

Review

Recent advances of pharmaceutical crystallization theories

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ABSTRACT

As a technology of separation and purification, crystallization plays a vital role in diverse industries such as inorganic salt, pharmaceutical, and food industries, which has a huge impact on purity, crystal polymorph, crystal morphology, and particle size distribution of final products. In the past few decades, with the rapid advancement of experimental approaches and molecular simulation methods, considerable advances in the interpretation of crystallization mechanisms have been obtained, promoting the investigation and understanding of crystallization theories greatly. In this review, the advances of pharmaceutical crystallization theories in recent years from the perspectives of nucleation and crystal growth are summarized and discussed. Two thermodynamic models that are helpful in the study of the crystallization mechanisms will be introduced. In this section, the perturbed-chain statistical associating fluid theory (PC-SAFT) and a chemical-potential-gradient model will be introduced, which have been successfully applied in pharmaceutical solubility prediction, the research of dissolution mechanism as well as dissolution kinetics analysis. These two models are expected to be applied to the study of pharmaceutical crystallization process and mechanism. Furthermore, molecular simulation based on the interaction between particles can provide structural information, thermodynamics, and dynamics properties of complex systems at the molecular level, like intermolecular interaction and surface adsorption energies. Application and some shortcomings of molecular simulation, especially molecular dynamics simulation, in the field of pharmaceutical crystallization will be expounded.

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1. Introduction

As an ancient separation and purification technology, crystallization is widely applied in various industries, especially in pharmaceutical manufacture, which influences the nature of the final products considerably on purity, polymorph, crystal morphology, and size distribution [1,2]. The same pharmaceutical with different polymorphic forms has great differences in appearance, size, solubility, bioavailability, and so on [3]. Hence, to strengthen the understanding of pharmaceutical crystallization process and mechanism is very important in the pharmaceutical industry. Nucleation is the most important process in the crystallization, which determines the structure and properties of the final crystal, while crystal growth determines the crystalline morphology and dramatically affects its size distribution. Unfortunately, deep mechanistic insight into the nature of crystallization is still rare, and the control of crystallization usually depends on researchers' experience and time-consuming experimental screening. We focus herein on the pharmaceutical crystallization field and review advances in the research on the theories of pharmaceutical crystallization in recent years from four

aspects: pharmaceutical nucleation, crystal growth, the application of thermodynamics, and molecular simulation in pharmaceutical crystallization. The application of non-equilibrium thermodynamic models (the two-step chemical potential gradient model combined with PC-SAFT) and molecular simulation in the study of pharmaceutical crystallization mechanisms are mainly introduced.

Until now, classical nucleation theory (CNT) still occupies a dominant position in the nucleation from the liquids, which holds that a density fluctuation leads to the emergence of critical nuclei, namely, the density fluctuation and the structural fluctuation occur simultaneously [4]. For more than one hundred years, CNT has been generally used in many fields, but recently many investigations have shown that there is a considerable deviation between the experimental nucleation rates and the results obtained by this theory. In some cases, the nucleation rates measured by the experiment are even several orders of magnitude lower than theoretical results [5,6] because it's challenging to get access to accurate structural information in the nucleation process. Based on this, this paper will elaborate on the development of solution nucleation theory from the two aspects: CNT and non-classical nucleation theories (two-step nucleation theory and the pre-nucleation clusters), hoping to find the breakthrough point of research on drug nucleation. Different from CNT, non-classical nucleation theory can describe the nucleation process in more detail, which is expected to be suitable for

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the quantitative description of the crystallization process by combining with thermodynamics as introduced latter.

Compared with nucleation theory, crystal growth theories and process are relatively more transparent. In this part, some representative crystal growth theories will be introduced from two aspects: theories used to predict crystal morphology (Gibbs–Wulff growth law, Bravais–Friedel–Donnay–Harker rule, and Periodic Bond Chain theory) and some growth kinetics models (two-dimensional growth mechanism, Burton Cabrera Frank theory, and rough interface model). However, all of these theories or models have some limitations, lacking a unified theory for the understanding of growth mechanisms. It is known that crystallization is a combination of kinetics and thermodynamics, so deepening the investigation and understanding of kinetics and thermodynamics in the crystal growth is quite significant. To this end, the PC-SAFT for calculation of thermodynamic properties of components as well as the chemical-potential-gradient model for dissolution nature analysis and dissolution kinetics prediction will be introduced. It is expected that the two-step chemical potential gradient model can be modified to analyze pharmaceutical crystal growth kinetics and mechanism as the crystallization process of pharmaceuticals can be divided into two consecutive steps: diffusion and surface reaction. What's more, compared with other thermodynamic models, PC-SAFT can be applied to many complex systems including gases [7], liquids [8,9], polymers [10–12], and electrolytes [13], and can predict thermodynamic properties of ternary and even more complex systems based on binary data, which is quite suitable for the calculation of thermodynamic properties in complex crystallization systems.

In addition, with the rapid advancement of computer science and technique and the continuous updating in computational chemistry, molecular simulation based on quantum mechanics, classical Newtonian mechanics, and statistical mechanics plays an increasingly significant part in the field of fundamental scientific research. Limited by the development of experimental techniques, it is still very challenging to observe the microscopic-level crystallization process. Molecular simulations act as a powerful complement to experiments, which can provide an analysis of the structure, properties (miscibility, interaction forces, etc.), and reaction mechanism of a substance at the microscopic level. In recent years, nucleation phenomena in liquids have been successfully explained by molecular simulation, such as the nucleation of some colloidal particles and natural hydrates. And it has also been broadly applied to explore how different factors (solvents, supersaturation, and additives, etc.) affect crystal morphology and habit [14,15]. In this paper, we will introduce applications and shortcomings of molecular dynamics (MD) simulation in the researches of pharmaceutical crystallization.

2. Advances of Nucleation Theory

2.1. Classical nucleation theory

Nucleation means that the new phase forms with the disappearing of the old one. CNT was initially proposed by Gibbs more than a hundred years ago, which held the idea that nucleation is a competitive process between a driving force and a resistance (the supersaturation and the increase in surface free energy) [16]. CNT supposes that nucleation is a one-step process in which clusters aggregate spontaneously to generate a critical crystal nucleus. According to this assumption, crystals smaller than the critical nuclei tend to dissolve gradually, while those bigger than the critical size will keep growing. As shown in Fig. 1, the free energy of the bulk phase continuously decreases while the surface free energy (surface tension) increases with the formation of the new interface during the nucleation process. The changing value in Gibbs free energy is the sum of the bulk free energy and the surface free energy. For those spherical nuclei, the free energy change during the nucleation process is

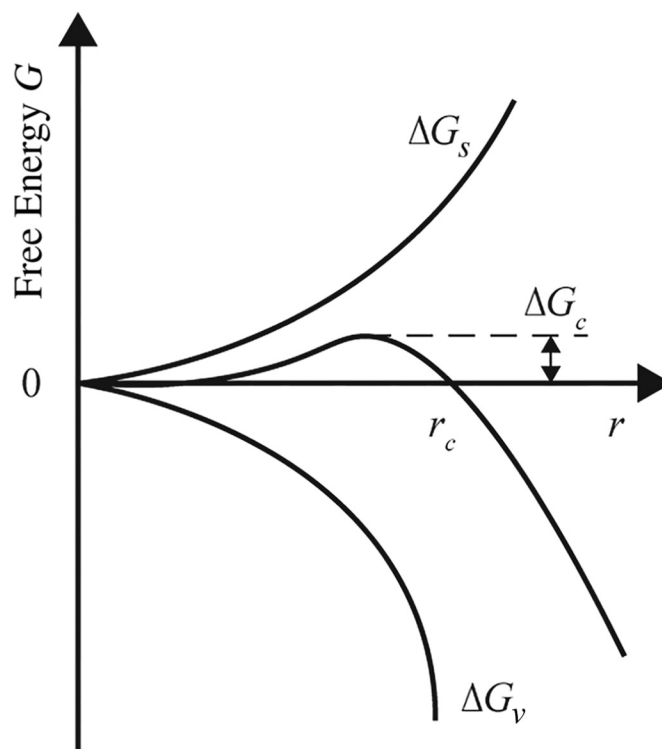


Fig. 1. The change of Gibbs free energy in the nucleation process.

expressed as Eq. (1):

$$\Delta G = -\frac{4}{3}\pi r^3 \Delta G_v + \Delta G_s = -\frac{4}{3}\pi r^3 \Delta G_v + 4\pi r^2 \gamma \quad (1)$$

where ΔG represents the free energy change per unit volume in the phase transition, ΔG_s is the surface free energy difference by the formation of the new interface, ΔG_v is the change of the free energy of the bulk phase per unit volume when the new phase is generated, r indicates the radius of the nucleus, and γ means the surface free energy per unit area in the new phase. When $d(\Delta G)/dr = 0$, the critical nuclei appear, and the total Gibbs free energy of the system reaches the maximum. It is shown that when the nucleus size is smaller than the critical size, the surface free energy (ΔG_s) is in the dominant position, and total free energy (ΔG) will increase to a peak. Meanwhile, the possibility of dissolution of the nucleus is higher than the possibility of persistent growth. Above the maximum free energy at the critical radius (r_c), the bulk free energy (ΔG_v) starts to dominate, and the total free energy (ΔG) gradually decreases as the crystal slowly forms. The nucleation energy barrier at the critical size (r_c) can be expressed as Eq. (2):

$$\Delta G_c = \frac{16\pi\gamma^3}{3\Delta G_v^2} \quad (2)$$

Based on CNT and Arrhenius reaction rate equation, the so-called steady-state nucleation rate can be defined as Eq. (3):

$$J = A \exp\left(-\frac{\Delta G_c}{kT}\right) \quad (3)$$

where k means the Boltzmann constant, A represents the pre-factor which is difficult to measure but very important, relating to the number of potential nucleation sites per unit volume, the migration velocity and adhesion rate of atoms, molecules or ions, etc. [17], which can be given

as Eq. (4):

$$A = \rho Z j \quad (4)$$

where ρ represents the number of sites that may nucleate per unit volume; Z means the Zeldovich factor, indicating the possibility that critical nuclei will continue to grow until the formation of the stable crystal, and j is a kinetic factor [14,17].

With time, the problems and limitations of CNT have become manifest. The nucleation rate predicted by CNT is considerably different from the experimental results. For some single-component fluids, such as ice, the error of homogeneous nucleation can even reach several orders of magnitude [18]. The main problems are as follows:

1. The nucleus is regarded as a spherical droplet in CNT. It is considered that the droplet density retains unchanged in the nucleation process, which is consistent with the macroscopic density of the crystal. What's more, the ordered structure of the nucleus is also in accord with the macroscopic crystal. But when the cluster contains only 20–50 molecules, the model cannot describe the nucleation process well [4,19].
2. CNT is based on the capillary hypothesis assuming that the surface free energy is as same as the free energy at the infinite and flat plane and independence with temperature and the interface curvature [1,20]. But Yau *et al.* proposed that the definition of surface free energy is unclear for the system with less than 100 molecules, and the nucleus cannot be approximated as a spherical [21].
3. CNT considers that clusters grow by adding one monomer at a time, but in fact, more than one monomer may bind to the nucleus at a time. Clusters existing in the solution can collide, split, and eventually coalesce to form nuclei, resulting in a large number of monomers integrate the nucleus at one time.
4. The theory is based on homogeneous nucleation, which does not consider the effect of lattice defects, impurity on nucleation [22].
5. CNT takes the size change as the sole criterion to judge whether clusters grow to the nuclei or not, that is, the fluctuation in local density indicates the generation of a new phase [23]. It is believed that density and structural fluctuations co-occur in the nucleation process, in other words, the change in density can cause the structural change in the crystallization process. But there is no necessary connection between these two phenomena in actual conditions.

2.2. Non-classical nucleation theory

Although CNT has been widely applied because of its simplicity and intuition, it is obviously deficient because of the great deviation between the theoretical nucleation rates and the experimental rates. Recently, with the rapid advancement of experimental approaches and computer simulation methods, non-classical nucleation theory has been put forward. Different from CNT, illustrating nucleation is a one-step procedure, the non-classical nucleation theory explains that solute molecules first aggregate with each other to form transient intermediates, and then these intermediates will rearrange themselves to form nuclei with the ordered structure in the nucleation process from solution [24]. These intermediates may be dense disordered clusters, which are proposed by two-step nucleation theory; it may also be small, thermodynamically stable aggregates involved in the pre-nucleation clusters (PNCs) [25].

Two-step nucleation theory is originally derived from protein nucleation. As early as 1997, when Wolde and Frenkel simulated the homogeneous nucleation of spherical proteins, it was found that there was a new nucleation pathway utterly different from CNT near the metastable fluid–fluid critical point, where disordered droplets would formed and rearranged to form nuclei larger than the critical nuclei. In this way, the nucleation rate increased by several orders of magnitude on account of the free energy barrier reduction in nucleation [26]. Galkin and his collaborators observed reversible liquid–liquid phase separation

between 308.15 K and 313.15 K and a dense phase contributing to the nucleation of HbS polymers when human hemoglobin nucleation was investigated [27].

Two-step nucleation theory is also suitable to analyze the nucleation of small organic molecules. In the research of nucleation of aqueous glycine solutions by non-photochemical photo-induced nucleation (NPLIN), Garetz and his co-workers found that glycine crystals with different polymorphs (γ and α) could be produced when near-infrared laser light was transformed between linear and circular polarization [28]. This result was contrary to CNT because it maintained that nuclei were formed by orderly and continuous aggregation of molecules and NPLIN could not lead to remarkable changes in the structure of ordered clusters. Therefore, the formation of glycine crystals with different forms must follow other more complicated approaches. Chattopadhyay *et al.* confirmed that the nucleation of glycine followed the two-step nucleation way when studying the glycine nucleation in a supersaturated solution by small-angle X-ray scattering (SAXA) [29].

Besides, the research of poly (N-isopropylacrylamide) (NIPA) nucleation by solid–solid phase transitions performed by Peng *et al.* confirmed that there existed intermediate liquid in the transition of square and triangular lattices, which followed two-step nucleation mechanism [30].

When investigating the nucleation process of gold and silver nanocrystals in aqueous solution by *in situ* electron microscopy, Loh with his co-workers divided the process into three steps, namely: formation of the solute-rich and solute-poor liquid phases by spinodal decomposition, amorphous nanoclusters forming from the liquid phase with more solute and its nucleation. This finding was also called as multistep nucleation, further confirmed that amorphous nanoclusters are direct precursors of nucleation from the solution, and the multistep nucleation mechanism may be feasible and quantifiable [31,32]. Guo *et al.* found three different two-step nucleation pathways by observing the nucleation process from the atomic scale, further revealed the kinetic mechanism of the two-step nucleation theory. They concluded that solid bond fluctuations played a significant part in the formation of intermediates and the precursors' packing density influenced the transformation of intermediates to crystals [32].

Pan and his collaborators derived the kinetic model based on the two-step nucleation theory [33,34]. As displayed in Fig. 2, the solute molecule is treated as state 0, the intermediate disordered cluster is perceived as state 1, and the final nucleus is described as state 2. The model

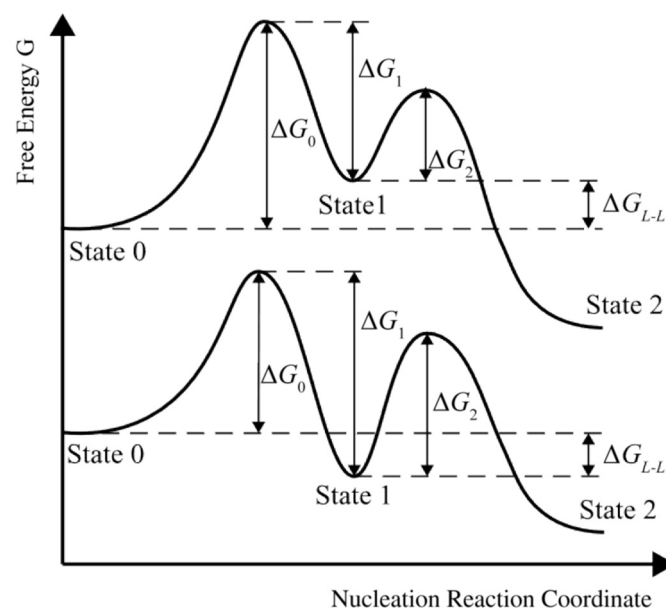


Fig. 2. Schematic diagram of the change of free energy in two-step nucleation theory.

assumes that the formation of disordered clusters is reversible, that is, while the solute molecules collide with each other to form clusters, some clusters will dissolve simultaneously, as emphasized in the upper part of Fig. 2. And the remaining disordered clusters will transform irreversibly into ordered crystal nuclei, as illustrated in the lower half of Fig. 2 [24,35]. Based on this process, Pan deduced the two-step nucleation rate by first-order approximation, expressed as Eq. (5):

$$J = \frac{U_0 U_2 \exp\left(\frac{\Delta G_0 + \Delta G_2}{RT}\right)}{U_0 \exp\left(-\frac{\Delta G_0}{RT}\right) + U_1 \exp\left(-\frac{\Delta G_1}{RT}\right) + U_2 \exp\left(-\frac{\Delta G_2}{RT}\right)} \quad (5)$$

where ΔG_0 , ΔG_1 , and ΔG_2 represent the free energy barriers in the formation, dissolution, and nucleation of disordered clusters respectively, U_0 , U_1 , and U_2 are the pre-exponential factors in these three kinetic processes. A comparison of CNT and two-step nucleation mechanism is summarized in Table 1.

The proposal of the two-step nucleation theory has dramatically promoted the understanding of the nucleation mechanism, but some problems still exist. There is some controversy about the state and stability of intermediates involved in non-classical nucleation. Early studies on protein nucleation have found that the structure of intermediates is disordered but some researchers in recent years have proposed that stable pre-nucleated clusters may be solute precursors of nucleation. When Gebauer *et al.* investigated the precipitation of calcium carbonate (CaCO_3), it was found that even for the under-saturated CaCO_3 solution, a stable pre-nucleation ion cluster as the intermediate of nucleation could still be found [36]. This mechanism explains the phenomenon of nanoscale phase separation well at the molecular level [25], and is also confirmed in some other systems such as phosphates, silica, iron oxides, iron (oxygen) (hydrogen) oxides, amino acids, and dimers [33,37,38].

Non-classical nucleation theory has greatly promoted the understanding of the solution nucleation mechanism, but there are still some problems. Firstly, both two-step nucleation theory and pre-nucleation clusters involve the liquid–liquid separation and the generation of intermediate clusters, but it is still questionable whether this process is necessary for nucleation and whether these clusters can form crystal nuclei. The nucleation of some proteins can still be observed on the liquid–liquid curve in researches. Secondly, whether the intermediate clusters are stable or not is still debatable. The views of two-step nucleation and the pre-nucleation clusters are entirely opposite, the former believes that the cluster is metastable, while the latter holds that it is stable. Thirdly, the non-classical nucleation mechanism is still very difficult to be described quantitatively, especially the local nucleation rate, which is crucial for understanding the nucleation mechanism and effectively controlling the crystallization process. Schöpe and his co-workers developed a mathematical method for calculating the local rate of the initial nucleus generated from dense droplets in order to test whether the existence of metastable dense droplets would accelerate the overall nucleation rate [39]. In addition, whether the spinodal decomposition theory can be

used to explain the formation of the solute-rich and solute-poor liquid phases by liquid–liquid separation is still unknown [31]. But for two-step nucleation theory, it is still not clear how the disordered intermediates rearrange themselves to form ordered nuclei, and which of the kinetic and thermodynamic factors dominates is still confused. It can be found that for different substances, the nucleation mechanism may vary considerably. The nucleation of most organic substances follows two-step nucleation theory [24] while pre-nucleation clusters may be more suitable for some inorganic substances [25]. And for simple substances, classical nucleation theory can explain the nucleation mechanism well. Presumably, these mechanisms are competitive rather than independent. When investigating calcium carbonate crystallization with *in-situ* TEM, Nielsen found that multiple nucleation pathways coexisted, including nucleation directly from solution and nucleation by forming metastable amorphous or crystalline precursor firstly [40].

In general, the non-classical nucleation theories represented by the two-step nucleation mechanism in recent years have profoundly promoted the progress of the nucleation mechanism, which is crucial for the effective control of the quality of crystalline products. However, because of some defects existing in these theories, CNT is still needed for rough understanding. Comparing to CNT, the non-classical nucleation theories described the nucleation process in more complex ways. But limited by experimental equipment, observation of the nucleation process of a substance (aggregation, phase separation, rearrangement, and so on) is still quite difficult. Molecular simulations might be an alternative method for the investigation of the nucleation mechanism in the short term. What's more, more nucleation energy barriers are involved in these nucleation ways, as a result of which, some more complicated and accurate thermodynamic models combined with molecular simulations are needed for the quantitative calculation of these barriers, especially for multi-component systems. Thermodynamics and molecular simulations will be introduced later.

3. Advances of Crystal Growth Mechanisms

Crystal growth is a process in which excessive particles existing in a supersaturated medium will deposit and grow on the formed crystal nuclei. Since Danish geologist Steno conducted systematic research of crystals for the first time in his book *DE solido intra solidum naturaliter contento* in 1669, the theory of crystal growth has made momentous progress over the past several hundred years. In this part, crystal growth theories will be introduced from two aspects: theories of the crystal morphology prediction (Gibbs–Wulff growth law, Bravais–Friedel–Donnay–Harker rule, and Periodic Bond Chain theory) and investigation on the growth kinetics (two-dimensional growth mechanism, Burton Cabrera Frank theory, and rough interface model).

Gibbs–Wulff growth law (equilibrium morphology model) is the principle of surface free energy minimization proposed by Gibbs based on thermodynamic equilibrium, that is, the surface free energy at the equilibrium state tends to be minimum as crystal growing [41,42]. One typical case of this theory is to predict the habit of C_{60} crystal

Table 1
The comparison of CNT and two-step nucleation theory

	CNT	Two-step nucleation theory
Core content	Competition of free energy in the bulk phase and the surface [16]	Existence and reorganization of disordered intermediates
Rate equation	$J = A \exp\left(-\frac{\Delta G_c}{kT}\right)$	$J = \frac{U_0 U_2 \exp\left(\frac{G_0 + G_2}{RT}\right)}{U_0 \exp\left(-\frac{G_0}{RT}\right) + U_1 \exp\left(-\frac{G_1}{RT}\right) + U_2 \exp\left(-\frac{G_{02}}{RT}\right)} [34]$
Advantages	Easy and broad practicability	Appropriate description of many phenomena that cannot be explained by CNT and further exploration of the nucleation mechanism
Disadvantages	Lack of accurate description of nucleation mechanism, application limits for too many hypotheses in the selected model	Ambiguous about the necessity of the formation and rearrangement of disordered intermediates for the formation of crystal nuclei, the way of reorganization, and questionable about the state and stability of the intermediates

growing in the vapor phase [43]. However, surface free energy is difficult to be measured as a result of the limit in practical application. Bravais–Friedel–Donnay–Harker rule (BFDH rule) is a refinement of Bravais law, which holds that the actual crystal faces of the crystal are often parallel to the net planes with the highest reticular density because the net planes with higher reticular density are less attractive to growth units [44–46]. A list of possible growth faces by taking the lattice and symmetry operations into consideration can be generated according to BFDH. The final crystal should be surrounded by those faces with the highest reticular density, because the normal growth rate of the crystal shows a negative correlation with the reticular density, and those crystal faces growing faster will gradually disappear [47]. This theory is currently employed to predict the external habit of the crystal by determining the important faces in the growth process. Zhou with his co-workers found a brand new crystal form of cisapride monohydrate and successfully predicted two different morphology of cisapride monohydrates by using the BFDH model in Materials Studio software [48]. BFDH rule is influenced observably by the strong bonding effects in the crystal, ignoring the energetics of the system. These two theories mainly explore the mechanism of crystal growth from the perspective of thermodynamics and crystal structure but are irrespective of the influence of growth environment and different conditions on crystal growth, which cannot well explain the diversity of crystal morphology.

Periodic Bond Chain theory (PBC theory) by Hartman and Perdok probes into crystal growth based on the geometrical characteristics of crystal structures and particle energy [49]. Surface free energy in equilibrium morphology theory and some other thermodynamic parameters are difficult to be measured practically. Therefore, Hartman and Perdok used attachment energy instead of surface free energy, *i.e.*, the ability of particles to attach to the crystal surface, to investigate the growth mechanism. The bonding rate increases with the increase of the bond energy, so the normal growth rate of the crystal face increases as the attachment energy increases [49]. PBC theory believes that a series of strong bond chains in the crystal structure are consistent with the periodic repetition of the particles. The crystal grows parallelly along the direction of the strongest bond and is divided into three planes: F, S, and K. The crystal plane K grows faster than plane S along the normal direction, the normal growth speed of plane S is greater than that of plane F. In recent years, based on the PBC theory, the attachment energy model (AE) and the modified attachment energy model (MAE) have been developed, which have been widely used in predicting the crystal morphology and habit of materials [50,51]. The predicted ideal crystal habit of dirithromycin growth from different solvents was in great accordance with the experimental findings, indicating the capability of the AE model to select suitable solvents for the crystallization of pharmaceuticals [52]. Different from the AE model

that only considers the growth of the crystal in a vacuum, the MAE model takes solvent effects into account, which can greatly help to explain the impact of different solvents on the crystal habit. However, the AE model and MAE model do not take the volume of the accessible phase space and entropic contributions into consideration. Matteo *et al.* developed a novel methodology based on the collective process of a new crystal layer formation instead of individual molecular processes to calculate the crystal shapes of urea from different solutions. In their work, the growth mechanisms were described by combing the free energy barrier and the kinetic expressions, and an enhanced sampling method (well-tempered metadynamics) was employed to estimate the thermodynamic and kinetic parameters which can address the shortcomings of the AE model to a certain extent [15].

Two-dimensional growth mechanism, so-called the layer growth theory or the Birth and Spread (B&S) model deems the crystal is smooth and non-embossed. The growth particles accumulate on the surface of the crystal with different positions (steps, kinks, surface-absorbed growth units, edge vacancies, and surface vacancies, as shown in Fig. 3), preferentially absorb to positions with stronger attraction, *e.g.*, kinks [53].

If the new crystal layer starts to grow before the previous layer has been grown, it is named step growth but still follows the two-dimensional growth mechanism. The limitation of this theory is the requirement of a high supersaturation degree because crystals must grow on a flat surface if all the optimal growth sites are occupied. Hence the mechanism cannot account for the fact of crystal growth at low supersaturation. Because of the shortcoming mentioned above, Frank put forward the screw dislocation growth mechanism (BCF theory) in 1949 [55–57]. Considering that actual crystals are often imperfect, he creatively proposed the existence of dislocation positions in the process of crystal growth. According to this theory, the crystal grows in layers at the beginning of growth, with the continuous accumulation of growth units, the distribution of impurities or thermal stress is uneven, and internal stress is generated inside the crystal, meanwhile the lattice gradually undergoes shear displacement along a net plane. If the shear displacement suddenly stops, a screw dislocation will appear before a step occurs at the misalignment. The particles grow layer by layer at the step by surface adsorption or molecular diffusion to form a screw step that will not disappear with the growth of the crystal, as a result of which the crystal can grow at very low supersaturation. Many crystallization processes follow this mechanism, such as SiC, diamond, natural hematite crystals [58]. Jia *et al.* found that the isothermal crystal growth rate of salicylic acids was fitted to BCF theory and the B&S model. It was found that the BCF theory could fit the experimental results at 283.15 K, whereas the B&S model showed a better fitting at 298.15 K [59]. The rough interface model proposed by Jackson shows that solute particles

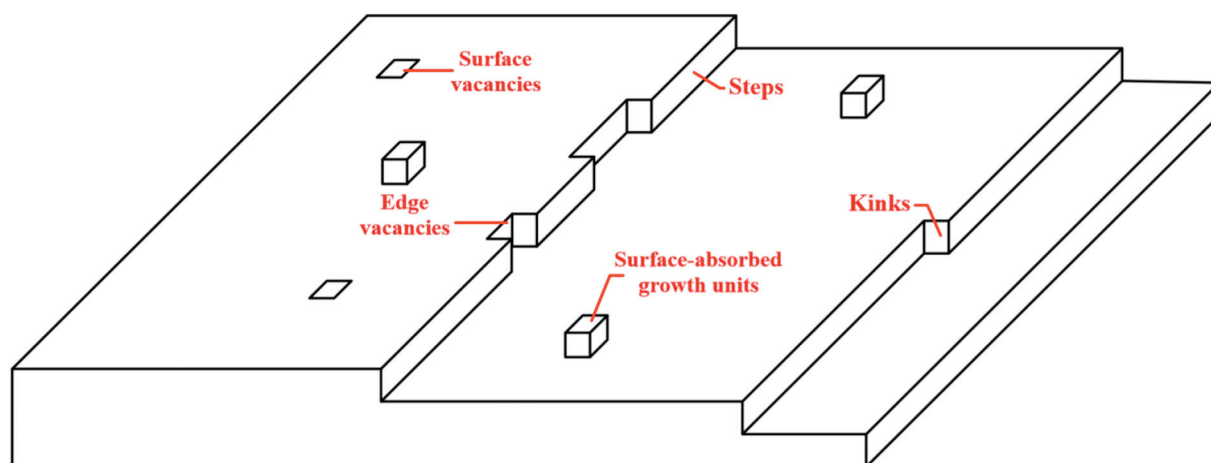


Fig. 3. The schematic diagram of the two-dimensional growth mechanism [54].

will bind to the crystal as soon as they reach the crystal surface [53,60,61]. This is a diffusion-controlled process and can be approximately calculated by statistical thermodynamic methods. These theories are usually used to investigate the crystal growth kinetics, the following Table 2 lists the kinetic models described by these three theories [53].

Some other crystal growth mechanisms are also proposed, including roughening transition theory [62,63], normal growth mechanism [64,65], and three-dimensional growth model [64]. But all these theories lay particular emphasis on the influence of the interface between crystal and environment on crystal growth, neglecting those impacts of microscopic and environmental factors.

All of the growth mechanisms mentioned above are based on the interface structure, but in fact, as a complicated phase transition process, besides the interface factors, the bulk phase of the crystal and the fluid layer close to the interface are also quite crucial, so the interface-phase model is generated. Li *et al.* divided the interfacial phase between the crystal phase and the environmental phase into the interfacial layer, adsorptive layer, and transitive layer, considered that the interface phase plays a quite significant part in crystal growth [66,67]. As studying the growth of potassium dihydrogen phosphate crystals (KDP), Yu *et al.* revealed the kinetics of solution structure adjustment in the growth boundary layer. It was believed that the growth unit was formed by the modification of the bulk phase structure in the growth boundary layer [67].

There is still a lack of unified crystal growth theory, most of the existing models are based on the interface structure, but ignore the influence of the bulk phase, especially the fluid layer where the solute concentration changes considerably. What's more, the existing mechanisms are inseparable from the growth units, but it is still unclear how these growth units to be generated, constructed, and entered into the crystal lattice. For the prediction of crystal morphology, Some more correction factors are needed for MAE because it just takes the effect of solvents on the morphology into consideration, ignoring some other factors (e.g., the volume of the accessible phase space, and entropic contributions). And these theories are often based on equilibrium thermodynamics and statistical physics, which is obviously inappropriate because crystal growth is a dynamic and nonequilibrium process. Therefore, it is essential to develop novel models based on non-equilibrium thermodynamic principles. Moreover, most existing crystal growth kinetic models use concentration difference as the crystallization driving force which is not accurate enough, especially for some complex multi-component systems. It is more suitable to use the chemical potential difference as the driving force for crystallization. Some thermodynamic models (e.g., PC-SAFT) with good prediction performance are needed for this way. By combining high-precision thermodynamic models with reasonable crystal growth kinetics models, the analysis of crystal growth mechanism, description and prediction of crystal growth kinetics can be achieved.

4. Application of Thermodynamics in the Research of Pharmaceutical Crystallization

Crystallization is a process of gas–solid, liquid–solid or solid–solid phase transition essentially, in which the gas, liquid or solid phase is

regarded as the parent phase to form crystals with a certain shape, size, and structure by nucleation and crystal growth processes. This phase transition process follows the basic principles of thermodynamics, so thermodynamic properties (solubility, supersaturation and crystallization heat, etc.) are crucial in the investigation of crystallization mechanisms. Taking the metastable zone width (MSZW) as an example, it plays a critical part in the crystallization process regulation [68,69]. As depicted in Fig. 4, MSZW generally refers to the area between the solubility curve and the supersaturation curve. The solution in this region is supersaturated, which is metastable and will not rapidly nucleate spontaneously so that the crystallization process becomes easy to be controlled. But due to the deficiency of experimental approaches, the application of thermodynamics in crystallization researches is still very cumbersome, and a large number of experiments combined with empirical models are still needed in most cases. Therefore, to reduce the experimental workload of crystallization research, it is very important to establish some thermodynamic models with predictive capability. As crystallization is a dynamic process, the development of non-equilibrium thermodynamic models is quite important for crystallization researches. In recent years, Ji has developed a chemical-potential-gradient model [12], which has been successfully employed to explore the pharmaceutical dissolution mechanism and predict the pharmaceutical dissolution kinetics by combining the perturbed-chain statistical associating fluid theory (PC-SAFT EoS) [70] based on intermolecular interaction. As a nonequilibrium thermodynamic model, it is expected to be helpful for the study of pharmaceutical crystallization mechanism.

The thermodynamic impetus of the crystallization process originates virtually the difference value between the chemical potential of solute at a specific moment and that at the thermodynamic equilibrium state. The thermodynamic equilibrium of the crystallization process not only determines the maximum crystallization capacity but also influences the choice of the crystallization technology and regulation of the crystallization process. Phase equilibrium and the solubility of the solute in the solvent are quite important in the crystallization process. For the study of pharmaceutical crystallization in solutions, the solubility of pharmaceuticals in various solvents and under diverse conditions is very significant, and the solubility is generally determined experimentally, which often consumes a large amount of time, human and material resources. Therefore, it is very substantial to establish theoretical models to infer the solubility of pharmaceuticals in solvents under different conditions based on intermolecular interactions. Perturbation Chain-statistical associated fluid theory (PC-SAFT) based on intermolecular interactions is one of the representative models for analyzing and predicting the solubility of pharmaceuticals in solvents. PC-SAFT holds that each solute or solvent molecule can be regarded as a spherical chain segment, which can interact with other chain segments through different interaction forces [71]. This theory assumes that the total residual Helmholtz energy of the system is the sum of the contributions of various interaction energies [72], including repulsion (hard-chain contribution, a^{hc}), van der Waals attraction (dispersive contribution, a^{disp}), hydrogen bonding (association, a^{assoc}) and ionic interactions (a^{elec}) as shown in Eq. (6):

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} + a^{elec} \quad (6)$$

Table 2
Kinetic models of the different growth mechanisms of crystal faces

Crystal growth theory	2-D growth mechanism	BCF mechanism	Rough interface model
Kinetic model	$R_i = A_0 \sigma^{5/6} \exp\left(\frac{B_0}{\sigma}\right)$ where R_i indicates the growth rate of a crystal face, σ means the relative supersaturation, A_0 and B_0 represents pre-exponential factors	$R_i = A_0 \sigma^2 \tanh\left(\frac{B_0}{\sigma}\right)$ where R_i indicates the growth rate of a crystal face, σ means the relative supersaturation, A_0 and B_0 represents pre-exponential factors	$R_i = A_0 \sigma$ where R_i indicates the crystal face's growth rate, σ represents the relative supersaturation, A_0 is pre-exponential factor

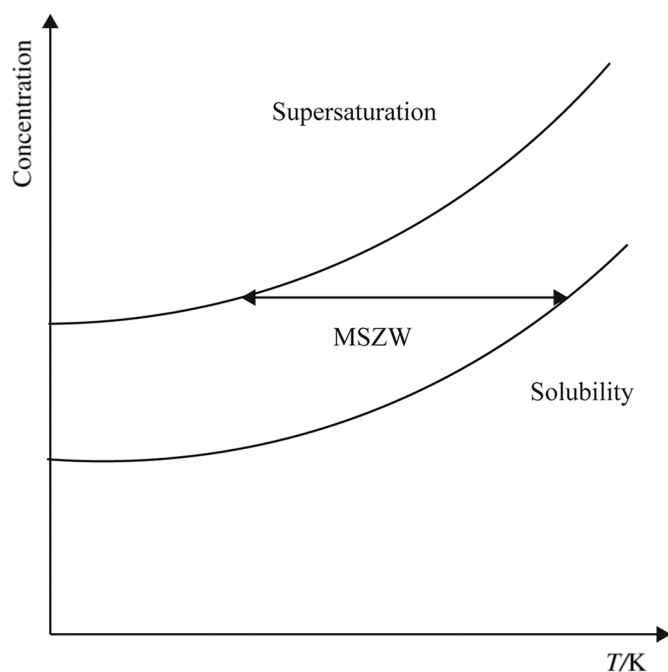


Fig. 4. Scheme of the metastable zone (MSZW).

In a system, if the residual Helmholtz free energy is known, then the compression factor Z can be calculated by Eq. (7) [70]:

$$Z = 1 + \rho \left(\frac{\partial(a^{\text{res}}/k_B T)}{\partial \rho} \right) \quad (7)$$

The residual chemical potential μ^{res} of the solute can be obtained by Eq. (8) [70]:

$$\frac{\mu^{\text{res}}}{k_B T} = \frac{a^{\text{res}}}{k_B T} + Z - 1 + \left(\frac{\partial \left(\frac{a^{\text{res}}}{k_B T} \right)}{\partial x_i} \right) - \sum_{j=1}^N \left(x_j \left(\frac{\partial(a^{\text{res}}/k_B T)}{\partial x_j} \right) \right) \quad (8)$$

The fugacity coefficients φ_i of solutes and solvents in mixtures can be calculated by compression factor Z and residual chemical potential μ^{res} , as shown in Eq. (9):

$$\ln \varphi_i = \frac{\mu_i}{k_B T} - \ln Z \quad (9)$$

According to the fugacity coefficients of solutes or solvents in mixtures and pure substances, the activity coefficients γ_i of solutes or solvents can be obtained by Eq. (10):

$$\gamma_i = \frac{\varphi_i}{\varphi_{0i}} \quad (10)$$

According to the calculated activity coefficient of the solute, combined with the phase equilibrium principle and conditions of the corresponding system, the solubility of the solute in solutions can be conveniently calculated, which dramatically reduces the workload of the experiment. Prudic *et al.* successfully predicted the solubility of various pharmaceuticals (artemisinin, indomethacin, and naproxen) in different solvents or polymers using PC-SAFT [70,73–75]. The effects of polymer type, polymer molecular weight, copolymer composition, and relative humidity in the air on the solubility of drugs in polymer excipients were also investigated [70,73–75]. Paus *et al.* studied the cinnarizine solubility in diverse organic solvents at different temperatures by using PC-SAFT [76]. The solubility of five different

pharmaceuticals (glibenclamide, griseofulvin, hydrochlorothiazide, indomethacin, and itraconazole) in amorphous and crystalline forms was also compared, which found that the solubility inferred by the PC-SAFT was quite better than that predicted by the conventional Gibbs free energy difference method [77].

In addition, by combining the PC-SAFT, Ji and Paus developed the chemical potential-gradient model, which was employed to explore and predict the dissolution kinetics of pharmaceuticals. The dissolution mechanism of crystalline pharmaceuticals and amorphous solid dispersions can be well investigated by this model. Conventional dissolution kinetics models, such as the Noyes–Whitney equation [78,79], the Weibull model [80], the Higuchi model [81,82], the Hixson–Crowell model [83,84], the Korsmeyer–Peppas model [85], the Baker–Lonsdale model [86], are typically empirical models. These models, which usually use the difference in concentration as the driving force for dissolution, have a weaker ability to predict dissolution kinetics and are not applicable to analyze the dissolution mechanism. The chemical-potential-gradient model [12] takes the difference of chemical potential as the thermodynamic impetus for the dissolution process, which can be used not only to analyze the dissolution mechanism but also to predict the dissolution kinetics of different pharmaceuticals. A schematic diagram of the dissolution process of the crystalline pharmaceutical is represented in Fig. 5. As displayed in Fig. 5, the crystalline pharmaceutical dissolution process in a solution can be roughly divided into two consecutive steps: in the first step, the crystalline pharmaceutical disintegrates, leading to the formation of a solid–liquid interface; in the second step, those solvated pharmaceutical molecules diffuse from the solid–liquid interface to the bulk phase of the solution [12].

The first step is the so-called surface reaction step, in which the chemical potential difference of the pharmaceutical between the solid phase and the solid–liquid interface is the thermodynamic driving force. The second step is the diffusion, and the chemical potential difference of the pharmaceutical between the solid–liquid interface and the bulk phase of the solution is regarded as its thermodynamic impetus. In this model, the surface reaction rate and diffusion rate are described by Eqs. (11) and (12) respectively:

$$J = k_s \left(\frac{\mu_i^s}{RT} - \frac{\mu_i^l}{RT} \right) \quad (11)$$

$$J = k_d \left(\frac{\mu_i^l}{RT} - \frac{\mu_i^b}{RT} \right) \quad (12)$$

where, μ_i^l refers to the pharmaceutical chemical potential ($\text{J} \cdot \text{mol}^{-1}$) at the solid–liquid interface; k_s and k_d refer to the rate constants of the surface reaction and the diffusion ($\text{mol} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$) respectively. The rate-controlling step in the dissolution process can be determined based on the values of k_s and k_d . In this model, the interfacial chemical potential of the pharmaceutical is obtained by the Statistical Rate Theory (SRT) [87], which is described by Eq. (13):

$$J = k_e \left(\exp \left(\frac{\mu_i^s - \mu_i^l}{RT} \right) - \exp \left(\frac{\mu_i^l - \mu_i^b}{RT} \right) \right) \quad (13)$$

where k_e means the equilibrium-exchange rate constant of the solute between the solid and liquid phase ($\text{mol} \cdot \text{m}^{-2} \cdot \text{s}^{-1}$). The k_e in the SRT can be calculated by Eq. (14):

$$k_e = \alpha_1 A_f x_i^l \sqrt{T} + 0.510 \alpha_2 \phi A_f \delta^2 \sqrt{\frac{\omega^3}{v} x_i^l} \quad (14)$$

where, α_1 and α_2 are the proportionality constants ($\text{mol} \cdot \text{m}^{-3}$), A_f means the fraction of the area of the interface for the transport, x_i^l means the solubility of the solute in mole fraction, T is the temperature (K), ϕ refers to a constant fraction of molecules that strike the solid surface, δ refers to the thickness of diffusion layer (m), ω is the axial fluid

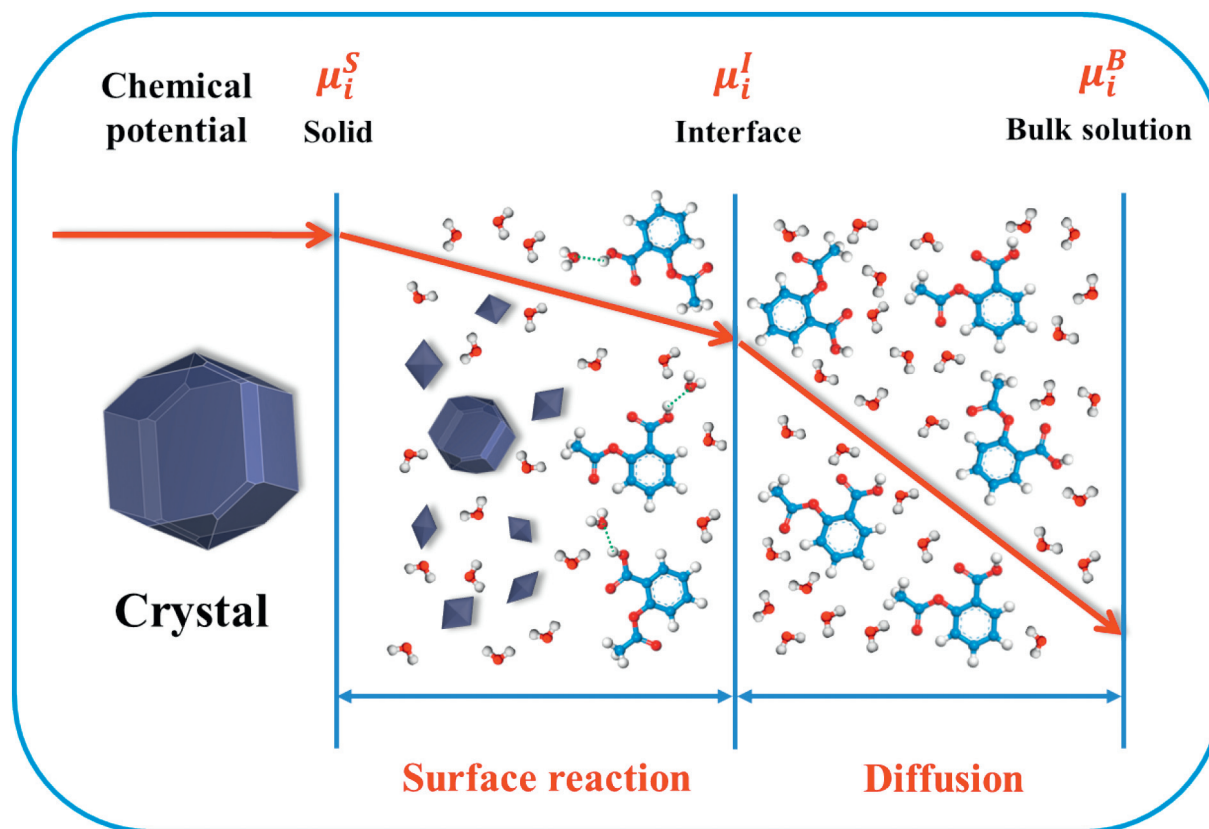


Fig. 5. The schematic diagram of the dissolution process of crystalline pharmaceuticals.

speed ($\text{r} \cdot \text{min}^{-1} \cdot \text{s}^{-1}$), and v is the kinematic viscosity of the solution ($\text{m}^{-2} \cdot \text{s}^{-1}$). The difficulty in the application of the chemical-potential-gradient model lies in obtaining the reliable chemical potential of the pharmaceutical in each phase during the dissolution process. The chemical potentials obtained by the PC-SAFT, as well as the statistical rate theory are further used to analyze the dissolution mechanism [12,70,88–93].

Ji *et al.* analyzed the dissolution kinetics of different paracetamol/Eudragit® formulations by using this model, which helped to select suitable excipients for controlled pharmaceutical dissolution [91]. The dissolution rate-controlling steps of different pharmaceuticals and their formulations under different experimental conditions were determined. Paus *et al.* adopted the two-step chemical potential-gradient model to investigate the dissolution mechanism of different pharmaceuticals (such as indomethacin, naproxen, and glibenclamide) in aqueous solutions and buffer solutions with different pH values and the dissolution rate-controlling steps (the surface reaction or diffusion) were identified [88]. They found that the dissolution mechanism of active pharmaceutical ingredients was affected by both the thermodynamic driving force and the kinetic rate constant. Effects of temperature, stirring rate, and the kinds of excipients on pharmaceutical dissolution kinetics and dissolution mechanism were also studied [12,89–93]. It was found that the solubility of drugs, the pH value of solutions, and the addition of excipients all had enormous impacts on the dissolution mechanism of pharmaceuticals. Ji *et al.* analyzed the dissolution mechanism of naproxen and indomethacin from solid dispersion at various temperatures, stirring rates, and pH values using the chemical-potential-gradient model and proposed suitable approaches to increase the dissolution rate of APIs. The dissolution kinetics of naproxen and indomethacin was predicted, which was consistent with the experimental data well [12]. What's more, based on the intrinsic dissolution kinetics of the pharmaceuticals and the surface-area reduction of the

pharmaceutical tablets in the dissolution process, Paus *et al.* predicted the dissolution kinetics of cylindrical tablets at different temperatures, stirring rates and pH values by combining PC-SAFT and the chemical potential gradient model [89]. The predicted results showed in great agreement with the results in the experiment.

In summary, the PC-SAFT can successfully predict the solubility of diverse pharmaceuticals under different conditions, and the combination of PC-SAFT with the chemical-potential-gradient model can be used to explain the dissolution mechanism of crystalline pharmaceuticals and their formulations. Compared with the dissolution process, crystallization is also a phase transition process essentially. Generally, crystallization also roughly follows two-steps: diffusion step and surface reaction step. Therefore, it is expected that the chemical-potential-gradient model can be modified to investigate the pharmaceutical crystal growth mechanism and predict its kinetics. The rates of diffusion and surface reaction during the crystallization process are expressed as Eqs. (15) and (16):

$$G = k_d \left(\frac{\mu_i^B}{RT} - \frac{\mu_i^I}{RT} \right) \quad (15)$$

$$G = k_s \left(\frac{\mu_i^I}{RT} - \frac{\mu_i^S}{RT} \right) \quad (16)$$

Parameters in the PC-SAFT can be determined by the model regression based on some existing experimental data. The equilibrium concentrations and chemical potentials under different conditions can be calculated (especially for some complex systems, *e.g.*, the ternary system with polymers), which is used for the further calculation of the crystallization driving force. The chemical potentials of a pharmaceutical in the bulk phase μ_i^B and in a solid state μ_i^S are calculated based on a thermodynamic model (*e.g.*, the PC-SAFT) and its bulk concentration

and solubility respectively. The interfacial chemical potentials of a pharmaceutical μ_i^l can be calculated by Eq. (17):

$$G = k_e \left(\exp\left(\frac{\mu_i^l - \mu_i^s}{RT}\right) - \exp\left(\frac{\mu_i^s - \mu_i^l}{RT}\right) \right) \quad (17)$$

Parameters k_d , k_s , and the constants $K_1 = \alpha_1 A_f$ and $K_2 = \alpha_2 A_f \delta^2$ are fitted to the experimental data based on Eqs. (15), (16) and (17). By comparing k_d and k_s , the rate controlling step of the crystallization rate can be further determined. The total rate constant k_t of pharmaceutical crystallization is calculated by Eq. (18):

$$\frac{1}{k_t} = \frac{1}{k_d} + \frac{1}{k_s} \quad (18)$$

And the crystallization rate of pharmaceuticals in aqueous solution is defined as the Eq. (19):

$$G = -\frac{1}{A} \cdot V \cdot \frac{dc_i^B}{dt} \quad (19)$$

According to Eqs. (15) and (16), the crystallization rate of pharmaceuticals can be expressed by the total rate constant k_t and the chemical potential difference of pharmaceuticals in the bulk phase and the solid phase, as shown in Eq. (20):

$$G = k_t \left(\frac{\mu_i^B}{RT} - \frac{\mu_i^S}{RT} \right) \quad (20)$$

Finally, the crystallization profiles of pharmaceuticals in aqueous solution can be calculated and predicted by combining Eqs. (18), (19) and (20). However, the determination of the interfacial chemical potential of pharmaceuticals is a great challenge. It is still questionable whether SRT is suitable to determine the interfacial chemical potential of pharmaceuticals during the crystallization process. Further research is required due to the complexity of mass transfer at the solid–liquid interface in the crystallization process. Molecular simulation may be a promising approach that can help to get access to more detailed information on the interfacial thermodynamic properties of pharmaceuticals at the molecular level.

5. Molecular Simulation

With the rapid development of experimental approaches (e.g., cryo-electron microscopy, *in situ* electron microscopy, and atomic force microscopy), researchers have gained an increasingly profound understanding of the thermodynamic and kinetic behaviors in the crystallization process of various substances [17,31]. However, it is still challenging to obtain microscopic details of molecules in the crystallization process, so that these advances are still far from a true understanding of the crystallization mechanism. Also, a large number of crystallization experiments are time-consuming and labor-requiring, which hinders the further development of industrial crystallization. Fortunately, computer simulations can not only explore the crystallization mechanism at the molecular level but also obtain the thermodynamic and kinetic properties of molecules. Therefore, it is necessary to introduce computer simulations into the field of crystallization research. Compared to traditional experimental methods, the process of molecular aggregation and crystal formation can be observed visually by molecular simulation. The application of experimental approaches in the study of crystallization is limited by two reasons: 1. size problem, crystallization is a process of transition from molecules to crystals, which requires ultra-high-resolution equipment to observe the process in real time; 2. time problem, nucleation usually takes places in a quite short time (nano-seconds) which is very hard to be captured by the existing instruments. For the thermodynamic method, a more detailed and

accurate description of the crystallization process is very important because it affects the accuracy and predictability of the model. Molecular simulations can help to observe the crystallization process at the molecular level, which is helpful for the establishment of a more accurate non-equilibrium thermodynamic model. It can be seen that all these problems can be solved by molecular simulations to a certain extent, which can be used as a supplement to existing research methods. Some successful applications of molecular simulations in the investigation of crystallization (e.g., the nucleation simulation and crystal habit prediction) will be introduced here. But some problems still exist in the application of molecular simulations, which will be discussed later.

Molecular simulations based on classical molecular force field and molecular mechanics are used to obtain the trajectories of molecules and predict the structure and properties of them by solving the Newton equation of motion. Molecular simulations mainly include the Monte Carlo (MC) and molecular dynamics (MD) simulation. MC simulation is an approach that employs stochastic simulation and probability statistics to gain the thermodynamic properties of a specific substance, which cannot acquire time-related properties such as nucleation rate [94]. With the continuous advancement of the fundamental theory, the researchers developed the Kinetic Monte Carlo method (KMC), which is an MC method specifically designed to simulate the long-term evolution of a system. Its core idea is the same as the MC: thermal perturbations simulation by pseudo-random numbers. In the KMC simulation, only the thermal disturbances causing the configuration transition are considered, and the evolution of the system with time rather than the equilibrium state is mainly simulated. Although the KMC method enlarges the simulation time scale of the system and relatively accelerates its sampling speed, it is generally applicable to the mean-field approximation system (such as reaction and diffusion systems). It only reflects the properties with the mean field approximation method, which is only suitable for low-dimensional space instead of investigating the microscopic process and scientific problems related to the mechanism. While the MD simulation method simulates the overall system by calculating the interaction potential and interaction force between molecules based on Newtonian mechanics. Therefore, this method can capture various time-dependent properties of the simulated system, for instance, the trajectory of the system, the diffusion coefficient, and so on. In summary, the MD simulation can be used to observe the molecular movement at the micro level, and obtain the molecular transfer properties at the interface during pharmaceutical crystallization. Schilling and his co-workers using MD and MC methods to study the nucleation process of hard sphere colloidal suspensions and found that the existence of low orientational bond-order precursors by comparing the simulated nucleation rate with experimental measurements [95]. In addition, MD simulation can achieve the ergodicity of each state, thus giving the values of macro statistics, such as the entropy and enthalpy of the system. In this part, some applications and shortcomings of molecular dynamics simulation in the field of pharmaceutical crystallization will be focused on.

Crystal nucleation is a rare event with comparatively slow growth, as a result of which the MD simulation is mainly used to study relatively simple systems in the early stage. Matsumoto with his collaborators studied the spontaneous nucleation process of ice using the MD simulation, which was found that the formation of long-lived hydrogen bonds led to spontaneous nucleation [96]. Subsequently, the same simulations were made by Vrbka and Mucha to investigate the homogeneous nucleation of ice in the subsurface and NaCl nucleation from the melt of nanodroplets successfully [97,98]. Li and his coworkers simulated ice nucleation by a coarse-grained water model and found the critical nuclei consisted of two polymorphs of ice (cubic ice and hexagonal ice) [99]. All these examples confirmed the great application prospect of MD in the field of crystallization. More importantly, MD simulation can be used to provide molecular interactions and cluster structures before crystal nucleation at the molecular level. For example, MD simulations were applied to calculate the intermolecular interactions between

fenofibrate and additives to select suitable crystallization inhibitors [100]. Studies on the nucleation process of urea from aqueous solution conducted by Salvalaglio *et al.* demonstrated that some hydrated dense clusters formed during nucleation, which followed a two-step nucleation mechanism well [101].

In addition to the fields mentioned above, researchers used MD simulation to predict pharmaceutical crystal morphology in recent years. By the utilization of MD simulations depending on the attachment energy model, Yang *et al.* analyzed the impacts of different solvents on the crystal habit of thiamine hydrochloride [102]. Based on the molecular structure, Zhang *et al.* successfully predicted the ibuprofen's crystal structure and habit by using MD simulations combining the AE model and the modified attachment energy (MAE) model [50]. Also, amorphous pharmaceuticals have attracted much attention in the field of the pharmaceutical industry recently due to their high solubility and bioavailability, but metastable amorphous pharmaceuticals are easy to recrystallize. Many existing studies have shown that polymers can effectively inhibit amorphous pharmaceuticals crystallization [103,104], but the ability and mechanism of polymers to inhibit crystallization is still unclear. Molecular simulation provides an effective means for screening polymers that effectively inhibit the crystallization of amorphous pharmaceuticals. Wang *et al.* investigated the polymer-drug interactions in amorphous solid dispersions (ASDs) and proposed that DFT could help to select and design suitable polymers to inhibit the crystallization of ASDs [105]. Poornachary *et al.* studied the influence of polymers (HPMC and PVP) on the growth kinetics of naproxen using molecular simulations. It was found that the interaction between the polymers and the specific crystal surface of naproxen or hydrophobic-hydrophilic interaction can effectively regulate the growth rate of naproxen in particular directions, which provides some guidance for choosing suitable polymer to adjust crystal morphology and size [106]. Mandal and his collaborators proposed a multi-scale method to simulate the growth of crystals in the presence of polymer excipients using a known coarse-grained model (CG). CG model has succeeded investigating the effects of cellulose polymers modified by different functional groups (such as acetic acid, hydroxypropyl, and succinic acid (Su) groups) on the crystallization of many small organic molecules (isoniazid, urea, sulfamethoxazole, prilocaine, oxcarbazepine, and phenytoin), which was found the properties of groups occupy a significant role in inhibiting crystal growth [107]. These examples showed that molecular simulations can help to select more suitable polymer inhibitors more easily, which can greatly save human and material resources comparing to try and error experimental methods.

It can be seen that molecular simulation has achieved extensive attention in the field of pharmaceutical crystallization recently, especially in predicting the crystal morphology of the final product and selecting a suitable crystallization inhibitor. In addition, molecular simulation has been widely applied to investigate the nucleation mechanism too. In 2009, Walsh *et al.* used MD simulation to study the spontaneous nucleation and growth of methane hydrate. It was found that the arrangement of methane adsorbed in the bowl-like structure before the formation of the hydrate was unpredictable, and the size of the nucleus and the position of the molecules all have an important influence on hydrate nucleation [108].

Although MD simulation has made some progress in the study of nucleation processes, there are still some problems. Major problems for the MD simulation in the investigation of crystal nucleation are usually the restraints of computing power, mainly involving time-scale problems, length-scale problems, and the collection of statistical data in the nucleation process. From molecular simulation sight, nucleation usually takes place on a long time scale. Assuming that the simulated system has 100,000 particles, a simulated box with a length of 12 nm is used. It means that the sampling is in the volume of 10^{-24} cm^3 , that's to say, the nucleation rate is equivalent to 10^{-24} s^{-1} . Then one nucleation event could be observed every 10^{24} s (10^{16} years), which means investigating the whole process of nucleation is almost impossible

[109]. As shown in the above example, the number of molecules contained in the simulation system and its size determine the available simulated time scale. Therefore, the second obstacle of MD simulation is the length-scale. Generally, the more details molecular simulation considers, the more accurate the simulation results are, but the computing power limits the scale that simulation can achieve. That is, whether the all-atom model is needed for the simulation. In many cases, the interaction between critical nuclei is considered in molecular simulation. However, because of the influence of periodic boundary conditions on nucleation, an abnormal nucleation rate is often generated. Therefore, the size of the simulation box significantly larger than that of the critical nucleus is required for the simulation of the nucleation process. Also, because the nucleation rate follows a Poisson distribution, it is far from adequate to accumulate a single nucleation statistics for the MD simulation, which requires a large number of statistical data. What's more, limited by insufficient computing power, it is needed to take as little time as possible to simulate practical problems with a long time span, which is the so-called equilibrium problem. For instance, if repeating the $1 \mu\text{s}$ experimental process in 1 ns, results may deviate from the experimental findings because the quasi-static process is non-equilibrium in the case of a too short time, and many properties may be entirely different.

For the above reasons, the application of MD simulation in the field of nucleation still needs great improvement. Therefore, researchers often choose fields system or make reasonable assumptions or approximations for some variables (such as supersaturation, undercooling, and interatomic potential), which is often called the coarse-grained method [110]. A case in point is that the early researchers often chose the hard-sphere model systems (colloid system) as the nucleation simulation object because the consideration of the interaction between these particles is not needed [111]. In this relatively simple system, it is supposed that the collision originates from the elastic collision between particles [112]. By applying the coarse-grained force field and meta-dynamics, Mandal and his coworkers simulated the crystallization process of phenytoin and predicted possible polymorphs [113]. The coarse-grained results of King *et al.* showed different aggregation pathways and nanoparticles in the process of CaCO_3 aggregation and crystallization, which is related to diverse mineralization stages [114]. These coarse-grained models greatly improved computational efficiency and speeded up the dynamics of the crystallization simulation. However, coarse-grained models are reduced-resolution models, which provide huge challenges to obtain accurate structural and thermodynamic properties. What's more, the selection of suitable force fields in the coarse-grained method is quite difficult.

The time-scale problem of standard brute force MD simulation leads to its limitations in the study of nucleation and the adoption of the Boltzmann sampling method [115]. The enhanced sampling method changes the way the system explores its configuration space so as to observe reasonable and effective nucleation events in the accessible time [112]. It is a non-physical sampling method, which can effectively calculate the difference of free energy while maintaining the reasonable distribution of the given statistical set state and getting rid of the constraints of Boltzmann statistics. For the nucleation process of supercooled liquids, the enhanced sampling method is generally based on the change in free energy, and umbrella sampling (US) [116] and metadynamics [117,118] are representatives. In these two methods, the surface free energy of the system is obtained by the coarse-grained method using ordered parameters or collective variables. How to select these parameters correctly influences the simulation results greatly [17]. An external bias is then added to modify the sampling of the configurational space and rearrange the free energy distribution, and calculate the free energy barrier finally. However, owing to the addition of external bias, this method affects the actual systematic kinetics to some extent and is not conducive to the recognition of the nucleation mechanism. So it also requires some additional simulation methods, such as MC and KMC simulations, to obtain nucleation kinetic

parameters. There is also a type of sampling methods based on ordered parameters called the path sampling method. These methods do not use external bias but use importance sampling to enhance the generation of natural fluctuations in the system. The path sampling methods are roughly divided into two types. The first type divides the path between the liquid phase and solid phase into a series of interfaces based on the values of ordered parameters, and samples the probability of each interface of the system to obtain the cumulative probability related to nucleation. Typical samples of this type are transition interface sampling [119,120] (TIS) and forward flux sampling [121] (FFS). Another approach of path sampling is to sample the full ensemble of trajectories, like transition path sampling [122] (TPS). Path sampling method combined with some other simulation methods, such as committer analysis distribution and thermodynamic integration, can easily obtain the critical nucleus radius and the free energy difference between solid and liquid phases. What's more, it will not change the system dynamics, so it can better explore the nucleation mechanism. Filion *et al.* investigated the nucleation process of hard spheres and predicted the nucleation rates by standard brute force MD simulation, MD simulations using the US and FFS [123]. It was found that the rates obtained by these three methods were in good agreement with the experimental results for high supersaturations.

In summary, MD simulation has made good progress in the field of crystallization, which greatly promotes the study of crystallization mechanism. However, for the application of MD simulations in the field of crystallization, there are still some limitations, such as the inadequacy of computing power and the inaccuracy of the force field. The most effective way to solve the problem of insufficient computing power is to adopt an effective sampling method to avoid the waste of computing power caused by traversing all situations. Therefore, it is necessary to develop some more efficient sampling approaches. The accuracy of the force field is also mainly relied on computing power. Due to the limited computing power, many details are neglected or coarse-grained, and the simulation scale and time are limited. Therefore, it is quite important to develop more efficient simulation methods and sampling methods.

6. Conclusions and Challenges

In this paper, some progress in the study on nucleation and crystal growth mechanism are reviewed. Successful applications and problems of thermodynamic models and molecular simulations in the field of pharmaceutical crystallization are also discussed. Although experimental approaches have developed rapidly in recent years, it is still hard to explain the crystallization mechanism from the molecular level through experiments. Therefore, it is urgent to develop new theoretical models and combine them with advanced physical characterization methods to study the mechanism of pharmaceutical crystallization.

As the most critical step in controlling crystallization, the time-scale and length-scale involved in nucleation are too small, which results in the imprecise mechanism. Previous studies have shown that CNT is not accurate and unique, while the multi-step nucleation pathway exists widely. However, there are still some deficiencies in the multi-step nucleation theory, especially the lack of quantitative analysis and precise kinetic data. This aspect of the research has a long way to go. Then, whether nucleation follows a single mechanism or whether there are multiple nucleation mechanisms is still debatable.

After years of development, a series of mature theories and models have been formed for crystal growth research, but these theories and models still have some limitations. In the future, more attention should be paid to the effects of the crystal phase, environmental phase, and interface on crystal growth rate. What's more, crystal growth is a dynamic process, as a result of which, many variables are difficult to measure accurately in the growth process. Therefore, the intervention of nonequilibrium thermodynamics is urgently needed to help investigate the crystal growth mechanism.

CNT proposed by Gibbs is usually applied to study the thermodynamic properties in the crystallization process based on the difference in free energy. This theory has been widely employed due to its simplicity. But CNT has a lot of assumptions, hence the results predicted by it are quite different from the actual observations. The chemical-potential-gradient model combined with the perturbation chain-statistic association fluid theory (PC-SAFT) has been successfully used in the study of the pharmaceutical dissolution mechanism and prediction of pharmaceutical dissolution kinetics. The model can be further developed and extended to the field of drug crystallization to analyze the mechanism of pharmaceutical crystallization and to achieve reliable prediction of drug crystallization kinetics.

With the rapid development of computer simulation technology, molecular simulations have gradually been applied in the crystallization, making it possible to investigate the crystallization process and mechanism at the molecular level. MD simulation is widely used, but its natural time-scale and length-scale problems limit its broad application. Although brute-force MD simulations can provide more accurate simulation results, it takes a lot of computing time at this stage. Fortunately, these shortcomings can be effectively avoided by some ingenious methods, such as using coarse-grained methods and enhanced-sampling simulations. However, the application of these methods is still limited to some simple systems, like the hard sphere system and the Lennard-Jones system. For some more complex systems including heterogeneous nucleation, the application of MD simulation is still difficult. Therefore, the combination of molecular simulations and advanced experimental approaches is expected to make greater contributions to the study of the nucleation mechanism. Moreover, the establishment of computational methods and models, such as the continuous improvement and enhancement of sampling approaches, are essential for the application of molecular simulation to a larger and more complex realistic system.

7. Future Perspectives

It is essential to investigate the mechanism of nucleation and crystal growth as they are the most critical steps of pharmaceutical crystallization. The vigorous development of various emerging analytical tools and approaches to further strengthen the observation and analyzing of the crystallization process from an experimental perspective is quite important. But limited by means of the experimental approaches, direct observation of the process of crystallization to analyze micro-mechanism is still quite difficult, so it is necessary to solve the existing problems from some other perspectives. As the basis of theoretical chemistry, thermodynamics has been widely used in various fields for many years because it can be used despite the lack of microscopic mechanisms and multiple parameters that are difficult to measure. In recent years, non-equilibrium thermodynamics was successfully applied to investigate the dissolution mechanism of pharmaceuticals, it is expected that this model is promising to be extended for pharmaceutical crystallization.

Molecular simulation, as a new research method, provides a novel way to solve scientific problems from a micro-perspective. Its tremendous application in various fields in recent years shows that it has great potential in the investigation of the crystallization mechanism, although there are still shortcomings like insufficient computing power. It was shown that the development and utilization of some more efficient molecular simulation methods, sampling approaches and computer technology (such as quantum computers) may greatly promote the application of molecular simulation in the field of crystallization. It is foreseeable that thermodynamics combined with molecular simulation will undoubtedly make a great contribution to the analysis of the crystallization mechanism. Future development trends and attractive research directions may be as follows:

1. The chemical-potential-gradient model based on non-equilibrium thermodynamics theory is promising to investigate the crystallization mechanism of pharmaceuticals. For the successful application of this model, how to get access to the reliable interfacial chemical potential of pharmaceuticals is the most important but rather difficult. Molecular simulation combined with *ab initio* atomistic thermodynamics which employs the information on the first-principles potential energy surface (PES) to calculate appropriate thermodynamic potential functions may be an effective means to obtain thermodynamic properties of pharmaceuticals at the interface.
2. Investigations of mass and heat transfer in the transition layer near the crystal interface during crystal growth may be constructive for studying the mechanism of crystal growth.
3. The formation of intermediate clusters in the nucleation process and the mechanism of the subsequent rearrangement process are still unknown, and it is still unrealistic to observe the entire nucleation process clearly by experimental means within its foreseeable time. To explore the nucleation process by molecular simulation methods will still be a hot spot, especially for the rearrangement process of the intermediate clusters. Therefore, the development of methods that can speed up the simulation process is critical, such as the coarse-grained method, and enhanced sampling.
4. Due to the development of non-equilibrium thermodynamics theory (e.g., chemical-potential-gradient model), the limitation of classical thermodynamics that does not involve process rate, which is quite important for the research of crystallization, has been broken. Furthermore, molecular simulation can help to calculate various energy barriers, interfacial free energies in the crystallization process, and multiple interaction parameters required by thermodynamics, which is helpful to establish more accurate and effective non-equilibrium thermodynamic models.

In summary, the further study of pharmaceutical crystallization urgently needs the involvement of diversified research approaches. Even though there are some restrictions or shortcomings in thermodynamics and molecular simulations, the cross-application of the two methods can effectively achieve complementary advantages, it can be predicted that they will productively promote the study and understanding of drug crystallization mechanism.

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