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Multiscale mathematical modelling of drug activation by co-grinding

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HIGHLIGHTS

- Nanonization improves the solubility of poorly water soluble drugs.
- Nanonization often implies recurring to co-grinding.
- A multiscale mathematical modelling of co-grinding was developed.
- The developed mathematical (MM) model can interpret the experimental data.
- MM is the rationale connection between mill set-up and co-ground drug properties.

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ABSTRACT

Since the 1980s, drug activation by grinding or co-grinding has evolved considerably, allowing the conversion of microcrystals into nanocrystals or amorphous phases, whose increased solubility brings a significant improvement in drug bioavailability. This has prompted many researchers to investigate and understand the entire grinding/co-grinding process. Therefore, the present work focuses on the multiscale mathematical modelling of these three aspects to establish a rational relationship between the mill setting and the properties of the milled drug. Based on the developed model, it was possible to correctly interpret and describe the experimental data obtained when we ground two poorly water-soluble drugs (nifedipine and nimesulide) with a stabiliser (cross-linked polymer; polyvinylpyrrolidone) in two mills (vibrational and planetary mills). Interestingly, despite the complexity of the whole phenomenon, the implementation of the model only required the use of a Microsoft Excel sheet in which a suitable user-defined function was embedded.

1. Introduction

Mechanochemistry and electrochemistry are the two pillars of nonthermally activated chemistry. Mechanochemistry is particularly concerned with the physicochemical transformations and chemical reactions of substances after the application of mechanical energy (Tkáčová 1993). Although mechanical energy has been used extensively by Homo sapiens since the beginning of the cognitive revolution 70000 years ago (Harari 2012), the term mechanochemistry did not appear in the scientific literature until the end of the 19th century (Ostwald 1919), probably in connection with the development of more refined and efficient mills.

Since then, however, mechanochemistry has rapidly evolved to find applications in the processing of mineral raw materials and the production of building materials, mineral fertilisers, functional ceramics, and metal alloys, to name a few examples (Colombo et al. 2009). Recently, mechanochemistry has also found interesting applications in the environmental field, such as in the remediation of soils contaminated with heavy metals (Concas et al. 2007; Montinaro et al. 2007; Concas et al. 2020a) and in the inerting of mine soils (Concas et al. 2020b). This wide variety of industrial applications stimulated researchers to understand and rationalise the way mechanical energy is transferred to the material to be ground in the grinding chamber. Thus, there are many excellent papers in the literature dealing with the mathematical modelling of this phenomenon (Burgio et al. 1991; Magini et al. 1994; Concas et al. 2006; Fadda et al. 2009). More recently, some works

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Nomenclature

F_i	i^{th} force	ΔC_p	difference between the liquid and the solid drug-specific heat capacity at constant pressure
f	frequency	Δh_{hcg}	experimentally determined co-ground system melting enthalpy referred to the system unit mass (drug plus polymer)
I	inertia moment	Δh_r	specific enthalpy correction (referred to as pure drug unit mass) representing the nano-crystals melting enthalpy reduction due to nano-crystal radius
i	i^{th} drug powder class	Δh_T	specific enthalpy correction (referred to as pure drug unit mass) representing the nano-crystals melting enthalpy reduction due to the reduction of the melting temperature
k	mass fraction of the whole drug mass involved in each collision	Δh_{mr}	specific melting enthalpy of nanocrystals of radius R_{nc}
$k_1, k_2, k_3, k_{-1}, k_{-2}, k_{-3}$	microstructural kinetics constants referring to the scheme reported in Fig. 3	$\Delta h_{\text{m}\infty}$	specific melting enthalpy of crystals of infinite radius
m	mass	Δ_{mix}	experimentally known physical mixture (i.e. before co-grinding) melting enthalpy concerning the mixture (drug plus polymeric carrier)
M_i	i^{th} moment	γ_{sv}	solid-vapour surface energy
n	collisions number	γ_{lv}	liquid-vapour surface energy
R_{nc}	nanocrystal radius	ρ_{s}	density of solid drug
t	time	ρ_{l}	density of liquid (melt) drug
$T_{\text{m}\infty}$	drug crystal melting temperature	ω	angular velocity
T_{mr}	drug nanocrystals melting temperature	ω_{d}	drug mass fraction in the co-ground material
v	velocity		
X_{a}	amorphous drug fraction		
X_{ai}	amorphous drug fraction after “i” collisions		
X_{c}	microcrystalline drug fraction		
X_{ci}	microcrystalline drug fraction after “i” collisions		
X_{nc}	nanocrystalline drug fraction		
Greek symbols			
$\chi_i(n)$	drug powder fraction that has undergone “i” collisions after “n” total collisions occurred in the grinding chamber		

focused on modelling the mechanism of mechanochemical reactions, using either deterministic/phenomenological methods (Delogu and Takacs, 2014; Colacino et al. 2018) or a stochastic approach (Delogu and Takacs, 2018; Carta et al. 2020). In these works, the nature and rate of mechanochemical transformations were quantified at different levels of detail and the individual collisions were modelled (Delogu and Takacs, 2014 and 2018). Colacino et al. (2018) described the mechanical stresses at the molecular scale and illustrated the formation of crystalline solid solutions, amorphous alloys, and metal-organic frameworks. Carta et al. (2020) took a multiscale modelling approach, moving from the macroscale to the microscale and considering the statistical nature of mechanical processing of powders. Our manuscript builds on the findings of this work and seeks to take a further step towards multiscale modelling of drug activation by providing a detailed description of two co-grinding processes.

Despite its great development, technical problems related to the contamination of the ground material originally prevented the spread of mechanochemistry in the pharmaceutical field (Colombo et al. 2009). However, the introduction of suitable mill linings and highly abrasion-resistant materials for grinding media in the 1980s (Yalkowsky 1981) enabled the successful dissemination of mechanochemistry in the pharmaceutical field as well. The reason for this success was due to two aspects: 1) the possibility of producing pharmaceutical products without the use of solvents (which can be difficult and expensive to eliminate and can alter the properties of the drug) and 2) the possibility of increasing the bioavailability (defined as the rate and extent to which the active drug is absorbed from a pharmaceutical form and thus becomes available at the site of drug action (Kwan 1997; Naidu et al., 2008)) of poorly water-soluble drugs. It is well known that the size reduction of drug microcrystals to nanocrystals (crystals extending from the (theoretical) dimension of the crystal cell to a few hundred nanometers) to the amorphous phase (recognisable as nanocrystals of vanishing size) is related to the reduction of

the melting temperature and enthalpy of the drug, leading to an increase in the solubility of the drug (Coceani et al. 2012; Hasa et al. 2014; Chiarappa et al. 2017). Since bioavailability depends on the permeability of the drug through cells and on the solubility of the drug in aqueous media (Abrami et al. 2020), it is clear why pharmaceuticals are so interested in the conversion of microcrystals into nanocrystals or amorphous phases. Indeed, mechanochemistry enables the mechanochemical “activation” of drugs, i.e., the possibility of imparting a certain desired potential (increased solubility and thus bioavailability) to the ground drug compared to the native drug. Considering that 40 % of marketed drugs (Loftsson and Brewster 2010; Devis and Walker 2018) and 70–90 % of new chemical entities (Gigliobianco et al. 2018; Bertoni et al. 2019) suffer from poor aqueous solubility (drugs of class II according to the biopharmaceutical classification (Amidon et al. 1995)) despite good permeability, the importance of drug activation becomes clear. Examples of commonly marketed drugs that are poorly soluble in water ($<100 \mu\text{g}/\text{cm}^3$ (Savjani et al. 2012)) include nonsteroidal anti-inflammatory drugs (NSAIDs), anticholesterol, antifungals, antibiotics, anticonvulsants, chemotherapeutics, antivirals, β -blockers, calcium channel blockers, and immunosuppressants (Grassi et al. 2000; Grassi et al. 2007; Hasa et al. 2011; Tsume et al. 2014; Baghel et al. 2016; Deshmukh et al. 2016). Given these considerations, it is not surprising that since the beginning of the third millennium, many researchers around the world have been studying drug activation (Boldyrev 2004; Bahl and Bogner 2006; Loh et al. 2015; Jug and Mura, 2018; Liu et al. 2020; Bertoni et al. 2022).

Since nanocrystalline and amorphous phases are not stable for obvious thermodynamic reasons (at least in terms of the lifetime required for a pharmaceutical product (months or years)), they tend to revert to the original microcrystalline state and lose their “activation” due to their large surface area. Therefore, the addition of at least one other component (stabiliser or carrier) to the ground material is required. For example, a mechanically treated drug sub-

stance can interact with the stabiliser via van der Waals or hydrogen bonds, resulting in pharmaceutically stable products that retain their activation. Typical stabilisers include cross-linked polymers and cyclodextrins (Colombo et al. 2009). The need to obtain co-ground materials with desired properties prompts to study the whole co-ground process from a theoretical point of view, in order to establish a rational relationship between the grinding conditions and the co-ground properties. For this purpose, it is necessary to understand all the partial phenomena of the process, i.e., the dynamics of the mill and the grinding media, the energy transfer to the mill charge (drug plus carrier), and the effect of the transferred energy on the drug microcrystals in terms of modern science and industrial requirements. Therefore, the aim of this work is to provide an example of mathematical multiscale modelling that allows to establish a link between the mill setting and the properties of the co-ground drug, using two different mills (vibrational and planetary) widely used in the pharmaceutical field.

2. Materials and methods

2.1. Materials

Micronized cross-linked polyvinylpyrrolidone (-(C₆H₉NO)-; PVP-Clm, BASF, Germany, pharmaceutical grade) obtained by popcorn polymerization in the form of a white, tasteless, odourless and water-insoluble powder (particle diameter in the range of (1–10) µm and average diameter = 4.5 µm) was used as a carrier (stabiliser). Two typical drugs of the class II (good permeability and poor water solubility) according to the biopharmaceutical classification (Amidon et al. 1995) were considered as model drugs. Nifedipine (C₁₇H₁₈N₂O₆; Mw = 346.34; NIF, Moehs Catalana S. A. (Spain), average particle diameter 5 µm), a calcium channel blocker, is a drug used to treat angina, hypertension, Raynaud's phenomenon, and preterm labour. It appears as a yellow crystalline powder (melting temperature (172.5 ± 0.2)°C (Bergese et al. 2004)). Nimesulide (C₁₃H₁₂N₂O₅S, Mw = 308.5; NIM, HEL-SINN, PambioNoranco, CH, average particle diameter 4.7 µm), is a nonsteroidal anti-inflammatory drug. It appears as a yellow crystalline powder (melting temperature (148.7 ± 0.2)°C (Coceani et al. 2012)).

2.2. Mill

2.2.1. Vibrational

The first grinding device used in this work, a Sweco DM1 (Florence, Kentucky, USA), is a vibrational mill, shown in Fig. 1. It consists essentially of a bowl containing an approximately toroidal grinding chamber (polyurethane) designed to contain the grinding media, the alumina cylinders (7200 cylinders with a height of 0.01 m and a diameter of 0.01 m for a total mass of 36 kg - this corresponds to the standard working conditions for this mill, as indicated in the DM1 data sheet), a high-density (3950 kg/m³) and abrasion-resistant material. The upper part of the grinding chamber is closed by a lid, while the bottom is connected by 8 springs to a metal structure anchored in the floor.

The body of the mill is rigidly connected to an electric motor that rotates a metal shaft equipped with two eccentrics: one at the top and one at the bottom of the shaft. The combination of shaft rotation (1400 rpm) and spring reaction causes a very complex movement of the grinding chamber, which in turn causes the grinding media inside the grinding chamber to jump and hit each other. The mixture to be ground (NIF and PVP-Clm, weight ratio = 1: 5 = 800 g: 4000 g) receives mechanical energy when it is trapped in the collision zone between two colliding cylinders.

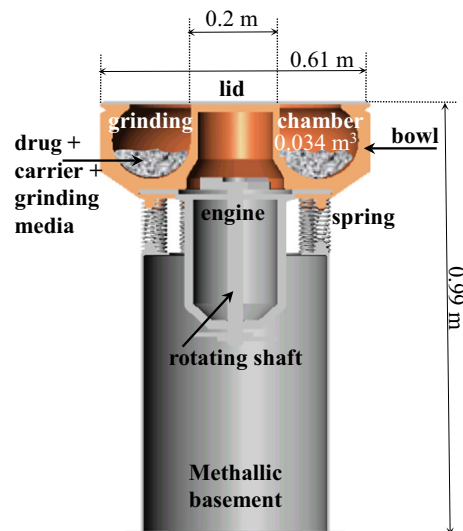


Fig. 1. DM1 schematic representation.

The impact can be punctual, linear or in a reduced area. At fixed times (7, 14, 21, 30, 60, 120, 180 and 240 min), the mill is stopped and a sample of the co-ground material is taken from the chamber for thermal analysis (measurements are made in triplicate).

2.2.2. Planetary

The second grinding device considered is a planetary ball mill (Pulverisette7, Fritsch GmbH, D) consisting of a rotating bowl (530 rpm; diameter = 0.14 m) supporting two counter-rotating cylindrical vessels (-633 rpm, internal volume 1.2*10⁻⁵ m³) made of agate. Each vessel contains seven grinding media (agate balls with a diameter of 0.01 m and a density of 2650 kg/m³) as well as 0.375*10⁻³ kg NIM and 1.125*10⁻³ kg PVP-Clm (weight ratio = 1:3), which are filled by removing the cap on the top of the vessel (according to the Pulverisette7 data sheet, these are standard working conditions). Since the number of grinding media is small, the wall effect is not negligible. The total number of collisions is caused not only by colliding balls, but also by the interaction of individual balls with the vessel walls. At specified times (30, 60, 120 and 240 min), the mill is stopped and a sample of the co-ground material is taken from the chamber for thermal analysis (measurements are made in triplicate).

2.3. Thermal analysis

Thermal analyses of the co-ground material were performed using a Perkin Elmer DSC 7 power-compensated differential scanning calorimeter (Norwalk, CT). Samples were placed in aluminium trays (6–7 mg) and then scanned under an N₂ flow of 20 cm³/min at a heating rate of 10 °C/min. Temperature calibration was performed at the same heating rate using Hg and In as standards. The determination of the fraction of drug microcrystals (X_c), newly formed nanocrystals (X_{nc}), and amorphous drug (X_a) was performed according to (Coceani et al. 2012). Briefly, X_c was determined according to the following equation:

$$X_c = \frac{\Delta h_{cg}(T_{m\infty}, \omega_d)}{\Delta h_{mix}(T_{m\infty}, \omega_d)} \quad (1)$$

where $T_{m\infty}$ is the drug melting temperature, ω_d is the drug mass fraction in the co-ground material (=0.166 NIF, 0.25 NIM), $\Delta h_{cg}(T_{m\infty}, \omega_d)$ is the experimentally determined co-ground system melting enthalpy referred to the system unit mass (drug plus polymer) while Δh_{mix} is the (experimentally known) physical mixture

(i.e. before co-grinding) melting enthalpy referred as to the mixture (drug plus PVP-Clm) unit mass evaluated at $T_{m\infty}$ and ω_d . X_{nc} is evaluated according to the following equation:

$$X_{nc} = \frac{\Delta h_{cg}(T_{mr}, \omega_d)}{\Delta h_{mix}(T_{m\infty}, \omega_d) - \omega_d(\Delta h_r + \Delta h_T)} \quad (2)$$

where Δh_{cg} is the experimentally determined co-ground system melting enthalpy referred to as the system unit mass (drug plus polymer) and evaluated at the nanocrystals melting temperature T_{mr} ($< T_{m\infty}$; as our carrier, PVP-Clm, is amorphous, Δh_{cg} is only due to NIF or NIM nanocrystals melting) while Δh_r and Δh_T are the specific enthalpy corrections (referred to pure drug unit mass) representing the nano-crystals melting enthalpy reduction due to nano-crystal radius (R_{nc}) reduction and melting temperature (T_{mr}) reduction as reported by (Zhang et al. 2000):

$$\begin{aligned} \Delta h_{mr} &= \Delta h_{m\infty} - \frac{3}{R_{nc}} \left(\frac{\gamma_{sv}}{\rho_s} - \frac{\gamma_{lv}}{\rho_l} \right) - \int_{T_{mr}}^{T_{m\infty}} \Delta C_p dT \\ &= \Delta h_{m\infty} - \Delta h_r - \Delta h_T \end{aligned} \quad (3)$$

where Δh_{mr} is the specific (J/kg) melting enthalpy of nanocrystals of radius R_{nc} , $\Delta h_{m\infty}$ is the specific (J/kg) melting enthalpy of crystals of infinite radius, ρ_s and ρ_l are, respectively, the density of the solid and liquid (melt) drug, γ_{sv} and γ_{lv} are, respectively, the surface energy (J/m²) competing to the solid-vapour and liquid-vapour interface while ΔC_p is the difference between the liquid and the solid drug specific heat capacity at constant pressure. The combination of Eq. (2) and the Brun equation (Brun et al. 1973), leads to:

$$\int_{T_{m\infty}}^{T_{mr}} \frac{\Delta h_{mr}}{T} dT = - \frac{2}{R_{nc}} \left(\frac{\gamma_{sl}}{\rho_s} + \gamma_{lv} \left(\frac{1}{\rho_s} - \frac{1}{\rho_l} \right) X_{nc}^{(1/3)} \right) \quad (4)$$

The simultaneous numerical solution of Eq. (3) and (4), implemented by Coceani (Coceani et al. 2012), allows evaluating X_{nc} , Δh_r and Δh_T .

3. Mathematical model

To mathematically model the effects of milling on drug microcrystals, one can consider a three-step approach. In the first step, the dynamics of the grinding media are simulated; in the second, the energy transfer to the drug powder when it is confined between the colliding media; and finally, in the third, the effect of the mechanically supplied energy on the drug microcrystals.

3.1. Mill dynamics

The first step of our multiscale mathematical modelling involves determining the impact frequency within the milling chamber. This in turn requires the simulation of the mill dynamics, which includes the dynamics of the bowl and lid, the motor and rotating shaft, and the dynamics of all the grinding media. Since this task has been solved previously (Castillo et al. 2004), we briefly summarise here the strategy used and the results obtained. The dynamics of the mill were determined by numerically solving the two cardinal equations for the dynamics of the mill and the grinding media:

$$m \frac{d\mathbf{v}}{dt} = \sum_{i=1}^n \mathbf{F}_i \quad (5)$$

$$I \frac{d\omega}{dt} = \sum_{i=1}^m \mathbf{M}_i \quad (6)$$

where m and I represent, respectively, the mass and the inertia moment of the particular object considered, t is time, $\mathbf{v}$ and ω are, respectively, the linear and angular velocity while $\mathbf{F}_i$ and $\mathbf{M}_i$ are, respectively, the i^{th} force and moment acting on the considered body.

Since in the case of the vibrational mill the number of grinding media was very high (~ 7200), only 200 of them were considered, while the rest (~ 7000) were grouped in a ring of the same mass, occupying the lower part of the grinding chamber (see Fig. 2). This simplification allowed to limit both the memory allocation and the CPU time of the numerical simulator to feasible values. The friction factor between the ring and the mill bowl was set so that the ring rotated at the experimentally detectable rotational speed of the grinding media. Each spring was simulated by a Voigt body in the axial and radial directions. The comparison between the experimental behaviour and the simulations showed that the normal spring stiffness is 17 kN/m, the radial stiffness is 6.73 kN/m, and the damping coefficient in the normal and radial directions is 50 kg/s.

The numerical solution of the cardinal equations suggests that the impact frequency (f) occurring in the grinding chamber is about 10^5 Hz for the vibrational mill and 780 Hz for the planetary mill. In the case of the planetary mill, due to the small number of grinding media (7 for each vessel), the cardinal equations were solved for each grinding media.

3.2. Energy transfer to drug powder

As Delogu and coworkers (Delogu et al., 2001) noted, energy transfer to drug powders is not a continuous process, but a discontinuous one, since mechanical energy is transferred only at impact. Furthermore, since only a small portion of the powder is affected at each impact, the entire powder consists of particles that have been impacted different numbers of times, i.e., never, once, twice, and so on. Consequently, in the course of mechanical treatment, the drug powder can be divided into different classes based on the number of times each class has been impacted after n impacts in the grinding chamber. Accordingly, at time t , which corresponds to n collisions, the powder can be divided into $(n + 1)$ classes, namely class $\chi_0(n)$, which has never had an impact, class that has had one impact ($\chi_1(n)$), class that has had two impacts ($\chi_2(n)$), and so on up to $\chi_n(n)$. Thus, n can also be understood as the number of classes (minus 1, $\chi_0(n)$ class) populating the grinding chamber at any given time. Since $\chi_i(n)$ represents the powder mass fraction subjected to i impacts, it follows that:

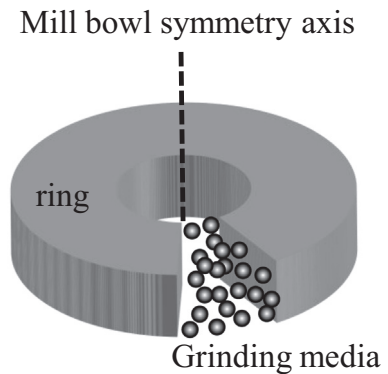


Fig. 2. Only 200 of the 7200 grinding media were considered in the simulation. The remaining 7000 were considered by a ring of the same mass filling the lower part of the grinding chamber. The friction coefficient between the “ring” and the grinding chamber wall was set to the experimentally determined rotation speed of the grinding media.

$$\sum_{i=0}^{i=n} \chi_i(n) = 1 \quad (7)$$

The time evolution of the $(n + 1)$ classes can be described by:

$$\frac{d\chi_0(n)}{dn} = -k\chi_0(n) \quad (8)$$

$$\frac{d\chi_i(n)}{dn} = -k\chi_i(n) + k\chi_{i-1}(n) \quad i = 1, \dots, N \quad (9)$$

where k is a kinetic constant representing the mass fraction of the drug powder effectively processed at each impact. Eqs. (8) and (9) simply state that the never impacted mass fraction (χ_0) decreases with n (or time t) as it feeds $\chi_1(n)$ while the i^{th} class (χ_i) increases proportionally to χ_{i-1} and decreases proportionally to χ_i . Assuming, obviously, that $\chi_0(0) = 1$ and that $\chi_i(0) = 0$, Eqs. (8)-(9) analytical solution reads:

$$\chi_i(n) = \frac{(kn)^i}{i!} e^{-kn} \quad 0 \leq i \leq n \quad (10)$$

3.3. Effect of mechanically supplied energy on drug powder

This step is modelled assuming that the energy associated with a collision, by acting on each fraction $\chi_i(n)$, transforms the microcrystals into nanocrystals and an amorphous phase according to the chained transformation shown in Fig. 3. It goes without saying that this is a simplifying hypothesis, since it is well known that collisions can be characterised by different intensities (Castillo et al. 2004), which translates into different effects on the crystal structure. However, for simplicity, we assume that the effect of collisions is independent of their intensity, bearing in mind that the introduction of a “collision efficiency” would allow this aspect to be taken into account. Similarly, we assume that there is no difference between particle-particle collisions and particle-wall collisions, although they may well differ in terms of their effects on the crystal structure.

The transformation scheme in Fig. 3 is based on the notion that the transformation of microcrystals into amorphous phase may or may not occur through the nanocrystal state. This reflects the hypothesis that an amorphous phase can be formed by successive crushing or melting of microcrystals. The resulting dynamics is described by the following differential-algebraic system of equations:

$$\frac{dX_{ci}}{di} = -(k_1 + k_3)X_{ci} + k_{-1}X_{nci} + k_{-3}X_{ai} \quad (11)$$

$$\frac{dX_{nci}}{di} = k_1X_{ci} - (k_{-1} + k_2)X_{nci} + k_{-2}X_{ai} \quad (12)$$

$$X_{ai} = 1 - X_{ci} - X_{nci} \quad (13)$$

where X_{ci} , X_{nci} , and X_{ai} represent, respectively, the microcrystal, nanocrystal and amorphous mass fractions in $\chi_i(n)$ fraction, while k_1 , k_2 and k_3 are the direct kinetics constants and k_{-1} , k_{-2} and k_{-3} are the inverse kinetics constants. The initial conditions of the grinding process required to solve Eqs. (11) – (12) are:

$$X_{ci} = 1; \quad X_{nci} = 0; \quad X_{ai} = 0 \quad (14)$$

Thus, it is assumed that at the beginning only microcrystals of the drug are present in the mill filling (polymer + drug). The model can easily accommodate other initial conditions that account for the presence of nanocrystals and/or amorphous drug, although this is not as common in the pharmaceutical field (Grassi et al. 2007). Based on the initial conditions expressed by Eq. (14), the analytical solution to the systems of differential equations consisting of Eqs. (11) and (12) is (see Appendix A for details):

$$\alpha = k_1 + k_3 + k_{-3}; \quad \beta = k_{-1} - k_{-3}; \quad \delta = k_{-3} \quad (15)$$

$$\varepsilon = k_1 - k_{-2}; \quad \varphi = k_{-1} + k_2 + k_{-2}; \quad \zeta = k_{-2} \quad (16)$$

$$\Delta = (\alpha + \varphi)^2 - 4(\alpha\varphi - \varepsilon\beta) = (\alpha - \varphi)^2 + 4\varepsilon\beta \quad (17)$$

Case I. a: $\Delta > 0$ and $\alpha\varphi \neq \beta\varepsilon$.

$$y_{1,2} = -\frac{1}{2} \left[(\alpha + \varphi) \pm \sqrt{\Delta} \right] \quad (18)$$

$$X_{ci}(i) = \left(\frac{\varepsilon + (\alpha\varphi - \beta\varepsilon)y_1 + \zeta}{y_2 - y_1} \right) \left(\frac{y_1 + \varphi}{\varepsilon} \right) e^{y_1 i} + \left(\frac{\varepsilon + (\alpha\varphi - \beta\varepsilon)y_2 + \zeta}{y_1 - y_2} \right) \left(\frac{y_2 + \varphi}{\varepsilon} \right) e^{y_2 i} + \frac{\varphi\tau - \zeta}{\varepsilon} \quad (19)$$

$$X_{nci}(i) = \left(\frac{\varepsilon + (\alpha\varphi - \beta\varepsilon)y_1 + \zeta}{y_2 - y_1} \right) e^{y_1 i} + \left(\frac{\varepsilon + (\alpha\varphi - \beta\varepsilon)y_2 + \zeta}{y_1 - y_2} \right) e^{y_2 i} + \frac{\alpha\zeta + \varepsilon\delta}{\alpha\varphi - \beta\varepsilon} \quad (20)$$

Case I. b: $\Delta > 0$ and $\alpha\varphi = \beta\varepsilon$.

$$X_{ci} = \frac{1}{(\alpha + \varphi)} \left(\alpha e^{-(\alpha + \varphi)i} + \varphi \right) \quad (21)$$

$$X_{nci} = \frac{\varepsilon}{(\alpha + \varphi)} \left(1 - e^{-(\alpha + \varphi)i} \right) \quad (22)$$

Case I. l: $\Delta = 0$.

$$y_1 = y_2 = -\frac{\alpha + \varphi}{2} \quad (23)$$

$$X_{ci}(i) = \frac{e^{y_1 i}}{\varepsilon} \left[\left(-\frac{\omega}{y_1^2} + i(\varepsilon + \zeta \frac{\omega}{y_1}) \right) (y_1 + \varphi) + \varepsilon + \zeta \frac{\omega}{y_1} \right] + \frac{1}{\varepsilon} \left(\frac{\varphi\omega}{y_1^2} - \zeta \right) \quad (24)$$

$$X_{nci}(i) = e^{y_1 i} \left(-\frac{\omega}{y_1^2} + i(\varepsilon + \zeta \frac{\omega}{y_1}) \right) + \frac{\omega}{y_1^2} \quad (25)$$

Case I. IIa: $\Delta < 0$ and $\varepsilon \neq 0$.

$$a = -(\varphi + \alpha)/2b = \sqrt{|\Delta|}/2 \quad (26)$$

$$X_{ci} = \frac{1}{\varepsilon} \left(\frac{\omega\varphi}{a^2 + b^2} - \zeta \right) + \frac{e^{ai}}{\varepsilon} \left[\left(-\frac{\omega}{a^2 + b^2} \varphi + \varepsilon + \zeta \right) \cos(bi) + \left(\frac{1}{b} \left(\varepsilon + \zeta + \frac{\omega a}{a^2 + b^2} \right) (a + \varphi) - \frac{\omega}{a^2 + b^2} b \right) \sin(bi) \right] \quad (27)$$

$$X_{nci} = \frac{\omega}{a^2 + b^2} + e^{ai} \left(-\frac{\omega}{a^2 + b^2} \cos(bi) + \frac{1}{b} \left(\varepsilon + \zeta + \frac{\omega a}{a^2 + b^2} \right) \sin(bi) \right) \quad (28)$$

Case I. IIb: $\Delta < 0$ and $\varepsilon = 0$.

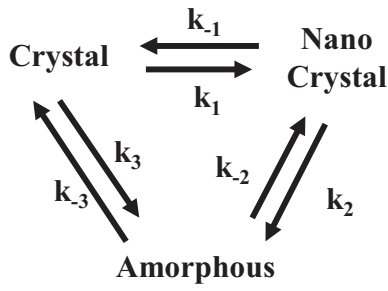


Fig. 3. Schematic of the chained transformation assumed for the transformation of microcrystals into nanocrystals and amorphous phases. k_1 , k_2 and k_3 are the direct microstructural constants, while k_{-1} , k_{-2} , and k_{-3} are the inverse microstructural constants.

$$X_{ci} = \frac{\delta\varphi + \beta\zeta}{\alpha\varphi} + e^{-\alpha i} \left(1 - \frac{\delta\varphi + \beta\zeta}{\alpha\varphi} \right) + \frac{\beta\zeta}{\varphi(\alpha - \varphi)} (e^{-\alpha i} - e^{-\varphi i}) \quad (29)$$

$$X_{nci} = \frac{\zeta}{\varphi} (1 - e^{-\varphi i}) \quad (30)$$

The total mass fraction of micro (X_c), nano (X_{nc}) and amorphous (X_a) drug phases are given by the following sums:

$$\begin{aligned} X_c(n) &= \sum_{i=0}^n X_{ci}(i) \chi_i(n) & X_{nc}(n) &= \sum_{i=0}^n X_{nci}(i) \chi_i(n) \\ X_a(n) &= \sum_{i=0}^n X_{ai}(i) \chi_i(n) \end{aligned} \quad (31)$$

Unknown parameters (k , k_1 , k_2 , k_3 , k_{-1} , k_{-2} , k_{-3}) were determined by nonlinear regression (Levenberg-Marquardt method), which minimized the distance of the model from the experimental data as a function of these degrees of freedom. To allow data fitting, the entire model was implemented in a Microsoft Excel file by using the “User Defined Function”, remembering that the link between “ n ” (number of collisions) and “ t ” (elapsed grinding time) was represented by the hit frequency “ f ” ($n = f \cdot t$) evaluated in section 3.1.

In summary, our model is based on the idea that the whole grinding phenomenon can be described by the union of two phases: the energetic part and the microstructural part. While the energetic part describes how the mechanical energy is supplied to the microcrystals, the microstructural part tries to describe the effect of the supplied mechanical energy on the internal structure of the microcrystals, i.e., the kinetics of their transformation into nanocrystals and amorphous phases. Accordingly, the mathematical core of our model is represented by Eq. (10), which refers to the energetic phase, and Eqs. (11)–(13), which refer to the microstructural phase. While the soundness of the first phase has been widely confirmed in the past, the microstructural part, although mathematically very powerful and flexible, has been proposed for the first time in this paper. On the other hand, the strength of our approach is the possibility to easily adopt other approaches for the microstructural phase. Moreover, at least to our knowledge, this is the first attempt to link the energy and microstructural phases. Obviously, knowledge of the collision frequency of the grinding media is mandatory.

4. Results and discussion

Fig. 4 shows, in the case of the vibrational mill, the comparison between the experimental data (X_c , black circles; X_{nc} , grey circles; X_a , white circles) and the model best-fitting model (X_c , solid line; X_{nc} , dotted lines; X_a , dashed line). Quite good agreement between the experimental data and the model best fit can be seen, and the robustness of the whole fitting procedure is ensured by the F-test. The 7 fitting parameters (k , k_1 , k_2 , k_3 , k_{-1} , k_{-2} , k_{-3}), which

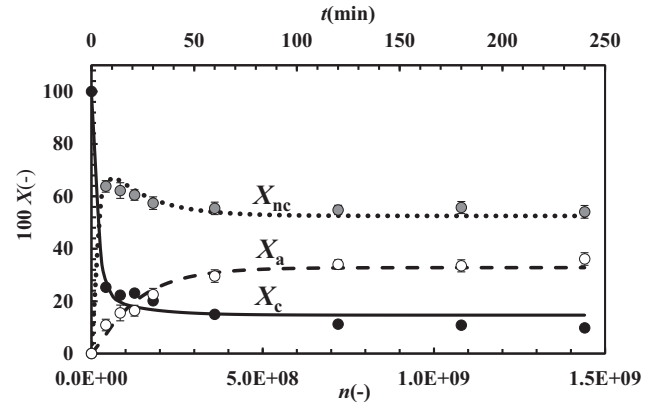


Fig. 4. Vibrational mill. Comparison between the experimental data (X_c , black circles; X_{nc} , grey circles; X_a , white circles) and the model best fit (X_c , continuous line; X_{nc} , dotted lines; X_a , dashed line). n (lower horizontal axis) and t (upper horizontal axis) indicate the total number of collisions and the elapsed time since the beginning of the co-grinding process, respectively. t and n are related to each other by the hit frequency f introduced in section 3.1.

are theoretically independent, were determined by model fitting to 16 independent experimental data, i.e., the mass fraction of microcrystals (X_c) and nanocrystals (X_{nc}) evaluated at each of the time points considered (i.e., 8 time points). The 8 amorphous mass fraction data (X_a), which depend on X_c and X_{nc} according to the obvious relation $X_a = 1 - X_c - X_{nc}$, cannot be considered as independent data. The robustness of the whole fitting procedure (95 % probability correctness) is ensured by the F-test, which shows that the theoretical F-test value $F(6, 9, 0.95)$ is lower than the experimental value (12.8). It can be seen that a rapid decrease in the initial microcrystalline fraction (X_c) is accompanied by an equally rapid formation of nanocrystals (X_{nc}) and a slower increase in the amorphous phase (X_a). Fig. 4 also makes it clear that a complete transformation of microcrystals into nanocrystals and amorphous phase is never achieved. Rather, a kind of equilibrium is reached after about $7 \cdot 10^8$ collisions, since X_c , X_{nc} and X_a do not change with increasing n (or time).

The model interprets this behavior by assigning nonzero values to the inverse kinetic constants k_{-1} and k_{-2} and by assigning higher values to the kinetic constants k_1 ($=0.677$) and k_{-1} ($=0.189$) related to the transformation of microcrystals into nanocrystals, and relatively lower values (one order of magnitude lower) for the kinetic constants k_2 ($=0.036$) and k_{-2} ($=0.058$) related to the transformation of nanocrystals/amorphous (see Fig. 3). Interestingly, the kinetic constants k_3 and k_{-3} related to the microcrystalline/amorphous transformation are zero, so the model interpretation of the experimental data suggests that the amorphous phase cannot form directly from the microcrystalline phase. It can be concluded that the formation of the amorphous phase, at least in this experimental setup, is due to the progressive crushing of the microcrystals and the progressive accumulation of defects within the microcrystals. It is important to remember that these results may depend on the carrier under consideration. In other words, holding all other co-grinding parameters constant, the use of a different carrier could lead to different results in terms of time variation of X_c , X_{nc} and X_a or, equivalently, to different values of the constants k_i and k_{-i} .

The model fit to the experimental data also shows that the parameter k ($=10^{-7}$) is very low, so that the mass fraction of drug powder processed at each impact is extremely low, indicating a relatively inefficient co-milling process. The first consequence of the low k value is the relatively small number of classes $\chi_i(n)$ populating the milling environment, as shown in Fig. 5.

Fig. 5 illustrates that at the beginning of the co-grinding process (~ 0.25 min), there are only four classes ($\chi_0(n)$, $\chi_1(n)$, $\chi_2(n)$, $\chi_3(n)$)

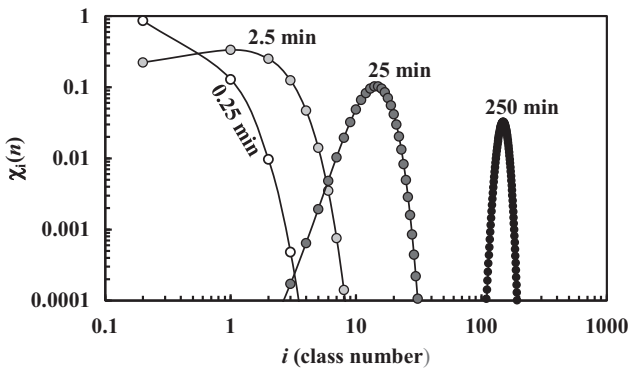


Fig. 5. Time evolution of classes whose mass fraction ($\chi_i(n)$) exceeds the threshold of 10^{-4} . Lower mass fraction values are considered negligible. For the duration of the entire co-grinding process (~ 250 min), a small number of classes (~ 200) meets this condition.

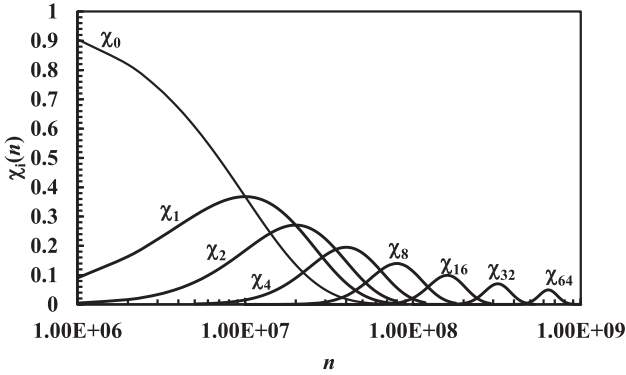


Fig. 6. Evolution of the mass fraction $\chi_i(n)$ related to some representative classes belonging to the 200 identified in Fig. 5. n indicates the total number of collisions that have occurred since the start of the co-grinding process.

whose mass fraction exceeds 10^{-4} , which is an arbitrary but reasonable threshold used to decide whether the mass fraction of a class is negligible or not. After 2.5 min, the number of classes increases to 9 ($\chi_0(n)$ – $\chi_8(n)$) and after 25 min, 29 classes meet our “suitability” criterion ($\chi_3(n)$ – $\chi_{31}(n)$). At the end of the co-grinding process (~ 250 min or $1.5 \cdot 10^9$ collisions), 84 classes are active ($\chi_{110}(n)$ – $\chi_{193}(n)$). This evidence suggests that despite the large number of collisions, the maximum number of classes populating the milling chamber does not exceed 200. For this reason, model fitting to the experimental data was based on a trial-and-error procedure, considering only classes $\chi_0(n)$ – $\chi_{200}(n)$ in the range $1 < n < 1.44 \cdot 10^9$. To illustrate the evolution over time of the different classes belonging to the individualized rank, Fig. 6 shows their evolution over time. It can be seen that, with the exception of the class never affected $\chi_0(n)$, which shows an exponential decrease, all other classes are characterized by a slow increase followed by a slow decrease. Interestingly, the position of the maximum characterizing each class decreases in intensity as the number of classes (i) increases and moves toward higher n values.

For this reason, for clarity, Fig. 6 does not show the evolution of classes whose rank exceeds 64. The second important effect of the small k value reflects the kinetics of the scheme shown in Fig. 3. To this end, Fig. 7 shows the evolution of X_c , X_{nc} , and X_a with reference to the previously determined kinetic constants (k_1 , k_{-1} , k_2 , k_{-2}) and assuming two different values of k : 1 and 10^{-3} . When $k = 1$, each collision affects the total charge mass, so the three curves on the left side of Fig. 7 are nothing more than the analytical model

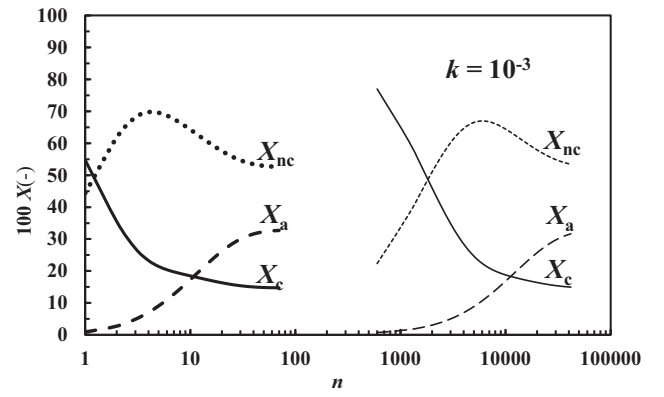


Fig. 7. Time evolution of the mass fraction of microcrystals (X_c), nanocrystals (X_{nc}) and the amorphous state (X_a) for different k values. The three curves on the left correspond to $k = 1$ and represent Eqs. (15)–(31), while the three curves on the right correspond to $k = 10^{-3}$.

solution of Eqs. (13)–(28). Under this limiting condition, about 64 collisions are sufficient to reach equilibrium between microcrystals, nanocrystals, and the amorphous phase (i.e., X_c , X_{nc} , and X_a become time and collision independent). On the other hand, if k decreases to 10^{-3} , about $4 \cdot 10^4$ collisions are required to reach the same equilibrium conditions. This means that the reduction in the efficiency of the co-milling process (proportional to k) translates into a delay in the kinetics of the conversion of the microcrystals into nanocrystals and the amorphous phase. This concept is further illustrated in Fig. 8, where $k = 10^{-5}$ and $k = 10^{-7}$ (the value determined by model fitting to experimental data) are considered. The shape of the time evolution of X_c , X_{nc} , and X_a is almost identical regardless of the k value, but the three curves are shifted toward higher collision numbers.

Thus, one of the most important aspects of the developed model is the possibility of separately identifying the role of the microstructural aspect, shown in Fig. 3, and the energetic, probabilistic aspect, represented by Delogu's approach (Delogu et al. 2001).

Fig. 9 shows the comparison between the model best fit (lines) and the experimental data (symbols) with respect to NIM co-grinding in the planetary mill. Similar to the NIF case (vibrational mill), there is a fairly good agreement between the experimental data and the model best fit. Interestingly, only the three direct microstructural constants ($k_1 = 7.560$; $k_2 = 0.085$, $k_3 = 7.738$) plus

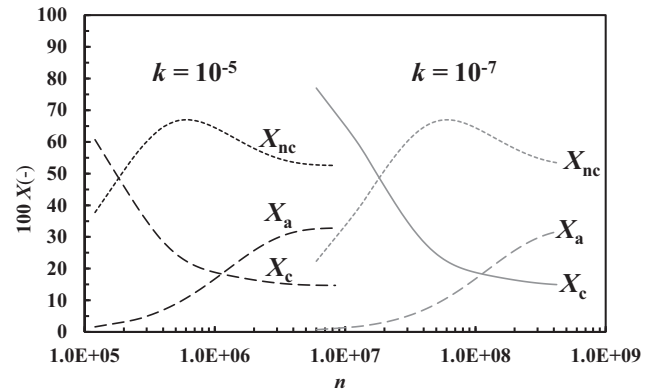


Fig. 8. Time evolution of the mass fraction of microcrystals (X_c), nanocrystals (X_{nc}) and the amorphous state (X_a) different k values. The three curves on the left correspond to $k = 10^{-5}$, while the three curves on the right correspond to $k = 10^{-7}$, with the last value obtained with the nonlinear data regression routine.

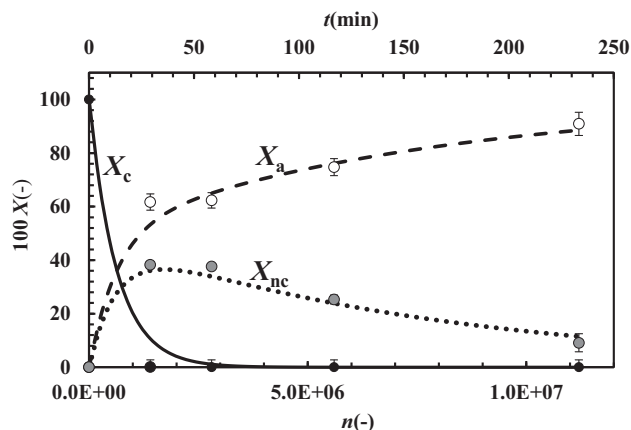


Fig. 9. Planetary mill. Comparison between the experimental data (X_c , black circles; X_{nc} , grey circles; X_a , white circles) and the model best fit (X_c , solid line, X_{nc} , dotted lines; X_a , dashed line). n (lower horizontal axis) and t (upper horizontal axis) indicate the total number of collisions and the elapsed time since the start of the co-milling process, respectively. t and n are related by the hit frequency f introduced in section 3.1.

k ($1.6 \cdot 10^{-6}$) are needed to fit the experimental data. In fact, the inverse constants turn out to be statistically equal to zero. With only 4 fitting parameters, the F-test ($F(3, 4, 0.95) < 7.6$) ensures the robustness of the fitting procedure. The comparison between the fitting parameters shows that k is more than an order of magnitude larger in the planetary mill than in the vibrational mill, even though the drug concentration (drug mass/grinding chamber volume) in the planetary mill is only ≈ 1.5 of that in the vibrational mill. Moreover, the active ingredient mass per grinding media in the planetary mill is $\approx$ half that in the vibrational mill. Therefore, it can be concluded that the planetary mill is more efficient than the vibrational mill. The differences between the two mills are also evident in the microstructural changes that occur during co-grinding. Indeed, in the vibrational mill, the microstructural transformations do not represent a concatenated process ($k_3 = k_{-3} = 0$), but a sequential one consisting of the reversible step 1 (crystal - nanocrystal) and step 2 (nanocrystal - amorphous). In the planetary mill, on the other hand, the process is concatenated, but the three steps are not reversible. Ultimately, all these differences reflect the fact that the vibrational mill leads to an equilibrium between X_c , X_{nc} , and X_a , while in the planetary mill the original microcrystals completely transition to the amorphous phase. The different structural and mechanical properties of the two drugs

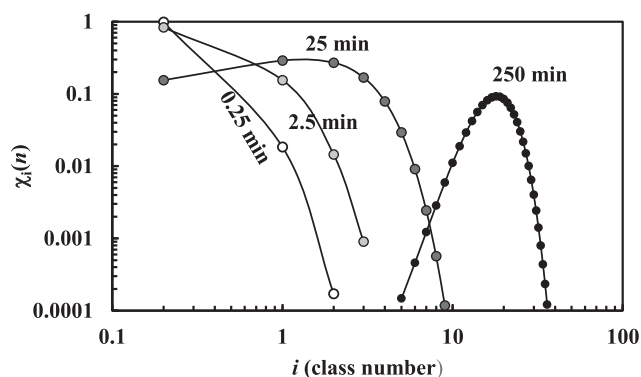


Fig. 10. Planetary mill. Time evolution of classes whose mass fraction ($\chi_i(n)$) exceeds the threshold of 10^{-4} . Lower mass fraction values are considered negligible. For the duration of the entire co-grinding process (~ 250 min), a small number of classes (~ 35) satisfies this condition.

may play an important role in this process, apart from the different energy involved in the vibrational and planetary collisions.

Finally, it is worthwhile to focus attention on the collision classes that populate the grinding chamber of the planetary mill. Fig. 10 shows, at various times, the classes whose mass fraction ($\chi_i(n)$) exceeds the threshold (10^{-4}) established for the vibrational mill (Fig. 5). Again, the classes that meet this condition are a small number, ranging from class "0" to class "35". This means that after 250 min, which corresponds to $1.17 \cdot 10^7$ collisions, the most affected drug fraction was involved in 35 collisions.

5. Conclusions

The proposed mathematical modelling at multiple scales made it possible to establish a rational link between the properties of the process (co-grinding) and the product (activated drug), a task rarely accomplished in the pharmaceutical industry where, despite its empirical nature, the trial-and-error approach is often preferred for its simplicity (Grassi and Grassi 2014). Although our approach is only the beginning of a modern strategy aimed at representing very complex phenomena such as the co-grinding of drugs with a stabiliser, it has the great advantage that it can potentially be applied to any type of mill and drug, provided that the hit frequency in the grinding chamber can be properly evaluated. Moreover, this strategy can also be considered for the study of other comminution processes aimed at obtaining nanocrystals and an amorphous phase. The combination of the energetic-probabilistic approach developed by Delogu and co-workers (Delogu et al. 2001) with the "microstructural" step we added allows us to see the effects of these two interlocking effects, the deciphering of which was not possible in the past. In fact, we found that in the mills considered, a relatively small number of collisions (at least in terms of the total number of impacts occurring in the grinding chamber) is sufficient to cause the transformation of microcrystals into nanosized coherent domains (crystallites), as proposed by (Bergese et al. 2004), and an amorphous phase. In the case of the vibrational mill, we were able to deduce that the direct conversion of microcrystals into the amorphous phase did not occur. Thus, the formation of the amorphous phase occurred through the progressive conversion of microcrystals into nanocrystals and the accumulation of defects in the nanocrystal structure. We then found that the conversion of microcrystals to nanocrystals occurs much faster than the conversion of nanocrystals to the amorphous phase and that both processes lead to a final equilibrium, so that the complete conversion of microcrystals to the amorphous phase does not occur. In contrast, the microstructural transformations in the planetary mill lead to a concatenated process that includes a transformation of microcrystals into nanocrystals and a transformation into the amorphous phase, resulting in a complete transformation of microcrystals into the amorphous phase. These results depend on both the different mill dynamics and the mechanical properties of the drug. In particular, the proposed approach has been shown to apply to different mills, such as the widely used vibrational and planetary mills. Consequently, it allows the comparison of different processes, highlighting their differences and similarities at the nanoscale, i.e., at a fundamental level. Finally, it should not be forgotten that despite the complexity of the phenomenon studied, the implementation of the model requires only the use of a Microsoft Excel file.

CRediT authorship contribution statement

Mario Grassi: Conceptualization, Methodology. **Italo Colombo:** Conceptualization, Methodology, Investigation, Funding acquisition. **Davide Manca:** Conceptualization, Software. **Alice Biasin:**

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Details about the analytical solution of the differential equation system composed by eqs (11) and (12).

In the light of Eq. (13), eqs(11) and (12) become:

$$\frac{dX_{ci}}{di} = -(k_1 + k_3)X_{ci} - k_{-1}X_{nci} + k_{-3}(1 - X_{ci} - X_{nci}) \quad (A1)$$

$$\frac{dX_{nci}}{di} = k_1X_{ci} - (k_{-1} + k_2)X_{nci} + k_{-2}(1 - X_{ci} - X_{nci}) \quad (A2)$$

Upon re-arrangement, we have:

$$\frac{dX_{ci}}{di} = -\alpha X_{ci} + \beta X_{nci} + \delta \quad (A3)$$

$$\frac{dX_{nci}}{di} = \varepsilon X_{ci} - \varphi X_{nci} + \zeta \quad (A4)$$

$$\begin{aligned} \alpha &= k_1 + k_3 + k_{-3}; & \beta &= k_{-1} - k_{-3}; & \delta &= k_{-3}; \\ \varepsilon &= k_1 - k_{-2}; & \varphi &= k_{-1} + k_2 + k_{-2}; & \zeta &= k_{-2} \end{aligned} \quad (A5)$$

From Eq. (A1) we have:

$$\frac{d^2 X_{nci}}{di^2} = \varepsilon \frac{dX_{ci}}{di} - \varphi \frac{dX_{nci}}{di} = X''_{nci} = \varepsilon X'_{ci} - \varphi X'_{nci} \quad (A6)$$

$$X_{ci} = \frac{X'_{nci} + \varphi X_{nci} - \zeta}{\varepsilon} \quad (A7)$$

Inserting Eq. (A7) into Eq. (A6) leads to:

$$\frac{dX_{ci}}{di} = X'_{ci} = -\frac{\alpha}{\varepsilon} (X'_{nci} + \varphi X_{nci} - \zeta) + \beta X_{nci} + \delta \quad (A8)$$

Finally, insertion of Eq. (A8) into Eq. (A6), leads to a second order differential equation with constant coefficients whose unknown is X_{nci} :

$$X''_{nci} + (\alpha + \varphi)X'_{nci} + (\alpha\varphi - \varepsilon\beta)X_{nci} = \alpha\zeta + \varepsilon\delta \quad (A9)$$

The solution of the associated homogeneous equation reads:

$$X_{nci} = C_1 e^{\gamma_1 i} + C_2 e^{\gamma_2 i} \text{ if } \Delta > 0 \quad (A10)$$

$$X_{nci} = (C_1 + iC_2)e^{\gamma_1 i} \text{ if } \Delta = 0 \quad (A11)$$

$$X_{nci} = (C_1 \cos(bi) + C_2 \sin(bi))e^{ai} \text{ if } \Delta < 0 \quad (A12)$$

where:

$$\begin{aligned} \Delta &= (\alpha + \varphi)^2 - 4(\alpha\varphi - \varepsilon\beta) = (\alpha - \varphi)^2 + 4\varepsilon\beta; \\ y_{1,2} &= -\frac{1}{2}[(\alpha + \varphi) \pm \sqrt{\Delta}] \end{aligned} \quad (A13)$$

$$a = -(\varphi + \alpha)/2 \quad b = \sqrt{|\Delta|}/2 \quad (A14)$$

The solution of the not homogeneous Eq. (A9) can be obtained employing of the arbitrary constants method:

Case Ia: $\Delta > 0$ and $\alpha\varphi \neq \beta\varepsilon$

The arbitrary constants method requires solving the following equation systems:

$$\frac{dC_1}{di} e^{\gamma_1 i} + \frac{dC_2}{di} e^{\gamma_2 i} = 0 \quad (A15)$$

$$\begin{aligned} \frac{dC_1}{di} \frac{d}{di}(e^{\gamma_1 i}) + \frac{dC_2}{di} \frac{d}{di}(e^{\gamma_2 i}) &= \frac{dC_1}{di} \gamma_1 e^{\gamma_1 i} + \frac{dC_2}{di} \gamma_2 e^{\gamma_2 i} \\ &= \alpha\zeta + \varepsilon\delta \end{aligned} \quad (A16)$$

whose solution allows the determination of C_1 and C_2 :

$$C_1(i) = \frac{\omega}{y_2 - y_1} \frac{1}{y_1} e^{-y_1 i} + A_1 \quad (A17)$$

$$C_2(i) = \frac{\omega}{y_1 - y_2} \frac{1}{y_2} e^{-y_2 i} + A_2 \quad (A18)$$

$$\omega = \alpha\zeta + \varepsilon\delta \quad (A19)$$

Constants A_1 and A_2 can be determined assuming that $X_c = 1$ and $X_{nc} = X_a = 0$ for $i = 0$. Inserting Eq. (A17) –(A18) into Eq. (A10) leads to Eq. (19) – (20).

Case Ib: $\Delta > 0$ and $\alpha\varphi = \beta\varepsilon$

When $\alpha\varphi = \beta\varepsilon$, Eq. (A9) simplifies to:

$$X''_{nci} + (\alpha + \varphi)X'_{nci} = \alpha\zeta + \varepsilon\delta \quad (A20)$$

Setting $X''_{nci} = Z'_{nci}$, Eq. (A20) can be reduced to a first-order differential equation with constant coefficients whose solution can be obtained by defining:

$$Y_{nci} = \zeta - (\alpha + \varphi)Z_{nci} \quad (A21)$$

Thus, we have:

$$-\frac{1}{(\alpha + \varphi)} \frac{dY_{nci}}{di} = Y_{nci} \quad (A22)$$

whose solution is:

$$Y_{nci} = Y_{nci}(0)e^{-(\alpha + \varphi)i} \quad (A23)$$

In the light of Eq. (A21) and remembering that $X_c = 1$ and $X_{nc} = X_a = 0$ for $i = 0$, it follows:

$$X'_{nci}(0) = Z_{nci}(0) = \varepsilon * 1 - \varphi * 0 + \zeta = \varepsilon + \zeta \quad (A23)$$

Thus, in the light of Eq. (A4), we have:

$$\frac{dX_{nci}}{di} = \frac{\zeta}{\alpha + \varphi} + \frac{(\alpha + \varphi)(\varepsilon + \zeta) - \zeta}{\alpha + \varphi} e^{-(\alpha + \varphi)i} \quad (A24)$$

Remembering that being $k_1 > 0$, the condition $\alpha\varphi = \beta\varepsilon$ implies $\delta = \zeta = \xi = 0$. Finally, Eq. (A24) solution yields to Eq. (21) and (22).

Case II: $\Delta = 0$

The arbitrary constants method requires solving the following equations system:

$$\frac{dC_1}{di} e^{\gamma_1 i} + \frac{dC_2}{di} i e^{\gamma_1 i} = 0 \quad (A25)$$

$$\frac{dC_1}{di} \gamma_1 e^{\gamma_1 i} + \frac{dC_2}{di} [e^{\gamma_1 i} + \gamma_1 i e^{\gamma_1 i}] = \alpha\zeta + \varepsilon\delta = \omega \quad (A26)$$

whose solution allows to determine C_1 and C_2 :

$$C_1(i) = \frac{\omega}{y_1} e^{-y_1 i} \left(i + \frac{1}{y_1} \right) + A_1 \quad (A27)$$

$$C_2(i) = A_2 - \frac{\omega}{y_1} e^{-y_1 i} \quad (A28)$$

Constants A_1 and A_2 can be determined assuming that $X_c = 1$ and $X_{nc} = X_a = 0$ for $i = 0$. Inserting Eq. (A27) – (A28) into Eq. (A11) leads to Eq. (23) – (24).

Case I. Ila: $\Delta < 0$ and $\varepsilon \neq 0$.

The arbitrary constants method requires solving the following equations system:

$$\frac{dC_1}{di} e^{ai} \cos(bi) + \frac{dC_2}{di} e^{ai} \sin(bi) = 0 \quad (A29)$$

$$\frac{dC_1}{di} [ae^{ai} \cos(bi) - be^{ai} \sin(bi)] y_1 + \frac{dC_2}{di} [ae^{ai} \sin(bi) + be^{ai} \cos(bi)] = \omega \quad (A30)$$

whose solution allows to determine C_1 and C_2 :

$$C_1 = \frac{\omega e^{-ai}}{b(a^2 + b^2)} (a * \sin(bi) + b * \cos(bi)) + A_1 \quad (A31)$$

$$C_2 = \frac{\omega e^{-ai}}{b(a^2 + b^2)} (b * \sin(bi) - a * \cos(bi)) + A_2 \quad (A32)$$

Constants A_1 and A_2 can be determined assuming that $X_c = 1$ and $X_{nc} = X_a = 0$ for $i = 0$. Inserting Eq. (A31) – (A32) into Eq. (A12) leads to Eq. (27) – (28).

Case I. Ilb: $\Delta < 0$ and $\varepsilon = 0$.

In this case, the model solution simplifies as we have to solve two decoupled first-order differential equations:

$$\frac{dX_{nci}}{di} = -\varphi X_{nci} + \zeta \quad (A33)$$

$$\frac{dX_{ci}}{di} = -\alpha X_{ci} + \beta X_{nci} + \delta \quad (A34)$$

Assuming that $X_{nci} = 0$ for $i = 0$, Eq. (A33) solution leads to Eq. (30). Relying on Eq. (30), and assuming that $X_{ci} = 1$ for $i = 0$, Eq. (A34) solution leads to Eq. (29).

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ces.2022.118073>.

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