Molecular Engineering of Co-crystallization Process in Holt Melt Extrusion Based on Kinetics of Elementary Molecular Processes

**Abstract**

Continuous co-crystallization in a twin-screw granulator is a promising technology. In order to fundamentally optimize the process flow, it is necessary to investigate the kinetics of molecular interactions within the mixture and the effect of these interactions on co-crystal formation. In this study, the processes governing the co-crystallization of ibuprofen and nicotinamide were considered. Density functional theory calculations employing the Hirshfeld partitioning scheme were used to identify donor–acceptor sites on each molecule. A total of twenty-one different molecular interactions was identified (nine of ibuprofen and nicotinamide (resembling co-crystals), three of ibuprofen and itself (resembling the ibuprofen dimer), and nine of nicotinamide and itself (resembling the nicotinamide dimer)). Each interaction was defined as an artificial reversible reaction and the kinetics were calculated using the transition state theory of chemical reactions, where linear and quadratic synchronous transition methods were utilized to identify transition-state structures; the minimum energy path was determined using the nudged elastic band method. A kinetic Monte Carlo framework was used to study the collective/coupled effect of reactions on the progress of the co-crystallization process. it was found that operating at low temperatures (especially lower or very close to the melting temperature of ibuprofen) for longer residency times creates a safe route for maximizing the presence of ibuprofen and nicotinamide co-crystals. If the proposed route is applied, the purity and properties of the produced co-crystal would be significant, especially its desirable availability within the body.

**Keywords**: twin-screw granulator; hot melt extrusion; co-crystallization; kinetic modeling

# Introduction

In the pharmaceutical industry, co-crystallization is commonly used to improve the properties of drug formulations, such as flowability, tabletability, and solubility [[1](#_ENREF_1)]. Co-crystallization involves mixing an active pharmaceutical ingredient (API) with low solubility with another pharmaceutically approved substance with better solubility (known as a conformer) [[2](#_ENREF_2)]. The benefit of co-crystallization is that the co-crystals are solid at room temperature [[3](#_ENREF_3)]. A co-crystal is usually formed through hydrogen bonds, π-π forces, and van der Waals interactions [[3](#_ENREF_3)]. This is very important because the formation of co-crystals does not change the pharmacological effects of drugs [[4](#_ENREF_4)].

Pharmaceutical industries utilize a twin-screw granulator for the co-crystallization process [[5](#_ENREF_5)]. Twin-screw granulators are versatile units because they enable continuous processing with a short residence time, flexibility, and the ability to conduct chemical reactions [[6](#_ENREF_6)].

Continuous co-crystallization using a twin-screw granulator has been the subject of many studies, both theoretical and experimental, as reviewed elsewhere [[7-10](#_ENREF_7)]. Experimental studies have mainly focused on individual operating parameters such as the type and rotation speed of the screw, screw configuration, temperature, residence time, and particle size distribution of the produced formulation, which provides very limited and strictly empirical insight into the co-crystallization process. This is because of the cost of the materials, maintenance, time required to conduct the experiments, device set-up and management, human resources, difficulties in implementing process analysis tools, and mainly the limitations in modifying or reconfiguring the twin-screw granulator. On the other hand, most of the currently reported theoretical studies are top-to-bottom approaches and require experimentally correlated parameters such as the particle size distribution as input. This sets a limit on conducting a parameter-free investigation of the continuous co-crystallization process, for which no prior experimentation would be needed.

Parameter-free investigation of the continuous co-crystallization process can be achieved by using a bottom-up theoretical approach, where the properties of the materials and mixtures are calculated from scratch using computational techniques such as density functional theory and molecular dynamics [[11](#_ENREF_11)]. The importance of a bottom-up approach is that it can be applied to any system of materials; therefore, it can be used as a generic predictive tool.

Therefore, the aim of this study is to employ a bottom-up theoretical approach to discuss the following: (1) What type of inter/intra-particle interactions are possible between molecules during co-crystallization? (2) What are the characteristics of these interactions? (3) To what extent do such interactions remain and evolve during co-crystallization? (4) What types of structures (co-crystals/dimers) emerge as a result of the interaction between molecules? and (5) most importantly, how do these interactions govern co-crystal formation and quality? Obtaining insight into such kinetic characteristics should be helpful in the design and optimization of the process for achieving optimal product formulations.

In the present study, the co-crystallization of ibuprofen and nicotinamide is considered. This system was chosen because ibuprofen is frequently used to treat pain and fever [[12](#_ENREF_12)]. The poor solubility of ibuprofen in the stomach results in sluggish absorption into the bloodstream and low bioavailability [[13](#_ENREF_13), [14](#_ENREF_14)]; therefore, fast relief cannot be achieved [[15](#_ENREF_15)]. The addition of nicotinamide, as a conformer, to ibuprofen and the formation of a co-crystal has been advised to mitigate the poor solubility of ibuprofen (due to the higher solubility of the co-crystal) and low bioavailability of the drug [[16](#_ENREF_16)]. In addition, relevant data are available in the literature [[17-19](#_ENREF_17)] enabling assessment of the reliability of the present approach.

This report is organized as follows: First, an overview of the methodology is given in the Section 2, followed by detailed data collection and construction of molecular models. The results are discussed and compared with available data reported in the literature. The associated data are freely available as specified in the data availability section.

# Theoretical background

To determine the type and number of different inter/intramolecular interactions, the local sites on each molecule where donor-acceptor exchange can be realized must first be identified. The prominent inter-molecular interactions occur through donor-acceptor exchange. This requires calculation of the surface charge density and potential [[17](#_ENREF_17)]. To achieve this, density functional theory calculations were performed to determine the surface charge density and potential. The chemical structures of ibuprofen and nicotinamide molecules were retrieved from the National Institute of Standards and Technology Reference Database Number 69: <https://webbook.nist.gov/chemistry>. Density functional theory calculations and relaxation of the molecules were carried out using generalized gradient approximations with the Perdew-Becke-Ernzerhof functional [[20](#_ENREF_20)] including implicit solvent [[21](#_ENREF_21)] (as described by the COnductor-like Screening Model [[22](#_ENREF_22)]) and thermal smearing [[23](#_ENREF_23)] (for enhanced self-consistent field calculations [[24](#_ENREF_24), [25](#_ENREF_25)]), using the double numerical basis and d-polarization function [[26](#_ENREF_26)] level of theory. The double numerical basis with d-polarization includes diffuse functions [[26](#_ENREF_26)] so that long-range effects, which are not negligible here, can be treated properly. The surface site charge densities [[27](#_ENREF_27)] were determined by employing the Hirshfeld partitioning scheme [[28](#_ENREF_28)].

In a mixture, each molecule can be involved in donor-acceptor exchange with the same type of molecule or another type. Donor-acceptor interactions between a molecule and the same type of molecule resemble dimers. For example, the dimer of ibuprofen involves the interaction of one ibuprofen molecule with another ibuprofen molecule. The same is true for the dimer of nicotinamide [[17](#_ENREF_17)]. The most interesting donor-acceptor exchanges occur when ibuprofen molecules interact with nicotinamide as these interactions are representative of plausible co-crystals of ibuprofen and nicotinamide. Therefore, in the nicotinamide and ibuprofen systems, three different macromolecular groups (pairs), namely, (1) ibuprofen dimers, (2) nicotinamide dimers, or (3) co-crystals of ibuprofen and nicotinamide can be found because of such molecular interactions. Hereinafter, these molecular interactions are referred to as elementary molecular processes.

To analyze the stability and formation properties of these macromolecular groups (pairs), the solvation and binding energies were calculated. Negative solvation and binding energies are more desirable, as a negative value reflects the spontaneity of pair formation and better stability [[29](#_ENREF_29)]. For this purpose, the respective molecular models were created by placing the molecules (involved) in close contact [[17](#_ENREF_17)] (known as molecular docking) and the same structure relaxation was performed using density functional theory calculations. The binding energies (*Eb*) as *Eb* = *Eij* – (*Ei* + *Ej*) were calculated, where *Ei* and *Ej* are the energies of ibuprofen and/or nicotinamide, and *Eij* is the energy of the pair. The thermodynamic solvation energy (with reference to water) was calculated following Hirano’s formulation [[30](#_ENREF_30)].

For each of these macromolecular groups (pairs), an artificial/intuitive reversible reaction path of the form *A* + *B ↔ AB* was defined, where *A* and *B* can be either ibuprofen and/or nicotinamide, and *AB* is the corresponding macromolecular group (pair). Here, the forward path is like an association reaction where *A* and *B* form *AB*, and the backward path is like a dissociation reaction where *AB* breaks to its building blocks (molecules) *A* and *B*. It is evident that this definition considers the non-equilibrium thermodynamic characteristics of elementary molecular processes. However, it should be emphasized that this does not suggest that these interactions are *reactions* in a chemical context, but this definition enables examination of the kinetics of elementary molecular processes leading to the formation of co-crystals and/or (undesirable) dimers, and the concentrations of each species can be calculated.

For each defined reaction, the transition state theory of chemical reactions formulated by Wigner Eyring et al. [[31-33](#_ENREF_31)] was used to calculate the reaction rate constants. The reaction rate constant is given as: , where *kB* is Boltzmann’s constant (1.38064852 × 10‒23 J.K‒1), *h* is Planck’s constant (6.626069934 × 10‒34 J.s), *R* is the universal gas constant (8.3144598 J.K‒1.mol‒1), and *T* is the temperature in Kelvin [[34-36](#_ENREF_34)]. In order to identify transition-state structures in each reaction, linear and quadratic synchronous transition methods were used in conjunction with vibrational analysis [[37](#_ENREF_37)]. The nudged elastic band method [[38](#_ENREF_38)] was used to identify the minimum energy path [[39](#_ENREF_39)]. Once all the transition state structures were identified, the energy of activation was defined as the difference between the reactant energy and energy of the transition state. When there is more than one transition state structure, the transition state has the highest energy [[40](#_ENREF_40)]. Transition state theory (the statistical mechanical model) was employed herein instead of the Arrhenius model because the activation energy *E* is temperature dependent, which is accounted for in transition state theory [[41](#_ENREF_41), [42](#_ENREF_42)].

Once all reaction kinetics were determined, the collective/coupled effect of these elementary molecular processes on formation of the pairs was studied over a wide range of temperatures, which encompasses the operating condition of holt melt extrusion using a twin-screw granulator. The kinetic Monte Carlo framework was used to couple these elementary molecular processes [[43](#_ENREF_43)]. In the kinetic Monte Carlo calculations, an initial particle configuration of 16384 (128 × 128) particles that contained equal amounts of ibuprofen and nicotinamide was used. The kinetics of the coupled elementary molecular processes were integrated over a relative period of 105 s. Five different temperatures were considered: 300, 325, 350, 375, and 400 K, and the conversion of ibuprofen and nicotinamide to each of the aforementioned pairs was determined.

# Results and discussion

In a prior publication, we discussed and presented in detail the quality of the data generated by the present density functional theory calculations by comparison with those reported in the literature, by considering a wide range of molecular properties [[17](#_ENREF_17)]; therefore, this discussion is excluded from the present study. The determined surface charge densities of ibuprofen and nicotinamide, through which the donor-acceptor exchanges, and consequently macromolecular groups (pairs), are possible, were identified using density functional theory calculations, as shown in Fig. 1 [[17](#_ENREF_17)].

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| --- | --- |
| **nicotinamide** | **ibuprofen** |
| Fig. 1. Surface charges of ibuprofen and nicotinamide as calculated using density functional theory [[17](#_ENREF_17)]. | |

Considering the surface charge densities of ibuprofen and nicotinamide, a total of 21 different donor-acceptor exchange interactions can be established. An ibuprofen molecule can interact with another ibuprofen molecule and form a dimer of ibuprofen through three different combinations of donor-acceptor exchanges, as shown in Fig. 2 [[17](#_ENREF_17)]. It was determined herein that two of these three dimers of ibuprofen, labeled as DI–1 and DI–2, were experimentally observed, as reported in the literature [[44](#_ENREF_44), [45](#_ENREF_45)]. A nicotinamide molecule can interact with another nicotinamide molecule and form a dimer of nicotinamide through nine different combinations of donor-acceptor exchanges, as shown in Fig. 3 [[17](#_ENREF_17)]. It was found that one of these nine dimers of nicotinamide, labeled DN–6, was experimentally observed, as reported in the literature [[46](#_ENREF_46)]. A nicotinamide molecule can interact with an ibuprofen molecule through nine different combinations of donor-acceptor exchanges to form a co-crystal, as shown in Fig. 4. Through a literature review, it was noted that the form labeled as CO–2 has been experimentally observed in a number of reports [[47-49](#_ENREF_47)]. Soares and Carneiro [[47](#_ENREF_47), [48](#_ENREF_48)] used in-line Raman spectroscopy to identify CO–2. Kelly et al. [[49](#_ENREF_49)] also suggested that CO–2 is a typical co-crystal of ibuprofen and nicotinamide.

|  |  |  |
| --- | --- | --- |
| **DI-1** | **DI-2** | **DI-3** |
| Fig. 2. Identified dimers of ibuprofen [[8](#_heading=h.26in1rg)] | | |

|  |  |  |
| --- | --- | --- |
| **DN-1** | **DN-2** | **DN-3** |
| **DN-4** | **DN-5** | **DN-6** |
| **DN-7** | **DN-8** | **DN-9** |
| Fig. 3. Identified dimers of nicotinamide [[8](#_heading=h.26in1rg)]. | | |

|  |  |  |
| --- | --- | --- |
| **CO-1** | **CO-2** | **CO-3** |
| **CO-4** | **CO-5** | **CO-6** |
| **CO-7** | **CO-8** | **CO-9** |
| Fig. 4. Identified co-crystals of ibuprofen and nicotinamide. | | |

The stability and formation of these macromolecular groups (pairs) are governed by the solvation and binding energies [[29](#_ENREF_29)]. A positive binding energy means there is an energy barrier for formation of the pair [[17](#_ENREF_17)]. A more negative solvation energy means that the process of solvation is more spontaneous, and consequently the dissolution index would be much higher [[29](#_ENREF_29)]. A high dissolution index is of great interest, as it means higher availability of the formulation in vivo. The calculated solvation and binding energies are shown in Fig. 5.

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| Fig. 5. Calculated binding and solvation energies. |

The corresponding path for each elementary molecular process representing the formation of each macromolecular group (pair) from donor-acceptor exchanges between ibuprofen and/or nicotinamide was determined. The elementary molecular processes associated with dimers of ibuprofen are shown in Fig. 6. Figure 7 shows the elementary molecular processes associated with the nicotinamide dimers. The elementary molecular processes associated with the co-crystals of ibuprofen and nicotinamide are shown in Fig. 8. Each path shows how ibuprofen and/or nicotinamide interact with each other to form a new macromolecular group. For each path, the barrier energy and energy release were calculated, as listed in Table 1. A positive energy barrier value indicates that input energy is required to initiate the corresponding elementary molecular process. On the other hand, a negative value of the energy barrier indicates that the corresponding elementary molecular process can occur spontaneously and favorably. A negative value of the energy release indicates that the corresponding elementary molecular process is exothermic. In an exothermic process, the end-point structure is more stable than the intermediate molecules. A positive value indicates that the corresponding elementary molecular process is endothermic. In an endothermic process, the end-point structure has a higher energy than the intermediates, and the process therefore tends to undertake the backward path and decompose to form molecules. The energy release from an exothermic process can promote another process, as it provides the energy input to overcome the energy barrier of the secondary process. Therefore, a proper coupling method should be considered to reliably and efficiently study the collective effects of these endothermic and exothermic processes on concentration changes. For this purpose, the kinetic Monte Carlo method was employed in this study.

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| **DI-1** | **DI-2** |
| **DI-3** | |
| Fig. 6. Path corresponding to formation of ibuprofen dimers. | |

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| **DN-1** | **DN-2** |
| **DN-3** | **DN-4** |
| **DN-5** | **DN-6** |
| **DN-7** | **DN-8** |
| **DN-9** | |
| Fig. 7. Path corresponding to formation of nicotinamide dimers. | |

|  |  |
| --- | --- |
| **CO-1** | **CO-2** |
| **CO-3** | **CO-4** |
| **CO-5** | **CO-6** |
| **CO-7** | **CO-8** |
| **CO-9** | |
| Fig. 8. Path corresponding to formation of ibuprofen and nicotinamide co-crystals. | |

Table 1. Calculated forward path barrier energy (), backward path barrier energy (), forward path reaction energy (), and backward path reaction energy (); all energies are in kcal/mol

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | *Co-crystals of ibuprofen and nicotinamide* | | | | | | | | |
|  | **CO-1** | **CO-2** | **CO-3** | **CO-4** | **CO-5** | **CO-6** | **CO-7** | **CO-8** | **CO-9** |
|  | -18.932 | -5.355 | -3.170 | 1.068 | -6.192 | 1.776 | 0.408 | -4.765 | -3.997 |
|  | -14.760 | -22.007 | -7.976 | -16.593 | -20.840 | 1.270 | -16.827 | -18.715 | -14.425 |
|  | -4.172 | 16.652 | 4.806 | 17.661 | 14.648 | 0.506 | 17.235 | 13.95 | 10.428 |
|  | 14.76 | 22.007 | 7.976 | 16.593 | 20.84 | -1.27 | 16.827 | 18.715 | 14.425 |
|  | *Dimers of nicotinamide* | | | | | | | | |
|  | **DN-1** | **DN-2** | **DN-3** | **DN-4** | **DN-5** | **DN-6** | **DN-7** | **DN-8** | **DN-9** |
|  | 0.371 | -2.107 | -2.369 | -1.975 | 0.205 | 0.161 | 0.166 | 0.261 | -2.385 |
|  | -11.810 | -8.447 | -10.789 | -2.930 | -3.627 | -15.878 | -11.738 | -12.011 | -2.267 |
|  | 12.181 | 6.34 | 8.42 | 0.955 | 3.832 | 16.039 | 11.904 | 12.272 | -0.118 |
|  | 11.81 | 8.447 | 10.789 | 2.93 | 3.627 | 15.878 | 11.738 | 12.011 | 2.267 |
|  | *Dimers of ibuprofen* | | | | | | | | |
|  | **DI-1** | **DI-2** | **DI3** |  |  |  |  |  |  |
|  | -5.051 | -5.038 | -4.933 |  |  |  |  |  |  |
|  | -12.653 | -2.208 | -2.737 |  |  |  |  |  |  |
|  | 7.602 | -2.83 | -2.196 |  |  |  |  |  |  |
|  | 12.653 | 2.208 | 2.737 |  |  |  |  |  |  |

Kinetic Monte Carlo calculations were used to capture the collective effects of the elementary molecular processes. In these calculations, an initial particle configuration of 16384 (128 × 128) particles containing equal amounts of ibuprofen and nicotinamide was used. The initial particle configuration is shown in Fig. 9. The coupled kinetics of elementary molecular processes over a period of 105 s were integrated. Five different temperatures were considered: 300, 325, 350, 375, and 400 K in order to encompass the actual operating conditions of holt melt extrusion using the twin-screw granulator. The final configuration of the particles at each temperature is shown in Fig. 10. The corresponding trajectories of the changes in the particle concentration are presented in the Supplementary Files MOV\_001-005. At temperatures higher than 350 K, an increase in the number of particles representing dimers of ibuprofen was observed (red dots). This is expected as the literature suggests that increasing the temperature above the melting temperature of ibuprofen (= 353.15 K [[45](#_ENREF_45), [50](#_ENREF_50)]) can promote the formation of ibuprofen dimers [[45](#_ENREF_45)]. The majority of particles correspond to co-crystals of ibuprofen and nicotinamide (green dots). For better visualization and discussion, the contours of the particle fraction are presented in Fig. 11. Note that the contours of the particle fraction for which the fraction values are smaller than 0.001 are provided in the Supplementary File.

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|  | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Particles** | | **Color legend** | | | | **H/S/L1** | **R/G/B2** |  | | **Name** | **Radius** | | Ibuprofen | 3 | 0/240/75 | 159/0/0 |  | | Nicotinamide | 1 | 160/240/45 | 0/0/96 |  | | ***1*** – RGB: Red/Green/Blue. ***2*** – HSL: Hue/Sat/Lum. | | | | | |
| Fig. 9. Initial configuration of 16384 particles containing equal amounts of ibuprofen and nicotinamide (left) and details of coloring scheme and particle sizes (right). | |

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| **T = 300 K**    **T = 325 K**    **T = 350 K** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Particles** | | **Color legend** | | | | **H/S/L1** | **R/G/B2** |  | | **Name** | **Radius** | | Ibuprofen | 3 | 0/240/75 | 159/0/0 |  | | Nicotinamide | 1 | 160/240/45 | 0/0/96 |  | | Co-crystals | | | | | | CO-1 | 4 | 80/240/40 | 0/85/0 |  | | CO-2 | 4 | 80/240/50 | 0/106/0 |  | | CO-3 | 4 | 80/240/55 | 0/106/0 |  | | CO-4 | 4 | 80/240/59 | 0/125/0 |  | | CO-5 | 4 | 80/240/65 | 0/138/0 |  | | CO-6 | 4 | 80/240/75 | 0/159/0 |  | | CO-7 | 4 | 80/240/80 | 0/170/0 |  | | CO-8 | 4 | 80/240/85 | 0/181/0 |  | | CO-9 | 4 | 80/240/95 | 0/202/0 |  | | Dimers of Ibuprofen | | | | | | DI-1 | 2 | 0/240/80 | 170/0/0 |  | | DI-2 | 6 | 0/240/85 | 180/0/0 |  | | DI-3 | 6 | 0/240/95 | 202/0/0 |  | | Dimers of Nicotinamide | | | | | | DN-1 | 2 | 160/240/50 | 0/0/106 |  | | DN-2 | 2 | 160/240/56 | 0/0/120 |  | | DN-3 | 2 | 160/240/66 | 0/0/140 |  | | DN-4 | 2 | 160/240/73 | 0/0/155 |  | | DN-5 | 2 | 160/240/80 | 0/0/170 |  | | DN-6 | 6 | 160/240/87 | 0/0/185 |  | | DN-7 | 2 | 160/240/92 | 0/0/195 |  | | DN-8 | 2 | 160/240/96 | 0/0/205 |  | | DN-9 | 2 | 160/240/106 | 0/0/225 |  | | ***1*** – RGB: Red/Green/Blue. ***2*** – HSL: Hue/Sat/Lum. | | | | |     **T = 375 K** |
| **T = 400 K** | |
| Fig. 10. Final configuration of particles at different temperatures and details of particle coloring scheme and size. | |

From Fig. 11, it can be seen that the majority of particles correspond to the ibuprofen and nicotinamide co-crystals CO–1, CO–2, and CO–5. The fraction of CO–2 within 1000 s was consistently higher than that at rest. Notably, in experimental reports by Soares and Carneiro [[47](#_ENREF_47), [48](#_ENREF_48)] and Kelly et al. [[49](#_ENREF_49)], the CO–2 structure was suggested to be a typical form of ibuprofen and nicotinamide co-crystal. Figure 11 clearly shows that when the temperature exceeded the melting temperature of ibuprofen, the fraction of ibuprofen dimers increased. Moreover, the higher the temperature, the faster the formation of the ibuprofen dimer. This is in agreement with previous reports [[17](#_ENREF_17), [45](#_ENREF_45)]. It was noted that there are two possible strategies for preventing the formation of ibuprofen dimers: (1) minimizing the residence time of the mixture within the twin-screw granulator or (2) avoiding temperatures higher than 350 K. In the pharmaceutical industry, short processing time is of great interest. This indicates that in order to implement a twin-screw granulator on the industrial scale, proper and reliable temperature controllers should be developed and installed. As shown in Fig. 11, the particle fraction of ibuprofen and nicotinamide co-crystal CO–1 initially increased. However, owing to the weak molecular interaction associated with CO–1, formation of the co-crystal tends to follow the backward path of the respective elementary molecular process in competition with other elementary processes. Considering the fraction of ibuprofen and nicotinamide co-crystal CO–5, it can be seen that the formation of this co-crystal is less affected by temperature. Based on the knowledge that CO–5 is less temperature dependent and mostly depends on the residence time, the twin-screw granulator can be operated at low temperatures (especially lower or very close to the ibuprofen melting temperature) for long residency times in order to create a safe route for maximizing the generation of ibuprofen and nicotinamide co-crystal CO–5. This opens the door for engineering a continuous co-crystallization process based on these elementary molecular processes.

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| Fig. 11. Fractions of different particles with non-negligible particle concentration. | |

It is interesting to observe the fraction of each co-crystal relative to the total number of co-crystals produced. This fraction can be interpreted as the frequency of each co-crystal over time. The relative fraction of each co-crystal is determined by dividing the corresponding particle fraction by the sum of the particle fractions of all co-crystals, as shown in Fig. 12, when the relative fraction is larger than 0.0001. It can be seen that ibuprofen and nicotinamide co-crystal CO–5 have the highest fraction. This co-crystal also showed favorable solvation and binding energies (see Fig. 5), indicating its desirable availability within the body. The bottom-up approach employed herein demonstrates the feasibility of producing high-end quality co-crystals by taking into account the elementary process that governs the type and concentration of co-crystals. It is suggested that the twin-screw granulator should be operated at low temperatures for longer residency times so that the target co-crystal, that is, CO–5, could be produced as a major particle. However, a short processing time is of great interest in industrial operating units, and current co-crystal formulation practices follow a short residence time at higher temperatures (but not far from the melting temperature of ibuprofen). Considering the relative fraction of co-crystals in Fig. 12, it is concluded that co-crystals of CO–2 and CO–5 are the main species produced in co-crystallization units under current industrial operating conditions. This can explain the observation of CO–2 in experimental reports by Soares and Carneiro [[47](#_ENREF_47), [48](#_ENREF_48)] and Kelly and coworkers [[49](#_ENREF_49)].

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| Fig. 12. Frequency of each co-crystal (averaged as fraction of representative particles over total co-crystal particles). | |

# Conclusion

This study presents a bottom-up computational approach combining density functional theory and kinetic Monte Carlo calculations. The developed approach was employed to identify the optimal operational parameters in a twin-screw granulator for engineering the co-crystallization process on the molecular scale. To achieve this aim, all possible interactions between two molecules (the API and conformer) were first identified. The kinetics of the formation of macromolecules by interaction of the API and conformer were studied. The kinetics were calculated using transition state theory and the nudge elastic band. A total of 21 different macromolecules was identified in a mixture of ibuprofen and nicotinamide: nine co-crystals, nice nicotinamide dimers, and three ibuprofen dimers. The collective effect of the molecular processes resulting in these 21 different macromolecules was studied using kinetic Monte Carlo and kinetics approaches, as derived from density functional theory calculations. It was highlighted that the maximum population of ibuprofen and nicotinamide co-crystals can be engineered by running a twin-screw granulator at low temperatures (especially lower or very close to ibuprofen melting temperature) for long residency times. The frequently encountered co-crystals of ibuprofen and nicotinamide observed in the literature could be explained based on elementary molecular processes. The approach presented here can be easily used to identify and manipulate the optimal operational parameters for a target molecular structure.

# Data availability

The associated data of this paper can be found under ***Downloads*** page at: <https://sites.google.com/view/makhansary>, using tag ID = ***CoCryM.ElmtMolPro***.

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# Declaration of interests

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.

# CRediT author statement

**Milad Asgarpour Khansary**: Conceptualization, Methodology, Programming, Computations, Validation, Writing- Reviewing and Editing. **Gavin Walker**: Supervision. **Saeed Shirazian**: Reviewing and Editing.

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