Controlling phase transformation during milling in the pre-formulation of Active pharmaceutical Ingredients

Ghaidaa Sulaiman Hameed
department of pharmaceutics /Collage of pharmacy / Al-Mustansiriya University

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Corresponding Author email:
ghaidaahameed@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0003-1470-6808

Abstract:

A high percentage of active pharmaceutical ingredient are available in the insoluble crystalline phase. During pharmaceutical processing such as milling there are many issues can be initiated due to the transformation of this crystalline materials. Some transformation might be positively solving the active pharmaceutical ingredients (APIs) problems such as solubility and dissolution rate while others might negatively affect these factors which render the APIs into inactive compound. Therefore, during the pre-formulation study, all of these issues must be resolved to ensure drug stability and hence its bioavailability. This review will shed the light on the most popular transformations that happened, factors affecting them, and the characterization methods used for the detection of phase formed. The studying of these factors, will help to avoid them in future

Key words: *Milling, transformation, amorphous, crystalline*

السيطرة على تحول الحالة خلال الطحن قبل تصييغ المواد الصيدلانية الفعالة

غيداء سليمان حميد
فرع الصيدلانيات، كلية الصيدلة/ الجامعة المستنصرية

الخلاصة:

توجد نسبة عالية من المكونات الصيدلانية الفعالة في الطور البلوري غير القابل للذوبان. خلال المعالجة الصيدلانية مثل الطحن هناك العديد من القضايا التي يمكن أن تبدأ بسبب تحويل هذه المواد البلورية. قد يكون هذا التحول حلًا إيجابيًا لمشاكل المكونات الدوائية النشطة (sAPI) مثل الذوبان وسرعه التحرر . بينما قد يؤثر التحول الآخر سلبًا على هذه العوامل التي قد تؤدي الى فقدان فعاليته. لذلك في دراسة ما قبل الصياغة يجب حل كل هذه المشاكل لضمان استقرار الدواء وبالتالي توافره الحيوي. ستلقي هذه المراجعة الضوء على التحول الأكثر شيوعًا الذي يحدث والعوامل المؤثرة فيه وطريقة الكشف عن الطور المتكون. ان دراسة هذه العوامل سوف يساعد على تجنبها في المستقبل.

الكلمات المفتاحية: الطحن، التحول، عديم الشكل، متبلور

Introduction:

Mechanochemistry was firstly introduced by Faraday in 1820 which involves mechanochemical transformation that can be induced by milling [1]. The development of the mechanochemistry was grown in 1980s under the field of pharmaceutical preparation [2]. Milling, intended mainly for particle size reduction which is important in pharmaceutical processing for improving flow property, enhancing the drug dissolution and ensuring uniformity

of the content [3, 4]. The reduction of the particle size such as in the preparation of nanosuspensions [5] can results in increasing the formulation of wide range of dosage forms intended for topical, ophthalmic, oral and rectal etc. route of administration. In addition, milling can result in increasing the surface area and hence the dissolution of the drug [6, 7]. The enhancing of drug dissolution via particle size reduction was explained through Noyese-Whitney equation [8]. Meanwhile, polymorph interconversions can initiated during milling process unintentionally [1, 9].

During pharmaceutical processing, the possible solid transformation includes solid-solid transformation (phase transition), solid-liquid transformation (melting) and solid-gas transformation (condensation). Phase transition can be occurred either in one component system which is called transformation as in polymorphic transformation or in multicomponent system which is called physical interaction as seen in eutectic mixture and solid solution [10]. Recently, milling considered as a green process for the production of amorphous material due to exclusion of heat, solvents and chemical reactions [11, 12].

Polymorphic transformation was shown in many APIs during pharmaceutical processing such as indomethacin, nemodipine, carbama-zepine, flufenamic acid, chlorpropamide and gabapentin [13-17].

Phase transformation types

The application of stress in a single-phase material it could result in liberation of heat, polymorphic transformation, producing a new surface, accumulation of crystal defect, amorphization and chemical transformation. However, the application of stress on a multicomponent system, can results in solid stat reaction and producing a highly dispersed phase [18].

Milling can produce many phase transformations such as transformation from one polymorph to another like that occurs in the transformation of cimetidine and chloramphenicol [6, 19, 20]. In this case, milling can induce transformation from stable to metastable polymorph [21]. In addition, polymorphs can also be obtained from crystallization of solvent and melting, seeding, exposure to vapor and laser [22]. Figure 1 illustrate the transformation in the crystalline material after milling.

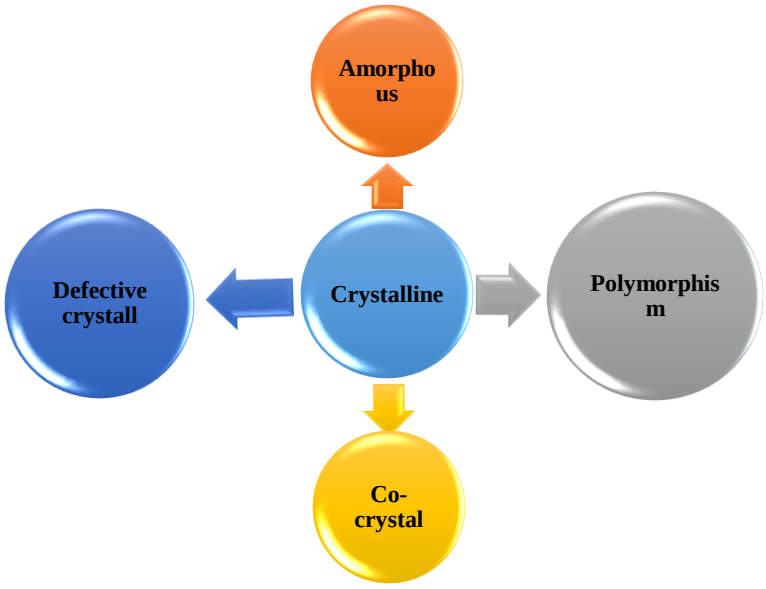

Figure 1: Transformation of crystalline material upon millling

Furthermore, amorphous material might be formed from the crystalline one. Theories that explained the transformation of the crystalline into amorphous material

suggested that the phase transformation either results from local melting of the crystalline material followed by rapid quenching or due to the accumulation of the crystalline defect [23] as illustrated in Figure 2. The defective crystal in this case possess high Gibbs free energy which results in less stability than the metastable phase therefore, they render amorphous [24]. Example on this transformation was the conversion of dexamethasone, tadalafil and rivastigmine [11, 25, 26] into amorphous form.

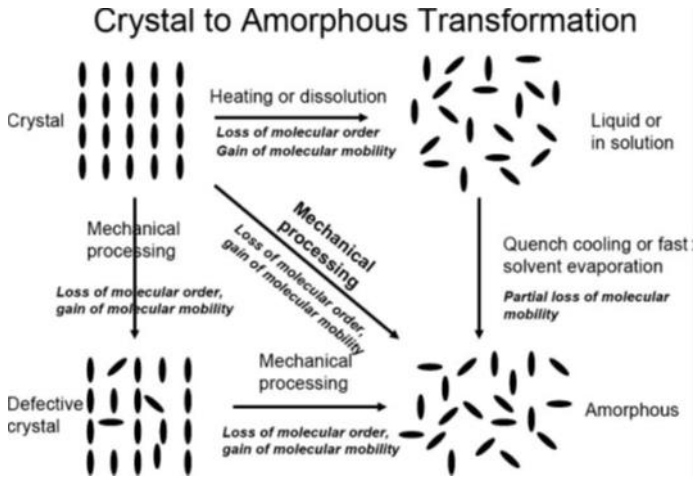

Figure 2: Schematic representation of the two pathways suggested to create the amorphous phase from the crystal during pharmaceutical processing (31)

Co-crystal formation is another transformation that happened in the (APIs). This occurs when two components are mixed together and milled, a physical interaction can be formed between two materials due to the formation of hydrogen bond between donor and acceptor groups in both compound [27, 28]. For example, the co-crystallization of caffeine-glutaric acid co-crystal and naproxen-lactose-tetrahydrate co-crystal [29, 30]. Finally, a crystalline defect can be resulted from the milling process. Such transformation was observed during milling of griseofulvin [31, 32] and alpha lactose [33].

Characterization of phase transformation

During the pre-formulation study the characterization of the (APIs) is important because this step determines the solubility and hence the biological activity of the API after formulation step. Recently, many tools are used to determine the phase transformation which can be used alone or in combination to detect the stability of the APIs prior to and following formulation. These include firstly; thermal analysis which can be performed by either: Differential Scanning Calorimetry (DSC) or Modulated Differential Scanning Calorimetry (MT-DSC) in which the presence and absence of glass transition temperature (Tg) is crucial in determining the presence of amorphous material. The presence of the exothermic and melting peak is critical factor for the detection of amorphous phase [34] as seen in Figure 3 which shows the DSC pattern of both sucrose and glucose before and after cryomilling (cryomilling is milling under liquid nitrogen -196 °C). The appearance of Tg indicates a formation of amorphous material. In the multicomponent system, the presence of a single Tg indicates a formation of a solid dispersion, while the appearance of multi Tgs in the mixture indicate that the mixture is not uniform [35]. Other techniques for the transformation of one phase to other can be characterized by powder x-ray diffraction (XRPD) in which

the absence of Bragg peaks (is a pronounced peak on the Bragg curve which plots the energy loss of ionising radiation during its travel through matter) indicates the lack of crystallinity [21]. However, Pinal *et. al.* showed that; although the Bragg peaks were absent in the cryomilled griseofulvin which is an indicator of amorphous formation, the DSC results showed the lack of the Tg. They interpreted this phenomena as crystalline defect which was happened after milling of griseofulvin [31]. XRPD method is important characterization method which requires only 10-30 mg of the sample to be detected within 3-8 minutes although there is a difficulty in the differentiation between a polymorphic mixture [22]. Meanwhile, thermal analysis requires less amount of the sample 2-4 mg with longer detection time 20-30 minutes or more depend on the targeted process with easier detection of the polymorphic mixture [22]. Other characterization methods are: Raman spectroscopy [36], polarized light microscopy [37], FTIR [38] and many others.

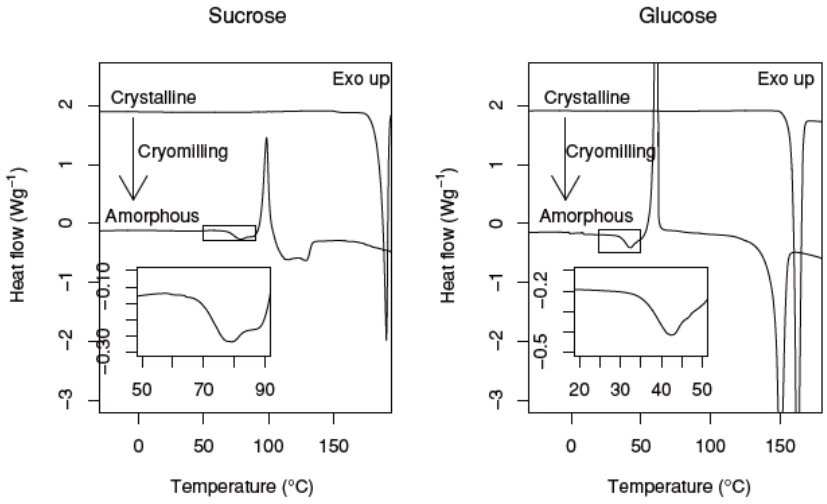

Figure 3: Differential Scanning Calorimetry Thermograms for Sucrose (left panel) and Glucose (right panel) Before and After Cryomilling, with Insets Showing the *T*g Region. "Crystalline" Samples have Been Offset by 2 Wg^{-1} (39).

The Role of Glass Transition Temperature (Tg)

The glass transition temperature is defined as the midpoint between rubbery and glassy phase [40]. It is important factor to control the drug stability [41]. It was reported that the molecular mobility of the compound increased with the reduction of the Tg; hence the stability was reduced. The Tg is an intrinsic material property, so that controlling its effects on the materials stability is limited to the temperature and humidity [42]. It has been previously reported that milling of APIs below the glass transition temperature results in amorphization, while milling above the glass transition temperature results in polymorphic transformation [24].

For this reason, milling should be performed at a relatively low temperature (below the material Tg) and out of humidity. For the APIs that have a low Tg, controlling the phase transition is performed using other materials that by mixing results in the elevation of the glass transition temperature thus inhibit its conversation during and after pharmaceutical processing. For example, incorporation of polymeric material that leads to the formation of amorphous solid dispersion such as ritonavir-copovidon and naproxen-PVP [43,44]. Furthermore, addition of other drug, amino acid or

carboxylic acid can also prevent recrystallisation of the drug through formation of co-amorphous system such as carbamazepine-benzoic acid, indomethacin and arginine [45, 46]. Finally, mixing two drugs such as lacidipine-spironolactone can result in stabilization via co-amorphous formation [47].

Milling Time

Increasing milling time results in increasing the amorphous content of the drug and, hence improving its dissolution. The increase in the milling time can lead to accumulation of the crystalline defect which transformed lastly into amorphous material [48]. Such effect was observed during milling of ketoconazole and griseofulvin in which there is a direct relationship between milling time and amorphous content of the these drugs [49]. Figure 4 shows the XRPD pattern of indomethacin at different times of milling. It's clearly seen that the Bragg peaks started to disappear with increasing milling time which reflect the losing of crystallinity and increasing amorphous content.

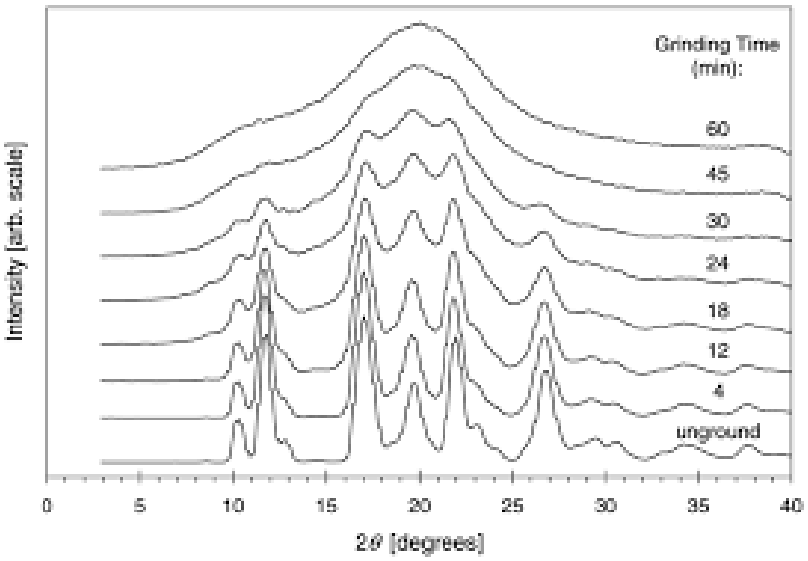

Figure 4. Powder X-ray Diffraction Patterns of Indomethacin Crystals Ground for Various Periods. Reproduced with Permission from Bates *et. al.* (50)

Controlling Milling Temperature

To control the phase transformation, it is important to control the temperature of milling according to the APIs Tgs'. It has been reported that milling above glass transition temperature results in melting of the crystal while milling below the glass transition temperature results in amorphization [23]. Although, milling has been reported to initiate phase transformation for many (APIs) such as piroxicam and indomethancin. There is a possibility of conversion of the amorphous material into crystalline material [51-53]. Recently, milling temperature has been reported to control the phase transformation of many APIs. Descamps *et. al*. investigated the effect of the milling temperature on the drug stability. They reported that the milling at temperature below the Tg of the drug resulted in formation of amorphous material and stabiliezd it. For example, the transformation of glucose at room temperature milling was not happened even when the milling time was performed for long time (14 hours), while its transformation to amorphous material was easier at -15 °C [21].

Heat increase the molecular mobility which lead to the instability of the active pharmaceutical ingredient. Thus, controlling milling temperature is important at this which can be performed

using cryomilling technique in which the material was milled of the material in a low temperature (-196 °C). During cryomilling, the effect of temperature on the materials during milling process can be excluded. During the milling of ketoconazole and griseofulvin as reported by Otte *et. al.* [54]. Another example on the effect of controlling temperature was seen in prioxicam in which milling at the room temperature results in amorphization, while at room temperature milling it was found to be difficult for amorphous material formation [55]. Controlling milling under liquid nitrogen temperature (-196 °C) not only results in controlling phase transformation but also excludes the drugs decomposition and solvent usage [39]. Milling under liquid nitrogen can also results in shortening the time required for obtaining amorphous state. For example, milling of indomethacin polymorph under 4 °C results in its amorphization within 2-4 hours, while cryomilling at -196 °C can amorphized indomethacin within 20 minutes [56].

Controlling humidity

As the glass transition temperature plays a significant role in the stability of the amorphous materials. Studying factors that controlling Tg are important such as the water content (water can be absorbed from atmosphere). Water causes reduction of the Tg and hence reduce the stability of the amorphous material due to the plasticizing effect of water [57]. The plasticizing effect of moisture on the amorphous carbohydrate results from the intra and inter hydrogen bond formation which leads to increase the molecular motion and reduce the internal friction [33]. The effect of water on amorphous mixture affected by the ability of the material to absorb water from the atmosphere [58]. The stability of a compound upon recrystallisation after milling depends on the physical interaction and H-bond formation between the mixed materials. For example, the stability of sulphonamide after milling with soluplus is better than its stability after addition of PVP. The researchers in this paper correlate the relationship between the stability of this mixture to the stronger interaction of sulphonamide with soluplus than with PVP [59]. Strong physical interaction like the H-bond formation between gabapentin and L-valine can leads to increase the stability of gabapentin during milling and consequently increases the resistance to humidity [60].

Conclusions

The phase transformation during and after pharmaceutical processing can be controlled in the early stage of pre-formulation. These parameters include selection of the milling temperature, exclusion of humidity effect, increasing milling time and introducing other materials during milling to ensure the physical stability and H-bond formation. All these considerations can effect on the stability during and after formulation. Before marketing it is important to ensure a proper wrapping and clear instructions of storage temperature to provide optimum bioavailability.

References

1- Jones W & Eddleston MD (2014) Introductory Lecture: Mechanochemistry, a versatile synthesis strategy for new materials. Faraday Discuss. 170:9-34.
2- Colombo I, Grassi G, & Grassi M (2009) Drug mechanochemical activation. J. Pharm. Sci. 98(11):3961-3986.
3- Naik S & Chaudhuri B (2015) Quantifying dry milling in pharmaceutical processing: a review on experimental and modeling approaches. J. Pharm. Sci. 104(8):2401-2413.

4- Brittain HG (2002) Effects of mechanical processing on phase composition. J. Pharm. Sci. 91(7):1573-1580.
5- Malik MM & Maraie NK (2018) Preparation and evaluation of famotidine nanosuspension. Al-Mustansiriyah Journal of Pharmaceutical Sciences (AJPS) 18(2):13-23.
6- Loh ZH, Samanta AK, & Heng PWS (2015) Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian journal of pharmaceutical sciences 10(4):255-274.
7- Sawant KK, Patel MH, & Patel K (2016) Cefdinir nanosuspension for improved oral bioavailability by media milling technique: formulation, characterization and in vitro–in vivo evaluations. Drug Dev. Ind. Pharm. 42(5):758-768.
8- Noyes AA & Whitney WR (1897) The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc. 19(12):930-934.
9- Priemel P, Grohganz H, & Rades T (2016) Unintended and in situ amorphisation of pharmaceuticals. Advanced drug delivery reviews 100:126-132.
10- Morris KR, Griesser UJ, Eckhardt CJ, & Stowell JG (2001) Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Advanced drug delivery reviews 48(1):91-114.
11- Krupa A, et al. (2016) High-energy ball milling as green process to vitrify tadalafil and improve bioavailability. Molecular pharmaceutics 13(11):3891-3902.
12- Khazaal N, Taha M, Basim M, & Amer H (2011) Quick Pharmaceutical steps for preliminary evaluation of a compund as a possible oral prodrug. Al-Mustansiriyah Journal of Pharmaceutical Sciences (AJPS) 9(1):1-6.
13- Guo Z, et al. (2011) A kinetic study of the polymorphic transformation of nimodipine and indomethacin during high shear granulation. AAPS PharmSciTech 12(2):610-619.
14- York P & Paradkar A (2016) Crystal engineering and particle design for the powder compaction process. Pharmaceutical Powder Compaction Technology, Second Edition, (CRC Press), pp 248-265.
15- Aaltonen J, Gordon KC, Strachan CJ, & Rades T (2008) Perspectives in the use of spectroscopy to characterise pharmaceutical solids. Int. J. Pharm. 364(2):159-169.
16- Tinmanee R, Stamatis SD, Ueyama E, Morris KR, & Kirsch LE (2018) Polymorphic and covalent transformations of gabapentin in binary excipient mixtures after milling-induced stress. Pharm. Res. 35(2):39.
17- Kichanov SE, et al. (2015) The polymorphic phase transformations in the chlorpropamide under pressure. J. Pharm. Sci. 104(1):81-86.
18- Boldyrev VV (2006) Mechanochemistry and mechanical activation of solids. Russian Chemical Reviews 75(3):177.
19- Bauer-Brandl A (1996) Polymorphic transitions of cimetidine during manufacture of solid dosage forms. Int. J. Pharm. 140(2):195-206.
20- Linol J, Morelli T, Petit M-N, & Coquerel G (2007) Inversion of the relative stability between two polymorphic forms of (±) modafinil under dry high-energy milling: comparisons with results obtained under wet high-energy milling. Crystal Growth & Design 7(9):1608-1611.
21- Descamps M & Willart J (2016) Perspectives on the amorphisation/milling relationship in pharmaceutical materials. Advanced drug delivery reviews 100:51-66.

22- Lee EH (2014) A practical guide to pharmaceutical polymorph screening & selection. asian journal of pharmaceutical sciences 9(4):163-175.
23- Fecht H (1992) Defect-induced melting and solid-state amorphization. Nature 356(6365):133.
24- Descamps M, Willart J, Dudognon E, & Caron V (2007) Transformation of pharmaceutical compounds upon milling and comilling: the role of Tg. J. Pharm. Sci. 96(5):1398-1407.
25- Oliveira PF, Willart J-Fo, Siepmann J, Siepmann F, & Descamps M (2018) Using milling to explore physical states: the amorphous and polymorphic forms of dexamethasone. Crystal Growth & Design 18(3):1748-1757.
26- Amaro MI, Simon A, Cabral LM, de Sousa VP, & Healy AM (2015) Rivastigmine hydrogen tartrate polymorphs: Solid-state characterisation of transition and polymorphic conversion via milling. Solid State Sciences 49:29-36.
27- Majumder M, et al. (2013) Application of hydrogen-bond propensity calculations to an indomethacin–nicotinamide (1: 1) co-crystal. CrystEngComm 15(20):4041-4044.
28- Fischer F, Joester M, Rademann K, & Emmerling F (2015) Survival of the Fittest: Competitive Co-crystal Reactions in the Ball Mill. Chemistry–A European Journal 21(42):14969-14974.
29- Chow PS, Lau G, Ng WK, & Vangala VR (2017) Stability of Pharmaceutical Cocrystal During Milling: A Case Study of 1: 1 Caffeine–Glutaric Acid. Crystal Growth & Design 17(8):4064-4071.
30- Sovago I, et al. (2016) Properties of the sodium naproxen-lactose-tetrahydrate co-crystal upon processing and storage. Molecules 21(4):509.
31- Feng T, Pinal R, & Carvajal MT (2008) Process induced disorder in crystalline materials: differentiating defective crystals from the amorphous form of griseofulvin. J. Pharm. Sci. 97(8):3207-3221.
32- Otte A, Zhang Y, Carvajal MT, & Pinal R (2012) Milling induces disorder in crystalline griseofulvin and order in its amorphous counterpart. CrystEngComm 14(7):2560-2570.
33- Caron V, et al. (2011) Solid state amorphization kinetic of alpha lactose upon mechanical milling. Carbohydr. Res. 346(16):2622-2628.
34- Peltonen L (2018) Practical guidelines for the characterization and quality control of pure drug nanoparticles and nano-cocrystals in the pharmaceutical industry. Advanced drug delivery reviews 131:101-115.
35- Zhao M, Barker SA, Belton PS, McGregor C, & Craig DQ (2012) Development of fully amorphous dispersions of a low Tg drug via co-spray drying with hydrophilic polymers. Eur. J. Pharm. Biopharm. 82(3):572-579.
36- Griffen JA, Owen AW, Burley J, Taresco V, & Matousek P (2016) Rapid quantification of low level polymorph content in a solid dose form using transmission Raman spectroscopy. J. Pharm. Biomed. Anal. 128:35-45.
37- Chattopadhyay B, et al. (2018) Accessing Phase-Pure and Stable Acetaminophen Polymorphs by Thermal Gradient Crystallization. Crystal growth & design 18(3):1272-1277.
38- Sanchez CC, Kalra A, Li T, & Jay M (2019) Solid-State Characterization of Three Polymorphs of an Orally Available Analog of Diethylenetriaminepentaacetic Acid. AAPS PharmSciTech 20(1):8.
39- Megarry AJ, Booth J, & Burley J (2014) Sucrose/Glucose molecular

alloys by cryomilling. J. Pharm. Sci. 103(7):2098-2106.
40- Condo P & Johnston K (1994) In situ measurement of the glass transition temperature of polymers with compressed fluid diluents. Journal of Polymer Science Part B: Polymer Physics 32(3):523-533.
41- Hancock BC, Shamblin SL, & Zografi G (1995) Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm. Res. 12(6):799-806.
42- Miller DP, et al. (2017) Physical characterization of tobramycin inhalation powder: II. State diagram of an amorphous engineered particle formulation. Molecular pharmaceutics 14(6):1950-1960.
43- Indulkar AS, Lou X, Zhang GG, & Taylor LS (2019) Insights into the dissolution mechanism of ritonavir-copovidone amorphous solid dispersions: importance of congruent release for enhanced performance. Molecular pharmaceutics.
44- 44. Dedroog S, Huygens C, & Van den Mooter G (2019) Chemically identical but physically different: A comparison of spray drying, hot melt extrusion and cryo-milling for the formulation of high drug loaded amorphous solid dispersions of naproxen. Eur. J. Pharm. Biopharm. 135:1-12.
45- Wu W, Wang Y, Loebmann K, Grohganz H, & Rades T (2019) Transformations between co-amorphous and co-crystal systems and their influence on the formation and physical stability of co-amorphous systems. Molecular pharmaceutics.
46- Jensen KT, et al. (2016) Preparation and characterization of spray-dried co-amorphous drug–amino acid salts. J. Pharm. Pharmacol. 68(5):615-624.
47- Wang Z, et al. (2019) Co-amorphous solid dispersion systems of lacidipine-spironolactone with improved dissolution rate and enhanced physical stability. Asian Journal of Pharmaceutical Sciences 14(1):95-103.
48- Kobayashi M, Hattori Y, Sasaki T, & Otsuka M (2017) Effect of ball milling on the physicochemical properties of atorvastatin calcium sesquihydrate: the dissolution kinetic behaviours of milled amorphous solids. J. Pharm. Pharmacol. 69(1):15-22.
49- Otte A & Carvajal MT (2011) Assessment of milling-induced disorder of two pharmaceutical compounds. J. Pharm. Sci. 100(5):1793-1804.
50- Bates S, et al. (2006) Analysis of amorphous and nanocrystalline solids from their X-ray diffraction patterns. Pharm. Res. 23(10):2333-2349.
51- Naelapää K, et al. (2012) Polymorphic form of piroxicam influences the performance of amorphous material prepared by ball-milling. Int. J. Pharm. 429(1-2):69-77.
52- Desprez S & Descamps M (2006) Transformations of glassy indomethacin induced by ball-milling. Journal of non-crystalline solids 352(42-49):4480-4485.
53- Löbmann K, et al. (2011) Coamorphous drug systems: enhanced physical stability and dissolution rate of indomethacin and naproxen. Molecular pharmaceutics 8(5):1919-1928.
54- Otte A & Carvajal MT (2011) Assessment of milling-induced disorder of two pharmaceutical compounds. J. Pharm. Sci. 100(5):1793-1804.
55- Kogermann K, Veski P, Rantanen J, & Naelapää K (2011) X-ray powder diffractometry in combination with principal component analysis–a tool for monitoring solid state changes. Eur. J. Pharm. Sci. 43(4):278-289.
56- Crowley KJ & Zografi G (2002) Cryogenic grinding of indomethacin polymorphs and solvates: assessment

of amorphous phase formation and amorphous phase physical stability. J. Pharm. Sci. 91(2):492-507.
57- Hancock BC & Zografi G (1994) The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res. 11(4):471-477.
58- Rumondor AC, Stanford LA, & Taylor LS (2009) Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions. Pharm. Res. 26(12):2599.
59- Caron V, et al. (2013) Amorphous solid dispersions of sulfonamide/Soluplus® and sulfonamide/PVP prepared by ball milling. AAPS PharmSciTech 14(1):464-474.
60- Wang J, et al. (2019) Investigating the Mechanism of l-Valine in Improving the Stability of Gabapentin Combining Chemical Analysis Experiments with Computational Pharmacy. AAPS PharmSciTech 20(3):114.