples at a 200-mA current and a 40-kV voltage using Cu-Kα radiation (λ = 0.15418 nm) on a SmartLab diffractometer (Rigaku Corporation, Japan). The scan range was 2θ= 5–45° at a rate of 4.0°/min with a 0.01° step interval.

DEM (discrete element method) simulation

DEM software (DEM solutions, EDEM) was used to predict planetary movement of a ball in the milling vessel. The method was used to simulate ball motion and analyze the energy generated from collision and friction between balls within the planetary ball mill [35]. The mechanical properties used in DEM simulation are shown in Table 1 [36]. The Voigt model provides the elastic relationship between the contact force and displacement of the particles, allowing two contacting particles to slip relative to each other, thereby introducing ball–ball and ball–wall frictional forces. The mass of the raw materials was relatively small compared to the mass of the balls and therefore had little effect on the movement and energy of the balls, despite occupying an appreciable volume inside the mill. Dynamic behavior calculated using the force on the balls, and the locations of the balls in the milling vessel during grinding, were simulated for 10 min. The number of ball–ball and ball–wall contacts was counted. The frictional energy per second (specific frictional energy, E_f) was calculated according to the following equation:

$$E_f = \frac{1}{WT}\sum_{j=1}^{n_c}\mu_d F_n u_j \quad (1)$$

where W is the loading amount of the balls, T is the simulation time, μ_d is the dynamic frictional coefficient, F_n is the normal contact force between ball–ball and ball–wall, N_c is the contact time, and u_j is the tangential component of relative displacement at each.

Electron spin resonance

Electron spin resonance (ESR) was analyzed by using ESR spectrometer (JEOL Co., Tokyo, Japan). About 30 mg of samples was put into a quartz ESR tube (φ = 5 mm). The optimized conditions were shown in Table 2 [37].

FT-IR (Fourier transform-infrared spectroscopy)

The IR spectra of samples were collected using an FT/IR-6100 from JASCO Corporation (Japan). The measurements were

Table 1
Parameter settings for DEM simulation.

Object	Setting parameter	Set value	Unit
Ball	Density of particle	6000	kg/m^3
	Poisson's ratio	0.30	–
	Young's modules	210	GPa
	Coefficient of restitution	0.899	–
	Coefficient of static friction	0.220	–
	Coefficient of rolling friction	1.0×10^{-5}	–
	Number of balls	8	EA
	Diameter of particle	10.0	Mm
Milling	Rotation speed	200, 250, 300, 400, 600	rpm
	Mill diameter	40.0	mm
	Mill depth	40.0	mm
	Revolution radius	70.0	mm
	Rotation-to revolution speed ratio	1.00: (−)2.00	–

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