Mechanical Activation by Ball Milling as a Strategy to Prepare Highly Soluble Pharmaceutical Formulations in the Form of Co-Amorphous, Co-Crystals, or Polymorphs

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Abstract: Almost half of orally administered active pharmaceutical ingredients (APIs) have low solubility, which affects their bioavailability. In the last two decades, several alternatives have been proposed to modify the crystalline structure of APIs to improve their solubility; these strategies consist of inducing supramolecular structural changes in the active pharmaceutical ingredients, such as the amorphization and preparation of co-crystals or polymorphs. Since many APIs are thermosensitive, non-thermal emerging alternative techniques, such as mechanical activation by milling, have become increasingly common as a preparation method for drug formulations. This review summarizes the recent research in preparing pharmaceutical formulations (co-amorphous, co-crystals, and polymorphs) through ball milling to enhance the physicochemical properties of active pharmaceutical ingredients. This report includes detailed experimental milling conditions (instrumentation, temperature, time, solvent, etc.), as well as solubility, bioavailability, structural, and thermal stability data. The results and description of characterization techniques to determine the structural modifications resulting from transforming a pure crystalline API into a co-crystal, polymorph, or co-amorphous system are presented. Additionally, the characterization methodologies and results of intermolecular interactions induced by mechanical activation are discussed to explain the properties of the pharmaceutical formulations obtained after the ball milling process.

Keywords: drug; amorphous; milling; co-crystals; polymorphs; mechanical activation

1. Introduction

Almost half of the oral administered commercial drugs have low solubility, which affects their bioavailability [1,2]. Several alternatives to modify the supramolecular structure of APIs have been proposed to overcome their low solubility; these strategies include amorphization [3–5], solid dispersion [6–9], preparation of co-crystals [10,11], and polymorphs [12–14], among others. These approaches to enhance solubility involve non-covalent interactions, such as the electrostatic or intermolecular interactions between API molecules and the components of pharmaceutical formulations. Non-covalent interactions are preferred because they do not alter the pharmacological activity of the APIs. The selection of each strategy to improve the drugs’ properties depends on the particular API’s chemical nature. Preparation methodologies of drug formulations also depend on API properties, such as structural and thermal stability. Considering that many APIs are thermosensitive, non-thermal emerging alternative techniques, such as mechanical activation or milling, have become an increasingly common preparation method for co-amorphous, co-crystals, and polymorph drugs.

Several publications present overviews of specific applications of milling for the development of pharmaceutical products. In 2013, Braga et al. [15] presented a summary of scientific literature on the preparation of only co-crystals, while Einfal et al. [16] published,
in the same year, a summary of amorphization of APIs by milling. Furthermore, in 2015
an overview of different milling techniques for improving the solubility of poorly water-
soluble drugs was published [17]; this last article covered different types of milling, but
focused its analysis on particle size reduction. Although these reviews are complete within
their specific scopes, the authors of the present work believe that ball milling is a technique
that has become one of the most widely used methods to enhance a drug’s physicochemical
properties. For this reason, a summary of recent research in preparing and characterizing
pharmaceutical formulations through ball milling to improve APIs’ physical-chemical
properties is worth an update on this topic.

The present review summarizes the most representative studies that applied ball
milling to obtain different formulations with the enhanced properties of either co-crystal or
co-amorphous systems, using low molecular weight components and polymorphs. First,
a general description of these types of formulations is presented. Then, an analysis and
comparison of the available information of milling conditions reported and their effects on
improving drug properties are discussed. Unlike previously published reviews, this is the
only work in which the solubility, phase transitions, structural stability, and characterization
results of intermolecular interactions induced by mechanical activation are compared and
presented together for co-crystals, co-amorphs, and polymorphs drugs.

2. Pharmaceutical Formulations Based on Structural Properties

2.1. Amorphous Pharmaceutical Formulations Prepared by Milling

An amorphous solid has no long-range order of molecular packing and lacks a well-defined
molecular conformation. Amorphization has been introduced as a promising alternative to
enhance drugs’ solubility in the last two decades. It has been demonstrated that amorphous
materials usually have a higher solubility and dissolution rate than their crystalline state [18,19].
The enhancement of solubility in amorphous materials can be explained, in terms of the ease
of overcoming intermolecular forces [20–22]. One of the most common techniques to achieve
amorphization is the process of melt quenching. This process consists of melting a crystalline
sample and then proceeding to rapid cooling, thus obtaining the amorphous state [23–25]. This
method presents disadvantages for thermosensitive drugs, since the high temperatures required
to achieve melting may result in thermal decomposition. The study performed by Wlodarski
et al. [26] is a clear example of the wide range of thermosensitive drugs that currently exist
with low solubility that cannot be obtained in the amorphous state by melt quenching. Due
to this drawback, mechanical stress is a non-thermal alternative introduced for amorphization.
It has been proven that milling allows for the transformations of the solid crystalline state of
matter, thus causing a shift from the crystalline form to the amorphous state [27,28]. The milling
process consists of decreasing the compound particle size, thus promoting the accumulation of
energy to such a degree that it goes over the critical value that causes a structural deformation
of the crystalline structure, which results in the amorphization of the material [29]. However,
due to having higher entropy and free energy than the corresponding crystals, the amorphous
state is inherently unstable, and recrystallization may occur [30]. The preparation of binary
systems forming intermolecular interactions has been reported to avoid recrystallization [30–33].
The selection of a co-former to obtain a co-amorphous system can be a second drug or an
excipient, such as sugars, organic acids, amino acids, or surfactants [34–37]. For the reviewed
studies in this work, the milling process for amorphization is solely reported under drying
conditions. It has been observed that the addition of a solvent in the milling process tends to
induce co-crystallization [38].

Besides amorphization, it is important to understand that ball milling is a technique
that can lead to the formation of a microcrystalline (or nanocrystalline) state, where this last
state involves particle size reduction without the deformation of the crystalline structure.
Microcrystallinity results in an increased surface area, higher drug solubility, and increased
dissolution rate [39].

There are multiple techniques, such as X-ray diffraction, dynamic light scattering, infrared
and Raman spectroscopy, differential scanning calorimetry, and scanning electron microscopy,
that are useful techniques for differentiating the microcrystalline and analysis of amorphous states. The following section presents drug formulations in the form of co-crystals.

2.2. Drug Co-Crystals Prepared by Mechanical Activation

Another strategy to enhance solubility with the mixtures of two components is the formation of co-crystals. Co-crystals have acquired different definitions over the years; generally, a co-crystal is a solid material composed of two or more molecules in the same crystal lattice.

Pharmaceutical co-crystals are crystalline single-phase materials composed of two or more compounds. Co-crystals typically consist of an API and one or more additional molecular or ionic compounds called “co-formers” that are kept together via hydrogen bond or electrostatic interactions [10,40–42]. A cocystal has a different crystal structure to either of the starting materials and, as a result, different physicochemical properties [43]. Figure 1 shows a schematic representation of a co-crystal structure, compared with a co-amorphous system and polymorph. Co-crystals are prepared by different methods, such as the supercritical anti-solvent (SAS) process [44], extrusion [45], freeze-drying [46], spray drying [47], and laser radiation [48]. However, chemical integrity is not always maintained with these preparation methodologies. Some limitations are sometimes encountered, like solubility of the components in a given solvent or solvent mixture and thermal degradation.

As a counterpart, mechanochemical methods have also proven effective for co-crystal formation; the preparation of co-crystal by mechanical activation can be achieved by dry and liquid-assisted grinding [49–51]. Several studies report the preparation of co-crystals by grinding with a mortar [52,53]. However, those results are not included in this review.

| Co-amorphous system | Co-crystal | Polymorph |
|---------------------|------------|-----------|
| ![Co-amorphous system](image1.png) | ![Co-crystal](image2.png) | ![Polymorph](image3.png) |

**Figure 1.** Schematic representation of API formulations: co-amorphous system, co-crystal, and polymorph.

2.3. Drug Polymorphs as a Result of the Milling Process

It is estimated that about 80–90% of organic compounds are polymorphic [54]. Polymorphic solids exist in multiple crystalline solid forms [55–58]. It is well-known that changing the arrangement of atoms, molecules, or ions within a crystalline lattice raises the differences in physicochemical properties, including the solubility and bioavailability [59]. Therapeutic efficacy is also affected by structural arrangements [54]. One example of a polymorphism affecting drug properties is when a drug interconverts into more and less soluble forms, thus limiting its absorption and bioavailability [12]. There is a wide range of methodologies to prepare polymorphs: crystallization from a single or mixed solvent [60], exposure to organic vapor [61], dehydation of solvates by heat or by slurry [62], seeding [63], laser-induced [64], or supercritical fluid crystallization [65] are some of these preparation methods. However, this review is focused on the obtention of polymorphic forms using ball milling. The occurrence of polymorphism is not limited to single component formulations, but its existence has also been documented in multicomponent systems, such as co-crystals, salts, solvates, and hydrates [57]. Some examples are addressed later in this review.

Below are some of the schematic representations of the previously described systems (see Figure 1).

Various factors can individually change and influence the final characteristics of an active pharmaceutical ingredient after milling. Therefore, it is necessary to identify the prevailing conditions under which amorphous systems, co-crystals, and polymorphs
are obtained using griding or milling. In the following sections, the analyses of each experimental condition are presented.

3. Factors Affecting Drug Formulations during the Mechanical Activation Process

Tables 1–3 present an overview of the experimental milling conditions, such as the instrument (type of mill), solvent, time, and temperature, which are reported for each type of drug formulation. The first column contains a code with one number and a letter identifying each drug formulation in all tables. In each code, the number refers to a consecutive numeration of the article reviewed, and the letter stands for the following criteria: A, amorphous; C, co-crystal; and P, polymorph.

3.1. Ball Milling Instruments

After reviewing the information presented in Tables 1–3, it can be inferred that a planetary ball mill is the type of mill most commonly used in all three types of drug formulations. Planetary instruments have vessels placed inside a rotating disk and can induce high energy to the powder to prompt changes. Zirconium oxide (ZrO$_2$) and stainless-steel milling jars are the most common cells used for polymorphs and amorphous, whereas stainless steel alone is the most used for co-crystals. In most cases, the milling jar material is the same as the milling balls, except for the work of co-crystals reported by Stolar et al. [66], who use a different material: polymethylmethacrylate for the milling jar and stainless steel for the balls. Only Manin et al. [67] report the use of agate. For oscillatory/vibrational mills, the milling speed ranges from 10 to 30 Hz for all drug formulations. The most common speed for amorphous and co-crystals is 30 Hz. No trend is observed for polymorphs. In planetary mills, values reported ranges from 4.2 to 10.8 Hz for amorphous, with 6.7 Hz being the most common value for all formulations (amorphous, polymorphs, and co-crystals).

3.2. Temperature during the Milling Process

From Table 1, it was observed that, for amorphous systems, most milling processes were carried out in cold conditions (4–6 °C) or cryogenic temperatures (cell dips in liquid nitrogen), whereas for co-crystals, the temperature commonly used for grinding was room temperature. For polymorphs, the milling temperatures reported range from cryogenic temperature to 130 °C, although room temperature was the most common condition (see Tables 2 and 3).

3.3. Phase Transformation Mechanism by Ball Milling and Temperature Effect

The process of amorphization by milling can be explained from different perspectives. One of them indicates that, when a crystalline material is milled under direct collision, the first thing that is caused is the reduction of the material’s particle size, which is accompanied by changes in morphology and crystallinity. Understanding that if this milling process is carried out below the glass transition temperature (Tg) of the material (because, at this point, the molecular mobility decreases), amorphization is facilitated [16,17,27,68,69]. For co-crystallization there are three accepted mechanisms using grinding methods, i.e., molecular diffusion, and eutectic formation, which are mediated by an amorphous phase. The molecular diffusion mechanism is representative of the solvent/liquid-assisted grinding method. When drops of solvent are used for a mixture with components that are similar, in terms of solubility, the liquid solvent serves as a medium for promoting molecular diffusion and facilitating the interaction between the drug and co-former [15]. Moreover, the eutectic co-crystallization mechanism suggests that, when two solids are in physical contact by grinding at the eutectic temperature, there is a liquid phase formation, where the solid remains from both original crystals work as seeds for the co-crystallization process. [70–72]. Lastly, grinding can also induce enough disorder in solid mixtures to promote an amorphous phase formation. Storage or milling conditions, such as solvents and water presence, can increase molecular mobility and promote the co-crystallization of previously formed amorphous phases [73].
The polymorph formation mechanism upon milling is strongly related to several factors induced by the mechanical stress of high-energy milling. The main factors are temperature and microstructural changes, such as the size of crystallites, crystalline defects, and lattice distortions; these factors are believed to work collectively.

As previously mentioned in the mechanism for amorphization by milling, when milling occurs below the glass transition temperature, the material leads to amorphization; however, when milling occurs at a temperature above \( T_g \), the material leads to polymorphic transformations, whereby in the formation of polymorphs by grinding the amorphous state is an intermediate state \([74,75]\).

In addition to temperature, experimental work shows that a certain extent of defects in the system are necessary to trigger the polymorphic transformation. For most crystalline compounds, the stress applied during mechanical milling can create new defects in their crystal lattices and contribute to lattice disorder. The nucleation and growth of the new lattice defects formed within the structure may result in solid-state polymorphic interconversion upon milling \([75,76]\). Evidence of these factors affecting the formation of polymorphs is the study of the conversion of ranitidine hydrochloride from form 1 into form 2 \([74]\). Grinding of form 1 generates large amounts of heat and vibrational energy, giving rise to grinding-induced crystal lattice disruption or process-induced disorder. The formation of an amorphous intermediate follows the elimination of form 1 crystals. Finally, through continuous milling, form 2 nuclei are produced.

An analysis of experimental data related to the temperature effect during phase transformation by milling is shown in Table 1. It was observed that, for amorphous systems, most milling processes were carried out in cold conditions (4–6 \(^\circ\)C) or cryogenic temperatures (cell dips in liquid nitrogen). This is consistent with the mechanism proposed, in which it was established that amorphization occurs at a temperature below the glass transition temperature. For co-crystals, the temperature commonly used for grinding was room temperature. This could be explained because mechanical activation generates heat during milling, and the sample is exposed to temperatures near or above the glass transition temperature. For polymorphs, the milling temperatures reported ranges from cryogenic temperature to 130 \(^\circ\)C, although room temperature was the most common condition (see Tables 2 and 3).

### 3.4. Solvent Effect

Dry ball milling (DBM) is when a sample is subjected to the milling procedure under dry conditions. Terms such as “wet grinding”, “solvent-drop grinding”, “liquid assisted grinding”, and “kneading” all imply that a solvent is involved, whether by intention or not (air humidity) \([15]\). In 2006, Friscic et al. changed the solvent drop grinding term into liquid-assisted grinding (LAG) \([77]\), which became the most frequently used expression to indicate a grinding process with a tiny amount of solvent \([15]\). According to Tables 1-3, most studies prepared the formulation by adding a solvent to induce co-crystallization. In contrast, co-amorphous and polymorphs were mainly obtained under dry conditions. Additionally, it has been observed that the addition of a small amount of solvent increases the rate of co-crystallization \([51]\) by a process called solution-mediated phase transformation \([78]\). Therefore, most co-crystals require adding a particular solvent to improve the miscibility of the drug and co-formers. Whereas, for polymorphs, adding a solvent also allows for accessibility to new metastable forms and a shorter experimental time to obtain new polymorphs \([79]\). It has been shown that the chemical properties of the solvent can lead to a specific polymorph \([79–83]\).

### 3.5. Effect Changing Composition

Most of the co-crystals prepared by milling use the 1:1 molar ratio; from all the articles reviewed, just five studies prepared co-crystals using molar ratios of 2:1 or 1:2. A similar situation was observed for co-amorphous formulations, although it was common to find
studies with molar ratios 1:1, 1:2, and 2:1. Just one study reported a formulation with a molar ratio 1:4 and 1:5 (see Table 1).

3.6. Milling Time

Tables 1–3 show that adequate milling time to produce an intended structural change varies between studies. When a thermosensitive drug is subjected to milling, it is necessary to program pauses at specific times to maintain low temperatures. Nonetheless, there are studies with no thermosensitive drugs that have reported milling times between 30 to 180 min with no breaks.

For the preparation of co-crystals, short periods between 20 to 60 min are reported, although one study reported 5 h [44]. Milling time for polymorphs is longer than for co-crystals; usually, the required time is longer than one hour, and one study even lasted 10 h [34]. Moreover, when there are more than two polymorphic structures of the compound, the increase in milling time can lead to several transformations or what is called two-step polymorphisms.

For co-amorphous, the milling time varies, depending on the type of mill and milling temperature; however, the most common time range is between 60 and 180 min.

In all drug formulations studied here, a difficulty emerges in characterizing all of the properties of the drug formulations obtained by milling with one single analytical method. As a result, in an effort to study their enhanced properties, a wide number of characterization techniques are used to study them. The most used techniques for characterization in all drug formulations (amorphs, co-crystals, and polymorphs) are XRD and thermal techniques, followed by FT-IR. That is the main reason why this review focuses on a detailed analysis of characterization results and the primary information that can be obtained from each characterization method.
### Table 1. Conditions of preparation of co-amorphs by ball milling method.

| #   | Drug 1 | Drug 2 Molar-Ratio | Amorphous Stability (Storage-Conditions) | Mill Type | Volume Cell Material | Balls-Num. Material and Sample Weight | Milling Frequency | Milling Temp. (°C) | Milling Time | Ref. |
|-----|--------|--------------------|------------------------------------------|-----------|----------------------|---------------------------------------|------------------|------------------|-------------|------|
| 1A  | Mebendazole | Twenty different amino acids 1:1 | Not reported | Oscillatory ball mill  | 25 mL Jar | 2 (d = 12 mm) stainless steel balls 1000 mg | 30 Hz | Not specified | 1, 5, 15, 30, and 60 min | [84] |
| 1A  | Carvedilol | | | | | | | | | |
| 1A  | Carbamazepine | | | | | | | | | |
| 1A  | Simvastatin | | | | | | | | | |
| 1A  | Indomethacin | | | | | | | | | |
| 1A  | Furosemide | | | | | | | | | |
| 2A  | Furosemide | Arginine | Dry conditions at 25 °C or 40 °C for 15 months of storage | Oscillatory ball mill | 25 mL Jar | 2 (d = 12 mm) stainless steel balls 750 mg | 30 Hz | 5 °C | 180 min | [85] |
| 2A  | Nitrofurantoin | | | | | | | | | |
| 2A  | Citrulline | | | | | | | | | |
| 3A  | Sulfathiazole | Polycrystalline | Storage at 4 °C over a year | Planetary mill | 50 cm³ ZrO₂ milling jars | 3 balls (d = 20 mm) ZrO₂. 2.5 g | 6.6 Hz | Room temperature | 10 h (15 h total) 10 min pauses after every 20 min | [86] |
| 4A  | Naproxen | Cimetidine 1:2, 1:1, 2:1 | Dry conditions at 4, 25 and 40 °C for up to 33 days or further extended to 186 days | Oscillatory ball mill | 25 mL stainless steel milling jar | 2 (d = 12 mm) stainless steel balls 1 g of sample per grinding cell | 30 Hz | 4 °C ± 2 °C | 60 min | [87] |
| 4A  | Cimetidine 1:2, 1:1, 1:2 | Citrulline | | | | | | | | |
| 5A  | γ-Indomethacin | Ranitidine hydrochloride 2:1, 1:1, 1:2 | Dry conditions at 4, 25, and 40 °C up to 30 days | Oscillatory ball mill | 25 mL stainless steel milling jar | 2 (d = 12 mm) stainless steel balls 1 g of sample per grinding cell | 30 Hz | 4 °C ± 2 °C | 60 min | [28] |
| 6A  | γ-Indomethacin | None | | Oscillatory ball mill | 25 mL stainless steel milling jar | 6 (d = 9 mm) stainless steel balls 1 g of sample per grinding cell | 30 Hz | 4 °C ± 2 °C immersion in liquid nitrogen | 6 h | [88] |
| 6A  | α-Indomethacin | None | | Not reported | | | | | | |
| 7A  | Tadalafil | None | | Not reported | | | | | | |
| 7A  | Not reported | | | | | | | | | |
| 7A  | Not reported | | | | | | | | | |
| 8A  | Glibenclamide | None | | Not reported | | | | | | |
| 8A  | Not reported | | | | | | | | | |
| 9A  | Trehalose dihydrate | None | | Not reported | | Polycarbonate vials (23.9 cm³) with steel end caps | Magnetic rod (no balls) 1 g | 15 cycles per second | Cryogenic temperature (liquid nitrogen) | 2 min milling, 1 min of cool-down (30 min total) | [90] |
| # | Drug 1 | Drug 2 | Molar-Ratio | Amorphous Stability (Storage-Conditions) | Mill Type | Volume Cell Material | Balls-Num. Material and Sample Weight | Milling Frequency | Milling Temp. (°C) | Milling Time | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 10A | Atenolol | Hydrochlorothiazide | 1:1, 1:2, and 2:1 | Stored in desiccators at 4 °C and 25 °C for 30 days | 6770 SPEX freezer/mill | Airtight tube | 1 g | 10 Hz | Cryogenic temperature (liquid nitrogen) | 2 min milling, 2 min cool down (48 min total) | [91] |
| 11A | Furosemide | Tryptophan | 1:1 | Not reported | Oscillatory ball mill | 25 mL jars | 2 stainless steel balls (d = 12 mm) 500 mg | 30 Hz | 6 °C | 90 min | [92] |
| 12A | Dexamethasone | None | Not reported | High-energy planetary mill | 43 cm³ ZrO₂ milling jars | 7 ZrO₂ balls (d = 15 mm) 1.1 g | 6.6 Hz | Room temperature | 15 min milling, 5 min cool down (12 h total) | [27] |
| 13A | α-Lactose | None | Not reported | Planetary ball mill | 12 cm³ stainless steel jar | 50 stainless steel balls (d = 5 mm) 1 g | 6.6 Hz | 30 ± 5% relative humidity and 22 ± 3 °C | 20 min milling, 5 min cool down (1-20 h total) | [93] |
| 14A | α-D-Glucose | None | Not reported | High-energy planetary mill | 45 cm³ ZrO₂ milling jar | 7 ZrO₂ balls (d = 1.5 cm) 1 g | 5 Hz | −15 °C 25 °C | 20 min milling 10 min cool down (1 and 14 h total) | [68] |
| 15A | Mebendazole | Aspartame | 1:1/1:1:1 | Stored in desiccators at 40 °C and 25 °C up to 4 months | Oscillatory ball mill | 25 mL ball milling jars | 2 stainless steel balls (d = 12 mm) 500 mg | 30 Hz | 5 °C (cold room) | 90 min | [84] |
| 16A | α-D-Glucose | Phenylalanine | 1:1/1:1:1 | Not reported | Planetary ball mill | 12 cm³ stainless steel jar | 50 stainless steel balls (d = 5 mm) 1 g | 6.6 Hz | Room temperature | 20 min milling, 10 min cool down (1, 14 h total) | [95] |
| 17A | Carbamazepine | Furosemide | 11 different amino acids | Not reported | Mixer mill MM400 | 25 mL stainless steel jars | 2 stainless steel balls (d = 12 mm) 1000 mg | 30 Hz | 6 °C (cold room) | 90 min | [31] |
| 18A | Carvedilol | Salts of indomethacin | Lysine | Stored at 25 °C under dry conditions for up to 2 years | Vibrational ball mill | 25 mL milling jars | 2 stainless steel balls (d = 12 mm) 1000 mg | 30 Hz | 6 °C (cold room) | 60 min | [96] |
| 19A | Mebendazole | Trypotox | 0.1, 0.3, and 0.5 | Not reported | Vibrational ball mill | 50 mL stainless steel jars | 2 stainless steel balls (d = 12 mm) | 30 Hz | Room temperature 60, 120, and 150 min | unpublished data | [97] |
| #  | Drug 1          | Drug 2 Molar-Ratio | Amorphous Stability (Storage-Conditions) | Mill Type                      | Volume Cell Material | Balls-Num. Material and Sample Weight | Milling Frequency | Milling Temp. (°C) | Milling Time | Ref. |
|----|----------------|--------------------|-----------------------------------------|--------------------------------|---------------------|--------------------------------------|------------------|------------------|--------------|------|
| 20A| 18 different drugs | NaTC natural bile acid surfactant sodium taurocholate 1:1 | Stored at 22 ± 2 °C | Oscillatory ball mill | 25 mL stainless steel jar | 1 stainless steel ball (d = 15-mm) 1 g | 25 Hz | Room temperature and −10 ± 2 °C | 180 min, total time, with 10 min. break every 30 min | [37] |
| 21A| Carbamazepine | Arginine | Not reported | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 6 °C | 90 min | [98] |
| 22A| (S)-Naproxen | L-arginine | Stored at 25 °C, and 40 °C under dry conditions | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 1 g | 30 Hz | 6 °C | 60 min | [99] |
| 23A| Griseofulvin | Aspartic Ac Lysine Methionine Valine Tryptophan | Stored at 23–28 °C under dry conditions up to 12 months | High-energy planetary ball mill | Stainless steel crucible | 3 stainless steel balls 2.5 g | 9.3 Hz | Not specified | 6 h, with 0.5 min pauses every 30 min | [100] |
| 24A| Naproxen Tryptophan and proline | Dipeptide 1:1 Aminoacid mixtures 1:1:1 | Stored at 40 °C under dry conditions up to 332 days | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 1 g | 30 Hz | 6 °C | 90 min | [101] |
| 25A| Mebendazole Dipeptide 1:1 | Aminoacid mixtures 1:1:1 | Stored at 40 °C under dry conditions up 4 weeks or 3 months | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 5 °C | 90-180 min | [102] |
| 26A| Oxaprozin RameβCD | RameβCD-Arg. 1:1:1 | Not reported | High-energy vibrational micro mill | Not specified | Not specified | 24 Hz | Not specified | 30 min | [103] |
| 27A| Furosemide γ-Indomethacin | Arginine 1:1 | Not reported | Vibrational ball milling | 25 mL stainless steel jar | 2 stainless steel ball (d = 9 mm) 500 mg | 25 Hz | 6 °C | 99 min | [104] |
| 28A| Indomethacin Furosemide | L-tryptophan 1:1 | Not reported | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 1500 mg | 30 Hz | 6 °C | 0, 5, 15, 30, 45, 60, and 90 min. 3 or 6 h | [105] |
Table 1. Cont.

| #  | Drug 1 | Drug 2 | Molar-Ratio | Amorphous Stability (Storage-Conditions) | Mill Type | Volume Cell Material | Balls-Num. Material and Sample Weight | Milling Frequency | Milling Temp. (°C) | Milling Time | Ref. |
|----|-------|--------|-------------|------------------------------------------|-----------|---------------------|--------------------------------------|-----------------|-----------------|-------------|-----|
| 29A | Naproxen | Naproxen sodium 2:1, 1:1, and 1:2 | Stored at 40 °C under dry conditions up to 2 weeks or 2 months | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 4 °C | 90 min | [106] |
| 30A | Carvedilol | Glutamic Acid | Not reported | Vibrational ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 700 mg | 30 Hz | 6 °C | 60 min | [107] |
| 31A | Indomethacin | Arginine | Stored in refrigerator (≈5 °C) | Mixer mill MM400 | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | Not specified | 60 min, with 10 min pauses; cell would be in liquid nitrogen for 2 min | [36] |
| 32A | Simvastatin | Serine | Stored in desiccators at 4 °C | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 15 mm) 500 mg | 30 Hz | Not specified | 60 min, with 10 min pauses; cell would be in liquid nitrogen for 2 min | [108] |
| 33A | Indomethacin | Aspartic acid | Stored at 40 °C under dry conditions | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 6 °C | 90 min | [98] |
| 34A | Indomethacin | Phenylalanine | Stored at 40 °C under dry conditions up to 2 months | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 4 °C | 90–180 min | [109] |
| 35A | Carbamazepine | Citric acid | Stored at 40 °C under dry conditions up to 2 months | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 12 mm) 500 mg | 30 Hz | 4 °C | 90–180 min | [110] |
| 36A | Arginine | Glibenclamide | Stored at 4 °C, room temperature, and 40 °C up to 13 months | Oscillatory ball mill | 25 mL milling chambers | 2 stainless steel balls (d = 12 mm) 500 mg | 30 Hz | Not specified | 60 min, chambers were cooled in liquid nitrogen | [111] |
| 37A | Glutamic acid | Glibenclamide 1:1 and 1:1:1 | Stored at 40 °C and 25 °C in desiccators under dry conditions up to 6 months | Oscillatory ball mill | 25 mL stainless steel jar | 2 stainless steel ball (d = 1.2 cm) 500 mg | 30 Hz | 5 °C (cold room) | 30, 60, and 90 min | [112] |
Table 1. Cont.

| #  | Drug 1          | Drug 2 Molar-Ratio | Amorphous Stability (Storage-Conditions) | Mill Type        | Volume Cell Material | Balls-Num. Material and Sample Weight | Milling Frequency | Milling Temp. (°C) | Milling Time | Ref. |
|----|-----------------|--------------------|------------------------------------------|------------------|---------------------|---------------------------------------|------------------|-------------------|--------------|-----|
| 38A| Mefenamic acid  | Meglumine 1:1, 1:2, and 1:4 | Not reported                              | Planetary ball mill | Not specified       | 5 stainless steel balls (d = 10 mm)   | 4.16 Hz          | Not specified     | 20 min       | [113]|
|    | Indomethacin    | PVP 1:1, 1:2, and 1:4 |                                          |                   |                     |                                       |                  |                   |              |      |
| 39A| L-methionine    | Rutin 1:1, 1:2, 2:1 | Not reported                              | Planetary ball mill | 45 mL zirconia jar  | 8 YTZ balls (d = 10 mm)               | 10 Hz            | Room temperature  | 12 h with a break every 10 min | [114]|
|    | Naringin hydrate|奎宁 1:1, 1:2, 2:1 |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Quercetin dihydrate|                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Hesperidin      |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Chlorothiazide   |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Indapamide      |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Triamterene     |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Nifedipine      |                        |                                          |                   |                     |                                       |                  |                   |              |      |
| 40A| Benzamidine     | Gliclazide 1:1, 1:5, or 5:1 | Stored in a desiccator at 22 ± 2 °C, and 40 °C under relative humidity up to 180 days | Oscillatory ball mill | 25 mL stainless steel milling jar | Stainless steel ball (d = 15 mm) 0.25 g | 25 Hz          | Cromilling inmersing jars in liquid nitrogen for 5 min prior to milling, 7.5 min milling | 180 min, with a cool down period of 15 min after every 30 min | [38]|
|    | Arginine        | Glutamic acid 1:1, 1:2 |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Glutamic acid   |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Aspartic acid   |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Tryptophan      |                        |                                          |                   |                     |                                       |                  |                   |              |      |
|    | Glycin          |                        |                                          |                   |                     |                                       |                  |                   |              |      |
| 41A| Candesartan cilexetil | Hydroxypropyl methylcellulose | Stored at 4 °C, 30 °C, and 40 °C under dry conditions up to 90 days | Planetary ball mill | 125 mL stainless steel grinding jars | 3 stainless steel grinding balls (d = 10-mm) 2 g | 9.3 Hz          | Room temperature  | 2.5 h        | [116]|
|    | Hydroxypropyl methylcellulose (HPMCAS) type M |                        |                                          |                   |                     |                                       |                  |                   |              |      |
Table 2. Conditions of preparation of co-crystals by grinding method.

| #  | Sample                                      | Molar Ratio | Method of Preparation | Milling Type | Instrument Brand                          | Milling Jar | Balls (# and Material)          | Milling Frequency | Milling Temp | Milling Time | Ref. |
|----|---------------------------------------------|-------------|-----------------------|---------------|-------------------------------------------|-------------|---------------------------------|-------------------|--------------|--------------|------|
| 1C | Nicotinamide: L- (+) - Ascorbic acid        | 1:1         | Assisted by solvent   | Vibrational   | Mixer Mill (IST 500)                      | Polymethylmetacrylate | Two stainless steel balls       | 30 Hz            | NR           | 60 min       | [66] |
| 2C | Salicylic acid: 2-pyridone Salicylic acid: 4-Pyridone | 1:1         | NR                    | Vibrational   | Mixer Mill (IST 500)                      | Polymethylmetacrylate | Two stainless steel balls       | 30 Hz            | NR           | 50 min       | [117]|
| 3C | Ciprofloxacin-thymol                         | 1:2         | Assisted by solvent (EtOH) | NR           | Retsch MM200 ball miller,                 | Stainless steel jar | One 15 mm stainless steel ball   | 25 Hz            | Room temperature | 60 min       | [118]|
| 4C | Urea-caffeine                               | 1:1         | NR                    | Oscillatory ball | MM400-Retsch GmbH, Haan                   |              |                                |                   |              |              |      |
| 5C | Brexpiprazol-Catechol Brexpiprazol-Succinic acid | 1:1         | NR                    | Nano Ball Mill (Fritsch Premium Line, FRITSCH GmbH, Idar-Oberstein, Germany) using | Stainless steel balls | 8.3 Hz                  | NR           | 120 min       |              |      |
| 6C | Quercetin-malonic acid                      | 1:1 and 1:2 | Solvent drop grinding | NR           | QQ-3SP2, Nanjing NTU Instrument Co.       | NR           | NR                | 6.6 Hz            | NR           | 5 h          | [44] |
| 7C | Paracetamol-trimethylglycine                 | 1:1         | NA                   | Planetary ball | QM-3SP2, Nanjing NTU Instrument Co.       | NR           | NR                | 25 Hz            | Room temperature | 30 min       |      |
| 8C | Meloxicam-benzoic acid                      | 1:1         | LAG                  | Retsch CryoMill | QQ-3SP2, Nanjing NTU Instrument Co.       | NR           | NR                | 25 Hz            | Room temperature | 30 min       |      |
| 9C | Acetazolamide and 4-hydroxybenzoic acid     | 1:1         | LAG                  | Planetary ball | QM-3SP04, gear type                      | 25 mL stainless steel milling jars | NR           | 25 Hz            | NR           | 30 min       |      |
| 10C| Furosemide-urea and carbamazepine-indomethacin | 1:1         | LAG                  |                    | Retsch MM400 ball mill                    | 50 mL jar, with two 5 mm stainless steel balls and drops of acetone  | NR           | NR           | 60 min       |      |
| 11C| Ciprofloxacin-nicotinic and isonicotinic acids | 1:1         | Assisted or not by solvent (EtOH) | NR           | Retsch MM400 mixer mill                   | 10 mL stainless steel jars | 1 stainless steel ball of 7 mm diameter, 100, 500 mg sample | 30 and 15 Hz     | NR           | 30 min       |      |
| 12C| Pyrazinamide-diflusinal                      | 1:1         | LAG                  | Oscillatory ball mill | Mixer Mill MM400 | 25 mL stainless steel milling jars | NR           | 15 Hz            | Room temperature | 60 min       |      |
| 13C| Acetazolamide-4-amino benzonic acid         | 1:1         | With solvent         | Planetary ball   | Fritsch micro mill Pulverisette 7        | 12 mL agate grinding jars | Ten 5 mm agate balls | 8.3 Hz            | NR           | 30 min       |      |
| 14C| Acetazolamide-nicotinamide-2-pyridone       | 1:1:1       | LAG with ethyl acetate and tetrahydrofuran solvents | Planetary ball | QM-3SP04, gear type | 25 mL stainless steel milling jars | NR           | 15 Hz            | Room temperature | 60 min       |      |
| #   | Sample                                      | Molar Ratio | Method of Preparation | Milling Type           | Instrument Brand                  | Milling Jar                          | Balls (# and Material) | Milling Frequency | Milling Temp     | Milling Time | Ref.   |
|-----|---------------------------------------------|-------------|-----------------------|------------------------|------------------------------------|--------------------------------------|-------------------------|-------------------|-----------------|--------------|--------|
| 15C | β-Lapachone-resorcinol                     | 1:1         | LAG                   | NR                     | Retsh Mixer Mill (Model MW 200)    | Stainless steel jar together         | A stainless steel ball  | 20 Hz             | NR              | 20 min       | [127]  |
| 16C | Norfloxacin-nicotinic acid                  | NR          | NT and LAG            | Oscillatory ball system| Mixer Mill MM 400, Retsch GmbH and Co | Stainless steel jars                 | 7 mm diameter stainless steel ball | 15 Hz             | NR              | 30 min       | [128]  |
| 17C | Chlorothiazide, D-proline, L-proline        | 1:1         | NT and LAG            | Oscillatory ball       | Retsch (MM400, Retsch)             | NR                                   | NR                      | 30 Hz             | NR              | 30 min       | [129]  |
| 18C | Praziquantel, poloxamer f-127, and sucrose stearate | 20.1, 10.1, 10.2, and 10.3 | NT | High-energy vibrational ball | Mixer Mill MM 200, Retch, GmbH | 10 mL volume stainless steel grinding jars | Two 7 mm stainless steel grinding balls | 25 Hz             | 28.10–30.34 °C | 30 or 90 min | [130]  |
| 19C | Ferulic acid, urea, nicotinamide, and isonicotinamide (INA) | 1:1 and 1:2 | LAG       | NR                    | Retsh Mixer Mill (model MM301)     | Stainless steel grinding jar          | One 7 mm stainless steel ball | 20 Hz             | NR              | 20 min       | [131]  |
| 20C | Ketoconazole, fumaric acid, and succinic acid | 1:1:1 and 1:1 | NT and LAG | Oscillatory ball | Retsch MM 400 | 25 mL stainless steel jars | One stainless steel ball | 19 Hz             | NR              | 60 min       | [132]  |
| 21C | Itraconazole; 4-aminobenzoic acid; Itraconazole; 4-hydroxybenzamide | 1:1 2:1 1:2 | LAG         | Planetary micro       | Fritsch planetary micro mill, Pulverisette 7 | 12 mL agate grinding jars | Ten 5 mm agate balls | 8.3 Hz             | NR              | 40 min       | [133]  |
| 22C | S-ibuprofen: nicotinamide                  | 1:1         | N.R                   | Oscillatory ball       | MM400—Retsch                      | 10 mL ZrO2 milling jars               | One ball, 10 mm         | 30 Hz             | NR              | 60 and 10 min and 5 min pauses | [134] |
| 23C | Pyrazinamide: 4-aminosalicylic acid        | 1:1         | LAG                   | Planetary ball         | QMISP04, gear type, Nanjing University Instrument Factory | 20 mL stainless steel grinding tank | N.R                  | 20 Hz             | Room temperature | 40 min       | [135] |
| 24C | Theophylline: 4-aminobenzoic acid          | 1:1         | N.R                   | N.R                   | MM 400, Retsch, Germany            | 10 mL jar                            | One ball, 8.74 mm, One ball, 13.72 mm | 30 Hz             | N.R              | Period times: 2.5, 10, 15, 20, and 25 min | [136] |
| 25C | Betulin-terephthalic acid                  | 1:1 2:1     | Assisted by solvent   | NR                    | SPEX 8000 mixer mill (CertiPrep Inc., Metuchen, NJ, USA) | 60 mL steel jar                      | Steel balls 6 mm        | NR                | NR              | Pre-milled: 5 min After solvent: 10 min | [137] |
| 26C | 5-Fluorocytosine:5-fluorouracil            | 1:1         | NT                    | SDG                   | Oscillatory                        | Mixer Mill MM400 RETSCH              | Two 7 mm stainless steel balls | 25 Hz             | Room temperature | 90 min SDG: 60 min | [138] |
| 27C | Nicotinamide: adipic acid (polymorph, form 2) | 1:1         | Assisted by solvent   | (acetonitrile)         | Retsch MM400 mill (in-house modified) | Stainless steel milling jar | Two 7 mm stainless steel balls | 30 Hz             | NR              | 60–90 min     | [139] |

LAG: liquid assisted grinding; NT: neat grinding, SDG: solvent drop-grinding; NR: not reported.
Table 3. Conditions of preparation of polymorphs by mechanical activation.

| #  | Sample                          | Obtained Polymorph       | Mill Type                              | Milling Cell  | Ball (#, Material) Sample Weight | Milling Frequency | Milling Temperature | Milling Time and Solvent                        | Ref. |
|----|---------------------------------|--------------------------|----------------------------------------|---------------|---------------------------------|-----------------|-------------------|-----------------------------------------------|------|
| 1P | Ranitidine hydrochloride        | Ranitidine, form 2 (with traces of form 1) | Oscillatory ball mill (mixer mill MM501, Retsch GmbH and Co., Weinheim, Germany) | 25 mL Stainless steel | 2 stainless steel balls (d = 12 mm) 1 g s | 30 Hz | 12 ± 3 °C | 180 min, stop every 30 min to scrape and remix powder | [74] |
|    |                                 |                          |                                        |               |                                 | 35 °C            | 120 min, stop every 30 min to scrape and remix powder |                          |      |
|    |                                 |                          |                                        |               |                                 | 12 °C            | 240 min, stop every 30 min to scrape and remix powder |                          |      |
| 2P | Chlorhexidine dihydrochloride   | 2-step polymorphism produces ChxHC form 2 as a precursor of form 3 | High-energy planetary mill (Pulverisette 7; Fritsch, Idar-Oberstein) | 43 cm³ ZrO₂ | 7 ZrO₂ balls (d = 15 mm) 1 g | 6.6 Hz | Room temperature | 12 h (15 min milling periods with 5 min rests) | [140] |
| 3P | Γ-sorbitol                      | A form sorbitol          | High-energy planetary micro-mill (Pulverisette 7; Fritsch, Idar-Oberstein) | 45 cm³ zirconium | 7 zirconium balls (d = 15 mm) 1 g of sample | 6.6 Hz | Room temperature | 10 h | |
| 4P | Rivastigmine (RHT form 2)       | RHT form I               | Retsch planetary ball mill PM100      | 50 mL stainless steel | 3 stainless steel balls (d = 20 mm) 1 g | 6.6 Hz | Room temperature | 3 h (stopping at 15 min, 30 min, 1 h and 2 h) | [141] |
| 5P | o-Amino benzoic acid (mixture of FII and FIII forms) | FIII form | Oscillatory ball mill (Mixer mill MM400, Retsch GmbH and Co., Germany) | 25 mL Stainless steel | One stainless steel ball (d = 15 mm) 0.5 g 30 µL of solvent | 25 Hz | Room temperature | 2.5 h (30 min milling periods with 15 min pauses) | Solvent: valeric acid (FIV and FIII) | [54] |
|    | m-Amino benzoic acid (FIII form) | FIV form | | | | | | | |
|    | o-Amino benzoic acid (mixture of FII and FIII forms) | FIV and FIII | | | | | | | |
|    | p-amino benzoic acid β-PABA     | FIV form | | | | | | | |
|    | o-Amino benzoic acid (mixture of FII and FIII forms) | FL form (FII converts to FIII and subsequently FIII converts to FL) | | | | | | | |
| 6P | Dexamethasone                   | DEX form A and B         | High-energy planetary mill (Pulverisette 7; Fritsch, Idar-Oberstein) | 43 cm³ ZrO₂ | 7 ZrO₂ balls (d = 15 mm) 1.1 g | 6.6 Hz | Room temperature | 12 h (15 min milling periods, with 5 min rests) | [27] |
| #  | Sample             | Obtained Polymorph | Mill Type                        | Milling Cell          | Ball (#, Material) Sample Weight | Milling Frequency | Milling Temperature | Milling Time and Solvent                              | Ref. |
|----|--------------------|---------------------|----------------------------------|-----------------------|----------------------------------|-------------------|--------------------|-------------------------------------------------------|------|
| 7P | Sofosbuvir (anhydrous form 1) | Form A or B          | Vibrational ball mill (MM400, RETSCH) | 5 mL stainless steel   | 2 stainless steel balls (d = 5 mm), 50 mg, 10 µL of Solvent | 25 Hz            | Room temperature | 30 min solvent: water or methanol                      |      |
|    |                    | Form A (form 1 changes to form V) |                                  |                       |                                  |                   |                    | 30 min solvent: anisole, n-butyl acetate, or ethyl acetate | [79] |
|    |                    | Form A (form 1 changes into form B and then forms A) |                                  |                       |                                  |                   |                    | 60 min, solvent: tetrahydrofuran                       |      |
|    |                    | Form A (form 1 changes to form V) |                                  |                       |                                  |                   |                    | 20 min, solvent: butyl acetate or ethyl acetate       |      |
| 8P | Sulindac (form II)  | Form II and form I   | High-energy planetary mill (Pulverisette 7eFritsch) | 43 cm³ ZrO₂           | 7 ZrO₂ balls (d = 15 mm), 1 g    | 6.6 Hz           | Room temperature | 5 min solvent: anisole, n-butyl acetate, or ethyl acetate |       |
|    |                    |                      |                                  |                       |                                  |                   |                    | 600 min (10 min milling, with 5 min pauses)               | [69] |
|    | 1 - sorbitol       | A form sorbitol      |                                  |                       |                                  |                   |                    | 20 min (10 min milling periods, with 5 min pauses)      |      |
|    | Mannitol (β)       | a Mannitol           |                                  |                       |                                  |                   |                    |                                                       |      |
|    | Mannitol (δ)       | a Mannitol           |                                  |                       |                                  |                   |                    |                                                       |      |
| 9P | Gabapentin (GBP)   | GBP form I           | High-energy planetary mill (Pulverisette 7-Fritsch) | 43 cm³ ZrO₂           | 7 ZrO₂ balls (d = 15 mm), 1 g    | 6.6 Hz           | Room temperature (dry nitrogen atmosphere)              | 10 h | [75] |
|    | form I             | GBP form II          |                                  |                       |                                  |                   |                    | 130 °C 10 min                                          |      |
|    |                    | GBP form III         |                                  |                       |                                  |                   |                    | 110 °C 20 min                                          |      |
|    |                    | GBP form IV          |                                  |                       |                                  |                   |                    | 110 °C 30 min                                          |      |
| 10P| Famotidine (form B)| Form A (form B to A transformation ratio increased with milling time) | Oscillatory ball mill (Mixer Mill MM301, Retsch GmbH and Co., Germany) | 25 mL stainless steel | 2 stainless steel balls (d = 12 mm), 0.2 g | 15 Hz            | Room temperature | 120 min solvent: water or methanol                      |      |
|    |                    |                      |                                  |                       |                                  |                   |                    | 105 min solvent: anisole, n-butyl acetate, or ethyl acetate |     |
|    |                    |                      |                                  |                       |                                  |                   |                    | 120 min solvent: tetrahydrofuran                       |      |
|    |                    |                      |                                  |                       |                                  |                   |                    | 120 min solvent: butyl acetate or ethyl acetate       |      |
| 11P| GBP form III       | GBP form II          | Oscillatory ball mill (Mixer Mill MM301, Retsch GmbH and Co., Germany) | 25 mL stainless steel | 2 stainless steel balls (d = 15 mm), 0.2 g of sample | 20 Hz            | Room temperature | 60 min solvent: water or methanol                      |      |
|    |                    |                      |                                  |                       |                                  |                   |                    | 105 min solvent: anisole, n-butyl acetate, or ethyl acetate |     |
|    |                    |                      |                                  |                       |                                  |                   |                    | 2 min                                                   |      |
|    |                    |                      |                                  |                       |                                  |                   |                    | 30 min solvent: butyl acetate or ethyl acetate       |      |
|    |                    |                      |                                  |                       |                                  |                   |                    | 105 min solvent: butyl acetate or ethyl acetate       |      |
Table 3. Cont.

| #  | Sample                                      | Obtained Polymorph                             | Mill Type                                      | Ball (#, Material)                         | Milling Frequency | Milling Temperature | Milling Time and Solvent                                                                 | Ref. |
|----|---------------------------------------------|------------------------------------------------|-----------------------------------------------|--------------------------------------------|-------------------|---------------------|------------------------------------------------------------------------------------------|------|
| 12P| Ciprofloxacin salicylate (monohydrate)      | Form I (after 4 min of neat grinding)          | Fritsch planetary micro mill, model Pulverisette 7 | 12 mL agate                                | 10 agate balls (d = 5 mm) | 8.3 Hz               | NR                                                                                       | [143]|
|    |                                             | From 2 (after 9.5 min of neat grinding)         |                                               | 0.1 g                                       | 0.1 g              | 60 µL of solvent                  | 50 min, solvent: water, and the use of water/organic solvents decreases the time of existence for form I |      |
|    | Anhydrous ciprofloxacin salicylate          | Form II (after 17 min of neat grinding)         |                                               |                                            |                   |                                   |                                                                                          |      |
| 13P| γ-sorbitol                                  | Form α (complete transformation)                | High-energy planetary mill (Pulverisette, 7-Fritsch) | 43 cm³ ZrO₂                                | 7 ZrO₂ balls (d = 15 mm) | 6.6 Hz               | Room temperature (10 min milling periods, with 5 min rests)                              | [144]|
| 14P| Ethenzamide: ethylmalonic acid (Co-crystal)  | Form I (SDG with n-hexane)                      | Oscillatory ball mill (Mixer Mill MM301, Retsch GmbH and Co., Germany) | 10 mL stainless steel (d = 7 mm) | 1 stainless steel ball of EMA (1:1 molar ratio) | 20 Hz               | Room temperature, solvent: toluene, cyclohexane, or n-hexane                               | [145]|
| 15P| Caffeine: glutaric acid (co-crystal)         | Form I (after neat grinding and SDG with n-hexane, cyclohexane or heptane) | Oscillatory ball mill (Mixer Mill, Retsch GmbH and Co., Germany) | Stainless steel (volume NR)                | 2 stainless steel balls (d = NR) | 30 Hz               | Room temperature, solvent: n-hexane, cyclohexane, or heptane                             | [146]|

NR: not reported; SDG: solvent drop grinding.
4. Evaluation of Physicochemical Properties of Co-Amorphous, Co-Crystals, and Polymorphs Induced by Mechanical Activation

With the purpose of evaluating the outcomes of the milling process, different characterization techniques are applied to determine structural changes and their effects on the properties of the final pharmaceutical formulation. This section is divided into solubility evaluation, intermolecular interactions by spectroscopic techniques, such as Raman, Infrared, and ss-NMR, phase transitions by thermal analysis techniques, and structural characterization by X-ray diffraction. An overview of results for each kind of drug formulation (amorphous, co-crystal, or polymorph) is presented for each characterization technique. An additional section on characterization techniques by microscopy is included. This last section refers to the methods that have been used little, until the moment of elaboration of this review but that provide relevant information, regarding the formulation’s characteristics.

4.1. Evaluation of Solubility Enhancements as an Effect of the Milling Process

Solubility enhancement is an essential property for developing novel drugs. Solubility evaluation results may be expressed in different ways, for example, powder dissolution and intrinsic dissolution rate (IDR); however, both studies compare the solubility enhancement of the crystalline materials and formulation after milling. In the case of powder dissolution, analyses are performed using only the systems in powder. In contrast, the intrinsic dissolution rate (IDR) can be defined as the dissolution of a drug substance under specific conditions, such as a constant surface area and agitation speed [91].

Tables 4 and 5 provide an overview of the solubility results reported for amorphous, co-amorphous, and co-crystals. As mentioned before, in the first column of the tables, a code with a number and letter is used to identify each drug formulation. In each code, the letter stands for the following criteria: A—amorphous, C—co-crystal, and P—polymorph. Note that in Tables 4–6, the codes in the column are not consecutive numbers because not all articles analyzed their formulations with all the characterization techniques. Therefore, data are only exhibited in the tables when the articles performed those studies. All the articles report solubility enhancements in diverse ways, such as folds, solubility value, or dissolution rate, using various units. The articles that did not report folds have been marked with an asterisk (*); to simplify the analysis, those values were converted to folds using the formula:

\[
\text{Folds Increase} = \frac{\text{Increased solubility value}}{\text{Solubility value of crystalline or unprocessed material}}
\] (1)

It is important to mention that no information of solubility regarding polymorphs (obtained by milling) was found.

(a) Solubility for co-amorphous systems after ball milling

As seen in Table 4, it is relevant to note that a constant dissolution rate verifies that the drug in the co-milled sample does not recrystallize during dissolution. The steady behavior shows that the interaction between two drugs or drug-excipient in the amorphous binary system is strong and stable enough to prevent structural rearrangement during dissolution. Moreover, extended times in intrinsic dissolution studies (where no changes in rate are observed) show that bioavailability would not be decreased due to recrystallization in in vivo conditions [87]. Except from the LAG sample reported by Kasten et al. [96], the articles typically show a decrease in dissolution rate.
Table 4. Overview of solubility enhancement of amorphous systems prepared by ball milling.

| #  | Solubility Evaluation (UV, HPLC) | Sample | Ratio/Composition | Solubility Increment (Folds) | Ref. |
|----|----------------------------------|--------|-------------------|------------------------------|-----|
| 2A | HPLC (IDR)                       | Furosemide-arginine | 1:1               | 38                           | [85] |
|    |                                  | Nitrofurantoin-arginine |            | 20                           |     |
| 3A | UV (IDR)                         | Sulfadiazole-polyvinylpyrrolidone | Xpvp = 0.7 | 5.2                          | [86] |
|    |                                  | Sulfadimidine-polyvinylpyrrolidone |            | 26.5                         |     |
| 4A | UV (IDR)                         | Co-milled naproxen | 1:1               | 4                            | [87] |
|    |                                  | Co-milled cimetidine |            | 2                            |     |
| 7A | HPLC (Solubility)                | Tadalafil * | N/A                | 1.25 (in H2O)                | [26] |
|    |                                  |                |                   | 0.79 (in 0.1 M HCl)          |     |
|    |                                  |                |                   | 1.35 (Buffer pH = 6.8)       |     |
|    |                                  |                |                   | 1.83 (in water)              |     |
| 10A | UV (IDR)                        | Atenolol-hydrochlorothiazide | 1:1            | 12.5                         | [91] |
| 15A | HPLC (Powder dissolution studies) | Mebendazole-ASPA |                | 8.13                         | [94] |
| 17A | HPLC (IDR)                       | Fur-Phe, Fur-Pro, Fur-Trp | 1:1           | 0.9–1.0                      | [31] |
|    |                                  | Fur-Ile, Fur-Leu, Fur-Val, Ind-Ile, Ind-Leu, Ind-Met, Ind-Phe, Ind-Pro, Ind-Trp, Ind-Val, Meb-Met, Chz-Trp | 1:1 | 1.1–3.0                      |     |
| 18A | HPLC (IDR)                       | Indomethacin-lysine | 1:1             | 90                           | [96] |
|    |                                  |                |                   | 14                           |     |
| 23A | HPLC (Kinetic solubility studies) | Griseofulvin-trypthanol | 1:1 | 1.19                         | [100] |
| 25A | HPLC (Dissolution tests)         | Mebendazole-histidine-glycine | 1:1:1 | 19                           | [104] |
|    |                                  | Mebendazole-tryptophan-phenylalanine | 1:1:1 | 46                           |     |
| 29A | UV                              | Naproxen-NAP(Na) | 1:1             | 2.9                          | [106] |
| 30A | UV (IDR)                        | Carvedilol-l-glutamic acid | 1:1 | 12                           |     |
|    |                                  | Carvedilol-L-aspartic acid | 1:1 | 13                           | [107] |
|    |                                  | Carvedilol-L-glutamic acid |            | 14                           |     |
|    |                                  | Carvedilol-L-aspartic acid |            | 2                            |     |
| 31A | Dissolution studies              | Indomethacin-arginine | 1:1              | 1.4                          |     |
|    |                                  | Indomethacin-phenylalanine | 1:1 | 1                            | [36] |
|    |                                  | Indomethacin-tryptophan |            | 1                            |     |
| 33A | HPLC (IDR)                       | Carbamazepine-arginine-tryptophan * | 1:1:1 | 1.38                         |     |
|    |                                  | Carbamazepine-phenylalanine-tryptophan * | 1:1:1 | 1.2                          |     |
|    |                                  | Carbamazepine-tryptophan * | 1:1 | 1.08                         | [96] |
|    |                                  | Indomethacin-L-arginine * | 1:1 | 306                          |     |
|    |                                  | Indomethacin-L-phenylalanine * | 1:1 | 4.3                          |     |
|    |                                  | Indomethacin-L-tryptophan * | 1:1 | 2.4                          |     |
|    |                                  | Indomethacin-L-phenylalanine-L-tryptophan * | 1:1:1 | 3.35                         |     |
| 35A | UV                              | Carbamazepine-citric acid | 1:1 | 2.2                          | [110] |
|    |                                  | Carbamazepine-citric acid-arginine | 1:1:1 | 2.68                         |     |
|    |                                  | Carbamazepine-citric acid-arginine | 1:1:2 | 3.28                         |     |
|    |                                  | Carbamazepine-citric acid-arginine | 1:1:3 | 3.4                          |     |
There are many co-amorphous formulations prepared by milling, in which acidic and basic excipients were used to form salts. The article that shows the highest increase in solubility was published by Kasten et al. [31], using both DBM and LAG as preparation methods. They found that the co-amorphous salt formulations of basic AAs and acidic drugs had the most significant increase in dissolution rate. The use of amino acids, particularly arginine (a basic amino acid)-based salts, showed substantial dissolution enhancement, combined with acid drugs, approximately 140–431.8-fold, when compared to the amorphous drug, possibly due to strong molecular interactions attributed to salt formation. Therefore, the salt formation of an acid-basic system could be a meaningful approach to enhancing solubility properties in drug formulations. Other milling conditions were also analyzed for amorphs and co-crystals to determine if milling conditions directly affect the solubility of the obtained system. Apparently, long milling times do not affect the increase of solubility. Caron et al. [86] measured 15 h, in total, of effective milling, and sulfadimidine-polyvinylpyrrolidone had an increase of 26.5 times its solubility. Whereas Kasten et al. [31] milled a wide variety of samples for a total of 90 min and showed that increases in solubility ranged from 0.9 to 431.8 times.

For co-amorphous, milling time is relevant to obtaining the new drug formulation; nevertheless, once amorphization is achieved, longer milling times do not enhance solubility. This demonstrates that properties and possible interactions between drug–drug or drug–excipient are more important than long milling times to increase solubility. Finally, in Table 4, no trend is observed, regarding the type of mill or milling cell material towards affecting solubility enhancement. These milling conditions are relevant for the obtention of the amorphous and co-amorphous systems. Still, they do not seem to have an impact on the increase of the solubility of the sample. There is a possibility that 30 Hz might be the optimal milling frequency, as the highest increase in solubility was observed at this speed.
(at 1:1 molar ratio), but it should also be noticed that all these articles [31,85,94,96,102] used amino acids for the experiments, which could be a relevant factor influencing the solubility.

Table 5. Overview of solubility enhancement reported for co-crystal drugs.

| #  | Solubility Evaluation (UV, HPLC) | Sample                                      | Folds | Ref. |
|----|----------------------------------|---------------------------------------------|-------|------|
| 3C | In vitro                         | Ciprofloxacin-thymol (1:2)                  | 4     | [118]|
| 5C | UV                               | Brexpiprazol-catechol (1:1)                | 2.5   | [120]|
|    |                                  | Brexpiprazol-succinic acid (1:1)           | 2.5   |      |
| 6C | UV                               | Quercetin-malic acid (1:2)                 | 1.056 | [121]|
| 7C | UV                               | Paracetamol-trimethylglycine *(1:1)         | 0.82  | [44] |
| 11C| UV                               | Ciprofloxacin-nicotinic acid (1:1)         | 1.5   |       |
|    |                                  | Ciprofloxacin-isonicotinic acid (1:1)      | 20    | [124]|
| 13C| HPLC                             | Acetazolamide-4-aminobenzoic acid *(1:1)   | 2.5   | [67] |
| 15C| IDR                              | β-lapachone-resorcinol (1:1)               | 2     | [127]|
| 16C| UV                               | Norfloxacin-nicotinic acid (with EtOH) pH = 3 | No change | [128]|
|    |                                  | Norfloxacin-nicotinic acid (with EtOH) pH = 6.1 | 2     | |
|    |                                  | Norfloxacin-nicotinic acid (with EtOH) pH = 8.5 | <2   |     |
| 17C| UV (Powder dissolution)          | Chlorothiazide-L-proline hydrate (w/acetonitrile-water) | Lower value than | [129]|
|    |                                  | Chlorothiazide-D-proline hydrate (w/acetonitrile-water) | the initial drug |     |
| 19C| HPLC (In vitro release test)     | Ferulic acid-nicotinamide                  | 2.4   | [131]|
|    |                                  | Ferulic acid-isonicotinamide               | 3.1   | |
|    |                                  | Ferulic acid-urea                          | 1.1   |     |
| 21C| HPLC                             | Itraconazole-4-hydroxybenzamide form II (1:2) | 225   | [133]|
|    |                                  | Itraconazole-4-aminobenzoic acid (1:1)    | 64    |     |

(b) Solubility of co-crystals after grinding

Comparing results from Tables 4 and 5, the co-crystals’ primary preparation method is solvent-assisted, and solubility enhancement ranges from less than 1-fold to a maximum of 20 times. The works of Arabiani et al. [120] and Zhao et al. [44] have shown that it is possible to obtain co-crystals under dry conditions. Still, solubility was respectively little (1.056-fold) or not enhanced at all (0.86-fold, compared to paracetamol alone) (see Table 5). On the other hand, independently of the API, studies with amorphous systems clearly show a higher increase in solubility than co-crystals, as shown in Tables 4 and 5. Several authors have suggested that the physicochemical properties (melting temperature, solvation, etc.) of all the components of the co-crystal, as well as the solution properties of the medium (pH, surfactant, etc.), can significantly influence the solubility and dissolution of the co-crystals [127,147,148]. Other authors have mentioned that this induced improvement in solubility could possibly be the effect of the co-former being drawn out of the crystal lattice and into the aqueous medium [149]. For hydrophilic co-formers of co-crystals [121,124] interactions might be developed with -OH groups from water molecules by new hydrogen bonding, resulting in an enhancement of drug solubility. This theory is valid for a hydrophilic co-formers [44,127]; however, depending on the properties of the co-former, other factors, such as pH, could be more suitable to increase solubility, such as low pH for acid co-formers [124]. To sum up, it is necessary to release co-crystals in a suitable medium to improve dissolution behavior.
Table 6. Overview of structural characterization by spectroscopy of amorphous/co-amorphous drugs obtained by milling.

| #  | Sample                              | Analytical Technique | Wavenumber (cm⁻¹)/δ (ppm) | Interpretation                                      | Ref. |
|----|-------------------------------------|----------------------|---------------------------|---------------------------------------------------|------|
| 4A | Naproxen-cimetidine                  | Raman                | 670 (C=S-C str) 666 cm⁻¹ | Shift → unknown mechanism of interaction           | [87] |
|    |                                     |                      | 1601 (ring str) 1604 cm⁻¹| Shift → solid-state interaction of imidazole ring with naproxen |      |
| 5A | γ-Indomethacin-ranitidine hydrochloride | DRIFTS (FT-IR)      | 1717 and 1692 (C=O) 1723 and 1679 | Broadening and shift                              | [28] |
|    |                                     |                      | N/A                       | 1735 cm⁻¹ | Shoulder appearance                               |      |
|    |                                     |                      | N/A                       | 1723 (C=O) | Shift formation → conjugated carbonyl acid system  |      |
|    |                                     |                      | 1692 (C=N) 1679 cm⁻¹     | Shift → larger C=N double bond character or interaction at benzoyl C=O occurred |      |
|    |                                     |                      | 1620 (ac-nitro C=N str) 1610 | Shift → nitro group forming a bond with indomethacin and indirectly reducing the C=N double bond character |      |
|    |                                     |                      | N/A                       | 1579     | Small peak formation → interaction at the amidine moiety |      |
| 6A | γ,α-Indomethacin                     | Raman                | N/A                       | 1540 to 1700 and 2930 to 3100 cm⁻¹ | Large spectral differences → variations in molecular conformation and intermolecular bonding of amorphous forms | [88] |
| 8A | Glibenclamide                        | FT-IR                | 3315 (N-H str) N/A        | Absence of band upon cryomilling                  | [89] |
|    |                                     |                      | 1714 (C=O str) N/A        | Loss in intensity but clearly apparent            |      |
|    |                                     |                      | N/A                       | 1637 (C=N str) | New band → conversion of the amide to the imidic acid form |      |
| 9A | Trehalose dihydrate                  | Raman                | 30–400 (several peaks) N/A | Presence of only a broad peak (boson) → amorphous material | [90] |
|    |                                     |                      | 443, 835, 906, and 1449 433, 843, 912, and 1435 cm⁻¹ | Shift → amorphous transformation                 |      |
| 10A| Atenolol-hydrochlorothiazide         | FT-IR                | 3361 (N-H str) and 3169 (OH str) 3464 and 3357 cm⁻¹ | Shift | [91] |
|    |                                     |                      | 1636 (C=O str) 1664 cm⁻¹ | Shift → formation of intermolecular interactions  |      |
|    |                                     |                      | 1317 (-SO2 str) 1327 cm⁻¹| Shift → involvement of -SO2 in intermolecular hydrogen bonding |      |
| 11A| Indomethacin-arginine                | FT-IR                | 1613 (guanidine group) 1603 cm⁻¹ | Reduction of signal → possibly extremely weak interactions | [92] |
|    |                                     |                      | 1709 and 1738 cm⁻¹ (C=O) | N/A | Disappearance of peaks → possibly extremely weak interactions |      |
|    |                                     | ssNMR                | 159 ppm (guanidine resonance and 157 ppm (C5) | N/A | Overlap → not easy to identify salt formation |      |
|    | Furosemide-arginine                  | FT-IR                | 1670 (C=O) N/A           | Decrease of peak → salt formation                |      |
|    |                                     | ssNMR                | 169 and 173 ppm (C=O) 175 ppm | One broad resonance → similar environments in the mixture: π-π interactions involved |      |
| 15A| Piroxicam-ASPA                       | FT-IR                | 1377 1392 cm⁻¹ | Shift → possible interaction between components | [94] |
| 16A| α-D-glucose                          | Raman                | 769.2 and 838 N/A        | Presence of only the respective vibrational broadened bands → samples free of mutarotation and show anomeric purity | [95] |
|    | β-glucose                           |                      | 896.4 N/A                | Shift → possible interaction between components |      |
| 18A| Indomethacin-lysine                 | FT-IR                | 1713 (C=O str) N/A       | Disappearance of band → suggests ionization and salt formation | [96] |
|    |                                     |                      | N/A                      | 1586 and 1561 cm⁻¹ (COO⁻) | Broad peak → ionized carboxyl group for DMB and LAG, respectively |      |
| 19A| Mebendazole-tryptophan              | FT-IR                | 1717 (C=O) 1727 cm⁻¹    | Shift → loss of hydrogen bonds                    | [97] |
|    | Pioglitazona-tryptophan              | FT-IR                | 2930 (N-H) 1924 cm⁻¹    | Shift → formation of hydrogen bonds               |      |
Table 6. Cont.

| #   | Sample                              | Analytical Technique | Wavenumber (cm \(^{-1}\)/δ (ppm)) | Interpretation                                                                 | Ref. |
|-----|-------------------------------------|----------------------|-----------------------------------|--------------------------------------------------------------------------------|------|
| 20A | Mefenamic acid-NaTC                 | FT-IR               |                                    |                                                                                |      |
|     |                                     |                      | 754 and 776 747 and 769 cm\(^{-1}\) | Broadening and shift → loss of long-range order                                 |      |
|     |                                     |                      | 888 N/A                           | Intensity of strong, sharp band decreases                                       |      |
|     |                                     |                      | 1256 1219 cm\(^{-1}\)             | Shift and overlapping with band at 1193 cm\(^{-1}\) → changes in the hydrogen bonding network of mefenamic acid on amorphization | [37] |
|     |                                     |                      | 1329 1319 cm\(^{-1}\)             | Shift → changes in the hydrogen bonding network of mefenamic acid on amorphization |      |
|     |                                     |                      | 1509/1502 1507 cm\(^{-1}\)        | Split peak becomes a broad centered band                                          |      |
|     |                                     |                      | 1648 and 1196 1662 and 1193 cm\(^{-1}\) | Shift → no evidence for specific API-NaTC interactions; hydrogen bonding interactions can be ruled out |      |
| 21A | Indomethacin-arginine               | FT-IR               |                                    |                                                                                |      |
|     |                                     |                      | N/A 1590 cm\(^{-1}\) (indol)      | Peak structure of individual compounds transformed into a broad plateau with a small peak | [98] |
|     |                                     |                      | 1707 and 1734 N/A                 | Disappearance of peaks → carboxylic acid vibrations                             |      |
|     |                                     |                      | 1314 and 1219 1319 and 1222 cm\(^{-1}\) | Shift (chlorobenzene and indol, respectively) → changes in molecular environment |      |
| 22A | (S)-naproxen-L-arginine             | FT-IR               |                                    |                                                                                |      |
|     |                                     |                      | N/A 1568 cm\(^{-1}\) (C=O)        | New broad peak for the LAG sample → carboxyl group ionized                      | [99] |
|     |                                     |                      | N/A 1708 cm\(^{-1}\)             | New band appearance                                                             |      |
|     |                                     |                      | N/A 1543 cm\(^{-1}\) (C=O)        | New peak with lower intensity compared to LAG sample (DBM formulation)          |      |
|     |                                     |                      | N/A 1679 cm\(^{-1}\)             | Broad shoulder (DMB)                                                            |      |
| 23A | Griseofulvin-tryptophan             | FT-IR               | 3401 (NH and OH str), 3011 (CH str) | Enlargement and broadening of bands                                            | [100]|
|     |                                     |                      | N/A                               | New band appearance                                                             |      |
|     |                                     |                      | 1663 (QC, C=O) 1648 cm\(^{-1}\)  | Small displacement → formation of hydrogen bonding interaction                   |      |
| 24A | Naproxen-tryptophan                 | FT-IR               | 1369 N/A                          | Decrease of C=O band due to interactions with NAP                               |      |
|     |                                     |                      | 1650–1750 1699 cm\(^{-1}\)       | Transformation into a broad peak                                               |      |
|     | Naproxen-tryptophan-proline         | FT-IR               | 1581 1577 cm\(^{-1}\) (amide)     | Shift of small shoulder                                                         | [101]|
|     |                                     |                      | 1679 and 1728 cm\(^{-1}\) N/A    | Disappearance → indicates salt formation                                         |      |
|     | Naproxen-arginine                   | FT-IR               | 1540, 1600–1700 N/A              | Reduction of bands (amide and guanidyl) → Supports salt formation              |      |
|     |                                     |                      | 1550 (amide) 1556 cm\(^{-1}\)    | Shift → co-amorphous system                                                    |      |
|     | Naproxen-arginine-proline           | FT-IR               | 1610                               | Disappearance of band → co-amorphous blend                                      |      |
| 26A | Oxaprozin-randomly-methylated-βCD systems | FT-IR | 1725 1718 cm\(^{-1}\) (OXA carbonyl) | Reduction of intensity and shift → strong solid-state interactions between the components | [103]|
| 27A | Furosemide-arginine                 | FT-IR               | 1672 and 1562 N/A                 | Transformation of bands into shoulders → Salt formation upon co-amorphization |      |
|     |                                     |                      | 1591 1602 cm\(^{-1}\)            | Shift → salt formation upon co-amorphization                                  |      |
|     |                                     |                      | 1714 and 1689 N/A                | Disappearance of bands → salt formation                                         | [104]|
|     | Indomethacin-arginine               | FT-IR               | N/A 1680 and 1500 cm\(^{-1}\)    | Simultaneous formation of a band plateau → Salt formation                       |      |
|     |                                     |                      | N/A 1589 cm\(^{-1}\)             | Formation of a small peak → salt formation                                      |      |
Table 6. Cont.

| #   | Sample                                      | Analytical Technique | Wavenumber (cm\(^{-1}\))/δ (ppm)          | Interpretation                                                                 | Ref.   |
|-----|---------------------------------------------|----------------------|-------------------------------------------|--------------------------------------------------------------------------------|--------|
|     |                                             | FT-IR                | Crystalline, Co-Amorphous                 |                                                                                |        |
| 29A | Naproxen-NAP(Na)                            | FT-IR                | 1638–1682, 1639 cm\(^{-1}\)              | Disappearance of peaks and formation of a broaden single peak                  |        |
|     |                                             |                      | 1603, 1605 cm\(^{-1}\)                  | Shift                                                                         |        |
|     |                                             |                      | 1585–1574, N/A                           | Peaks weakened and broadened → formation of intermolecular interactions involving carbonyl groups | [106]  |
|     |                                             | Raman                | N/A, 747 cm\(^{-1}\)                    | Peak broadened and then disappeared → crystallization of NAP and NAP(Na)       |        |
|     |                                             |                      | N/A, 742 cm\(^{-1}\)                    | Appearance and increase in peak → presence of NAP indicates increasing presence of crystalline NAP |        |
|     |                                             |                      | N/A, 1383 cm\(^{-1}\)                   | Small shoulder peak after 10 min → decreased presence of NAP(Na)              |        |
| 31A | Arginine-indomethacin                       | FT-IR                | N/A, 1500–1750 cm\(^{-1}\)              | Formulation of a plateau                                                      | [36]   |
|     |                                             |                      | 1321 cm\(^{-1}\)                        | Presence of peak                                                              |        |
| 32A | Simvastatin-L-lysin                         | FT-IR                | 3442, 3350 cm\(^{-1}\) (OH)              | Broadening → no clear evidence of strong intermolecular interactions between the components | [108]  |
|     | Glibenclamide-L-serine                      | FT-IR                | 1356 and 1319, 1350 and 1312 cm\(^{-1}\) | Shift (aliphatic) → no clear evidence of strong intermolecular interactions between the components |        |
|     |                                             |                      | 1519, 1534 cm\(^{-1}\)                  | Shift (NH urea group) → intermolecular interaction                            |        |
|     |                                             |                      | 1584 (C=O), 1595 cm\(^{-1}\)            | Shift and merging → intermolecular interaction                                |        |
| 34A | L-tryptophan-indomethacin                   | Raman                | N/A, 1680 cm\(^{-1}\) (C=O)              | Appearance and increase in intensity of a broad band → loss of crystalline forms due to changed intermolecular environment | [109]  |
|     |                                             |                      | 1661 and 1582, 1609 cm\(^{-1}\)         | Loss of initial bands and formation of broad band                             |        |
|     |                                             | FT-IR                | 495, 532 cm\(^{-1}\)                    | Peak shift                                                                    |        |
| 35A | Carbamazepine-citric acid-arginine (1:1:1)  | FT-IR                | 1725, 1659, and 1628, 1568 (C=N)         | Shift of bands. C=O peak weakened and became a shoulder peak → formation of intermolecular interactions between components | [110]  |
|     | Carbamazepine-citric acid-arginine (1:1:2)  | FT-IR                | 1659, 1678 cm\(^{-1}\)                  | Peak strengthened and shifted → intermolecular interactions                    |        |
|     | Carbamazepine-citric acid-arginine (1:1:3)  | FT-IR                | 1659 and 1630, 1678 and 1682 cm\(^{-1}\) | Shift (guanidyl) → formation of a stronger interaction with the amide group and/or aromatic ring |        |
|     |                                             |                      | 1568 (C=N), N/A                          | Broadening of peak                                                            |        |
|     |                                             |                      | 1659 and 1630, 1634 and 1636 cm\(^{-1}\) | Shift (guanidyl) → formation of a stronger interaction with the amide group and/or aromatic ring |        |
|     |                                             |                      | 1568 (C=N), 1559 and 1589 cm\(^{-1}\)   | Formation of a doublet → formation of a stronger interaction with the amide group and/or aromatic ring |        |
| 36A | Glibenclamide-quercetin                     | FT-IR                | 1713 and 1649 (C=O), 1680 and 1650 cm\(^{-1}\) | Broadening and shift of peaks → amorphization                                | [111]  |
| 38A | Mefenamic acid-meglumine                    | FT-IR                | N/A, 1375 cm\(^{-1}\)                   | Formation of a new band → chemical interaction between carbonyl group and secondary amino group of the components | [113]  |
| 40A | Gliclazide-triamterene                      | FT-IR                | N/A, 3290 (N-H) cm\(^{-1}\)             | Formation of new H bonds                                                      | [38]   |
|     |                                             |                      | 1565 and 1530 (NH2), 1570 and 1536 cm\(^{-1}\) | Shift → formation of new H bonds                        |        |
| 41A | Quercetin-arginine                          | FT-IR                | 3405–3200 (OH) cm\(^{-1}\), N/A         | Loss of intensity → weak intermolecular bonding with the amino acid         | [115]  |
|     |                                             |                      | 1645 (C=O), 1654 cm\(^{-1}\)            | Shift → intermolecular H-bonding                                             |        |
| 42A | Candesartan cilexetil-hydrochlorothiazide    | FT-IR                | N/A, 1732 cm\(^{-1}\)                   | Visualization of band → occurrence of hydrogen bonds between the components | [116]  |
The results are similar to co-amorphous, in terms of the milling conditions to obtain co-crystals. As mentioned before, long milling times do not affect the increase of solubility. In fact, the longest milling time was performed by Zhao et al. [44] under dry conditions of paracetamol-trimethylglycine, and the solubility of the ball-milled co-crystals turned out to be lower than the paracetamol alone; the authors argue that supramolecular interactions, such as hydrogen bonding, might have caused this decrease in solubility. Anyway, only Shemchuk et al. [118] and Setyawan et al. [121] performed solubility studies at molar ratios different than 1:1. Still, no relation was observed to conclude that a specific molar ratio might render a higher increase in solubility. As previously mentioned for amorphs, in Table 5, no trend is observed regarding the type of mill, milling cell material, or milling speed towards affecting solubility enhancement.

To the authors’ knowledge, the solubility of polymorphs has not been studied in vitro or in vivo. Still, it would be worth analyzing whether there are significant differences in solubility between one form and the other, as one form of the crystalline drug could show better properties and, therefore, novel applications for therapeutics. A parameter related to improving properties, such as solubility or stability of a system, is the formation of the interaction between the formulation components. Therefore, the most widely used techniques for structurally analyzing co-amorphous, co-crystal, or polymorphous systems will be described then.

4.2. FT-IR Spectroscopic Evaluation of Intermolecular Interactions Induced by Ball Milling

Fourier transform infrared spectroscopy (FT-IR), Raman, and solid-state nuclear magnetic resonance (ss-NMR) are the primary intramolecular methods of probing the sample at the molecular level [16]. Tables 6–8 show an overview of the main spectroscopic results (FT-IR, DRIFTS, ATR-FT-IR Raman, and ss-NMR) reported to identify and study the structural rearrangement and possibility of recognizing new interactions in the formulation. Changes in the spectra from the initial crystalline materials to another form of the drug formulation (call it amorphous or co-amorphous system, co-crystal, or polymorph) might be expressed in different forms, such as peak formation, reduction of signal, the disappearance of peaks, and the merging of bands. The overall changes in each drug formulation will be explained in detail in the following subsections. Tables 6–8 show the analytical technique used, characteristic signals, and interpretation of each API change.

Table 7. Overview of structural characterization by spectroscopy of drug co-crystals obtained by milling.

| #  | Sample                  | Analytical Technique | Wavenumber (cm$^{-1}$) | Interpretation                                      | Ref.  |
|----|-------------------------|----------------------|------------------------|-----------------------------------------------------|-------|
| 1C | Nicotinamide: L-(+)-ascorbic acid | Raman               | 104, 146, 666, 1329 | 93, 133, 631, 1292 cm$^{-1}$ | Change form I $\rightarrow$ form II [66] |
| 4C | Urea-caffeine           | ATR-FTIR             | 1682 (C=O)             | 3341 (N-H)                                          | Shift $\rightarrow$ hydrogen bonding [119] |
|    |                         |                      | 1707                   | 3185                                                | Shift $\rightarrow$ hydrogen bonding |
|    |                         |                      | 809                    | N/A                                                 | Appearance of a new peak $\rightarrow$ co-crystal |
| 5C | Brexpiprazol-catechol (1:1) | Raman               | 1320.8, 1375.7, 1469.6, 1650.4 | 1223.4, 1284.1, 1321.47, 1375.2, 1495.4, 1668.3 | Shift, decrease in C=O str $\rightarrow$ hydrogen bonding [120] |
|    | Brexpiprazol-succinic acid (1:1) | Raman               | 1320.8, 1375.7, 1469.6, 1650.4 | 1226.8, 1292.2, 1332.6, 1381.6, 1497.4, 1665.7 | Shift, decrease in C=O str $\rightarrow$ hydrogen bonding |
| 6C | Quercetin-malonic acid  | FT-IR               | 3411 (O-H)             | 3427 (1:1) and to 3466 cm$^{-1}$ (1:2)              | Shift $\rightarrow$ co-crystal formation [121] |
|    |                         |                      | 1667 and 1612 (C=O)    | 1638 cm$^{-1}$ (1:2)                                | Disappearance and shift $\rightarrow$ co-crystal formation |
| #  | Sample                          | Analytical Technique | Wavenumber (cm\(^{-1}\))                                                                 | Interpretation                                                                                           | Ref.       |
|----|---------------------------------|----------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|------------|
| 7C | Paracetamol-trimethylglycine    | FT-IR               | 1647 (\(\text{CONH}_2\)), 1595, 1506, 1452 (\(\text{C}_8\text{H}_6\)), and 804 (\(\text{C}_6\text{H}_4\)) for PCA and 1400 cm\(^{-1}\) (C-N str) and 1323 (\(\text{COO}^-\)) for TMG. | No obvious difference in spectra of sample and co-crystal → proton transfer does not occur, no chemical reaction, this confirms co-crystal formation | [44]       |
|    |                                 | Raman               | 1643 (\(\text{C}=\text{O}\)), 1605 (\(\text{C}^-\text{N}\)), 1229 (\(\text{OH}, \text{aryl}\)), 1161 (\(\text{N-H}\)), 850 (\(\text{C}_8\text{H}_6\), \(\text{aryl}\)), and 789 (\(\text{C}^-\text{O}\)) | Shift and reduction of band intensities → molecular complex is a co-crystal                              |            |
|    |                                 |                      | 1454 (\(\text{C-N}\)) and 882 (\(\text{COO}^-\))                                         | Shift and reduction of band intensities → molecular complex is a co-crystal                              |            |
|    |                                 |                      | 1629, 1607, 1591, 1371, 1224, 1159, 858, and 774 cm\(^{-1}\)                             |                                                                                                         |            |
| 9C | Acetazolamide-4-hydroxybenzoic acid | Raman               | 251 (\(\text{NH, OH}\)), 1694 and 1738 (\(\text{sci of, CNH and tor -CH}_3\), and \(\text{C}=\text{O}, \text{oop bend of ring}\)) | Appearance of peaks → hydrogen bonding interaction leads to co-crystal formation                         | [123]      |
|    |                                 |                      | 1081 and 1120                                                                             | Weak broad peaks → co-crystal                                                                          |            |
|    |                                 |                      | 947 (\(\text{N-H, CH}_2\)) and 1372 (\(\text{HC=CH, O-H, C-N}\)) cm\(^{-1}\)             | Shift → co-crystal formation                                                                            |            |
|    |                                 |                      | 1284                                                                                     | Disappearance → co-crystal formation                                                                    |            |
| 11C| Ciprofloxacin-nicotinic acid/EtOH | FT-IR               | 1729 (\(\text{COOH}\)), 1627 (\(\text{C}^-\text{=ketone}\)), and 3200–2000 (\(\text{OH}\)) | Presence of bands and OH superimposed by C-H vib, absence of H bonding → co-crystal formation           | [124]      |
|    |                                 |                      | 1589 (asym \(\text{COO}^-\)) and 1375 (sym \(\text{COO}^-\))                            | Stretches of \(\text{COO}^-\) → co-crystal formation                                                   |            |
|    |                                 |                      | 1705 (\(\text{C}=\text{O}\)) and 1728 cm\(^{-1}\)                                       | Displacement and increase in intensity                                                                  |            |
|    |                                 |                      | 1589 (asym \(\text{COO}^-\))                                                            | Lower intensity and absence of bands attributed to vibrations of H bond → formation of new supramolecular synthons |            |
| 12C| Pyrazinamide-diflunisal          | Raman               | 244 (benzenic ring, \(\text{C-F}\)), 1185 (\(\text{O-H}, \text{HC=CH}\)), 1370 (\(\text{OH}, \text{O=C-O}, \text{C-H}\)), 1406 (\(\text{COH}, \text{C-H}\)) and 1750 (\(\text{C-O}, \text{C-O}, \text{C-N}, \text{C}=\text{O}, \text{C-C}\)) | Appearance of peaks → hydrogen bonding in COOH-pyridine hetero-synthon leads to co-crystal formation | [125]      |
|    |                                 |                      | 807                                                                                      | Disappearance → co-crystal formation                                                                   |            |
|    |                                 |                      | 458 and 1620                                                                              | Shift → co-crystal formation                                                                            |            |
| 14C| Acetazolamide, nicotinamide-2-pyridone | Raman               | 475, 857 (\(\text{CH, NH}\)), 928 and 1716 (\(\text{C}=\text{O, N-H, HO-C=O}\))           | Appearance of bands → hydrogen bonding interaction leads to co-crystal formation                        | [126]      |
|    |                                 |                      | 1014                                                                                      | Disappearance → co-crystal formation                                                                   |            |
|    |                                 |                      | 1260 (\(\text{O=-C-N-H}, \text{HC=CH}\)), 1466 (\(\text{C-H}, \text{O=C-NH}, \text{C-H}\)) and 1559 (\(\text{C-CH}, \text{HC=CH}, \text{NCH}\)) cm\(^{-1}\) | Shift → hydrogen bonding interaction leads to co-crystal formation                                     |            |
| #  | Sample                                      | Analytical Technique | Wavenumber (cm$^{-1}$) | Interpretation                                                                 | Ref.   |
|----|---------------------------------------------|----------------------|------------------------|-------------------------------------------------------------------------------|--------|
|    |                                             |                      | Crystalline            | Co-Crystal                                      |        |
|    |                                             |                      | 1716 (C=O)            | 1728 and 1707 cm$^{-1}$                                                        |        |
|    |                                             |                      | N/A                    | 365–2492 cm$^{-1}$                                                            |        |
|    | Norfloxacin-nicotinic acid                   | FT-IR               |                        | Displacement $\rightarrow$ New intermolecular interactions                    | [128]  |
| 16C| Chloretiazide-L-proline hydrate              | FT-IR               | 3337 (NH) cm$^{-1}$    | Broad peaks $\rightarrow$ hydrogen bonding                                      | [129]  |
|    | Chloretiazide-D-proline hydrate              | FT-IR               |                        | 1332 cm$^{-1}$                                                                |        |
| 17C| Praziquantel-poloxamer F-127 and sucrose steare | ATR-FTIR            | 1625                   | 1621 cm$^{-1}$                                                                |        |
| 18C| Ketoconazole-fumaric acid                   | FT-IR               | 1645 (C=O)            | Shift $\rightarrow$ strong hydrogen bonding                                    | [132]  |
|    | Ketoconazole-succinic acid                  |                      |                        | 1697 (C=O)                                                                    |        |
|    |                                             |                      | 1690 cm$^{-1}$         | Shift $\rightarrow$ participation in hydrogen bonding                          |        |
|    | Itraconazole-4-hydroxybenzamide (1:2)       | FT-IR               | 3469 (N-H) cm$^{-1}$   | More prominent band of form II $\rightarrow$ higher involvement in hydrogen bonds than form I | [133]  |
| 21C| Itraconazole-4-amino benzoic acid (1:1)     | Raman               | 3111 (C-H) cm$^{-1}$   | Sharp peak of form I $\rightarrow$ asymmetric stretching in both molecules    |        |
|    |                                             |                      | 1689 cm$^{-1}$         | Shift $\rightarrow$ participation in hydrogen bonding                          |        |
| 23C| Pyrazinamide-4-amino salicylic acid         | Raman               | 416, 781, 1055, 1662  | 366, 893, 1000, 1552, 1637 cm$^{-1}$                                           | [135]  |
|    |                                             |                      | New peaks $\rightarrow$ formation of a co-crystal                            |        |
| 25C| Betulin-terephthalic acid (w/acetone or isopropanol) | ATR-FTIR           | NR                     | 3300–3600 (OH) and 1020 (C=O) cm$^{-1}$                                       | [137]  |

N/A = not applicable, NR = not reported.

### Structural characterization of amorphous systems by spectroscopy techniques

Among the articles analyzed for amorphous and co-amorphous systems, the technique mainly used for spectroscopic characterization is FT-IR and Raman. For the infrared spectroscopy results, band shifting indicates that the system is suffering changes in the internal structure. It is important to notice is that a relation between the shifts and hydrogen bonding has been found, as shifts towards a higher wave number may be linked to the loss of hydrogen bonds [24], while a shift to a lower wavenumber is related to the formation of hydrogen bonding. A more stable amorphous state would be expected [97].

In the case of studies that performed Raman spectroscopy, all of them reported shifts in the spectra or band broadening, which conclude the possible formation of interactions between the components at a molecular level. It is essential to mention that both bathochromic and hypsochromic shifts happen due to variations in molecular conformation and intermolecular bonding of amorphous forms [88]. Due to the fact that Raman is not affected by the polarizability of water molecules, another meaningful use of this technique, along with UV imaging, is to study dissolution behavior, as it reveals potential changes in the physicochemical properties of the crystalline and amorphous drugs, as well as solid-state changes during dissolution; case in point, the co-amorphous systems prepared by Ueda et al. showed changes in the spectra of the samples, which were clear indicators of recrystallization [106]. Finally, from all the papers analyzed, it was observed that another application of Raman is to quantify the amorphous content of a drug as milling...
time increases; this is called apparent amorphicity (%) and has been studied to observe rising levels of amorphizing material [93,150].

**Table 8.** Overview of structural characterization by spectroscopy of drug polymorphs obtained by milling.

| # | Sample                  | Analytical Technique | Wavenumber (cm$^{-1}$)/δ (ppm) | Interpretation                                                                 | Ref.   |
|---|-------------------------|----------------------|---------------------------------|--------------------------------------------------------------------------------|--------|
|   |                         |                      | Polymorph I                     | Polymorph II                                                                   |        |
| 1P | Ranitidine hydrochloride | DRIFTS               | 1551 (form 1)                   | 1046 (form 2)                                                                  |        |
|   | form 1 (polymorph I)    |                      | Identification of each band     | presence of polymorph                                                          | [74]   |
| 4P | Rivastigmine (RHT form II) | ATR-FTIR            | 1694 (carbamate, form II)      | 1725 cm$^{-1}$                                                                 | [141]  |
|   |                         |                      | Band broadening and shift       | form II to I                                                                    |        |
| 6P | Dexamethasone           | ssNMR                | 14–155 ppm (form B)             | N/A                                                                            |        |
|   |                         |                      | Disappearance at high           | temperatures → change in conformational properties of the molecules             | [27]   |
| 10P| Famotidine (form B)     | Raman                | 3406 (N-H str) and 2897 (C-H sym str) (form B) | 3455 (N-H str), 3422, 2997 cm$^{-1}$                                                                 | [142]  |
|   |                         |                      | Clear observation of bands      | polymorphic conversion to form A                                               |        |
|   |                         |                      | 2920 cm$^{-1}$ (form A)         | N/A                                                                            |        |
|   |                         |                      | Increase in peak intensity      | presence of form A                                                             |        |
|   |                         |                      | 2897 cm$^{-1}$                  | N/A                                                                            |        |
|   |                         |                      | Decrease in peak intensity      | form B dropped off                                                             |        |
| 11P| Gabapentin (GBP) form I, II, III, and IV | FT-IR            | 1301, 799, 2930, 2153, 1615, 1547, and 1165 (form II) | N/A                                                                            |        |
|   |                         |                      | Appearance of peaks             | presence of form II                                                            | [76]   |
|   |                         |                      | 1699 and 1677 (GBP-lactam)      | Appearance of peaks                                                             |        |
|   |                         |                      | N/A                             | formation of traces of GBP-lactam due to heating effect                        |        |
|   |                         |                      | N/A                             | Appearance of specific peaks                                                  |        |
|   |                         |                      | 3150, 1523, 1397, 1377, 1087, 2121, 1621, 1576, and 1431 (form IV) | Appearance of peaks                                                             |        |
|   |                         |                      | N/A                             | presence of form IV                                                            |        |

N/A = not applicable.

Finally, in Table 6, the usefulness of NMR in amorphous systems is that it gives information regarding the thermal degradation of samples after milling. For example, Oliveira et al. [27] concluded during their study that the NMR spectrum of the milled dexamethasone was totally similar to that of the initial one, as it showed that a high-energy mechanical action is capable of amorphizing the sample without inducing chemical degradation, contrary to the spectra obtained from melt quenching, where the method of preparation may cause degradation.

(d) Structural characterization of co-crystals by spectroscopy techniques

FT-IR and Raman are the analytical techniques commonly used for co-crystal identification. As can be observed in Table 7, Raman spectroscopy is an advantageous technique for the analysis of co-crystals, particularly when the samples are hydrated because monitoring of water presents low Raman scattering [151], in comparison to FT-IR, which can have an uptake of humidity from the air and show the presence of a broad -OH band. Analysis from Table 7 shows that FT-IR does not seem to be the most common technique for interpreting co-crystal formation prepared by ball milling. However, there are some studies where FT-IR has been successfully used for identifying co-crystals [152,153]. In
these cases, co-crystals were prepared by methods other than grinding, such as solvent evaporation or sublimation.

In Raman, it has been suggested that the shift in the conformer to lower or higher wavenumbers with the corresponding reduction in the band intensities affect the distribution of the electron cloud and suggests the formation of a co-crystal and not simply a physical mixture [44]. Several studies argue that the spectra confirm the effect of hydrogen bonding interaction in the complex formed, which is key to co-formation, rather than a simple mixture of the two starting reactants [123].

A study performed by Elsei et al. [140] supports the idea of Oliveira et al. (mentioned in the spectroscopic techniques for amorphs section)—that when no changes are observed between the $^1$H NMR milled and non-milled spectra, it allows for confirmation that the samples can be safely ball-milled without inducing thermal degradation, compared to other techniques, such as melt quenching. This has been confirmed by $^1$H NMR, $^{13}$C, and $^{15}$N spectroscopy [154].

(e) Spectroscopic studies reported for polymorphs obtained by ball milling

Table 8 summarizes several authors’ interpretations, regarding the analysis of polymorphic transformations by spectroscopic techniques. During mechanochemical milling, certain forms of drugs can be produced; however, due to the low glass transition temperature of the drug (further discussed in the phase transition by thermal techniques section), they are not necessarily stable, which results in reversion into a more stable crystalline form. Therefore, identifying polymorphs is imperative for formulation developments and complying with the regulatory authorities [141]. As shown in Table 8, each polymorph of a drug exhibits specific bands that allow a clear identification in FT-IR and Raman. After polymorphic transformation, some bands may disappear (due to conversion from one form to another), and new peaks with increased intensity now show up, thus allowing for the identification of the new polymorph. Less common, but also seen, is the shift of bands, which also indicates polymorphism. Finally, regarding polymorphism, an example is presented here to make this section clearer: in the spectra of a ball-milled sample that shows peaks from two different forms, form A and form B, this would be an indicator that the mixture contains both polymorphs; this indicates that more milling time is necessary to reach full conversion into a specific form (from A $\rightarrow$ B or vice-versa), where only the peaks of one specific form will be noticeable.

ssNMR has been little used, but it is useful to observe that the disappearance of bands indicates a change in conformational properties, such as the arrangement of molecules in the unit cell and coarsening process [27]. The $^1$H NMR proton spin-lattice relaxation time measured at various temperatures may be used to differentiate between various polymorphic forms of a drug [155].

Contrary to amorphous systems and co-crystals, to the author’s knowledge, $^1$H NMR cannot be used in these cases to observe if the polymorph suffers thermal degradation, because proton NMR signals change as a new polymorphic form develop, but further investigation needs to be performed in this field.

4.3. Thermal Analysis Techniques to Study Phase Transitions Induced by Grinding

Regarding the thermal analysis of samples, the most commonly used technique reported for the study of milled formulations is differential scanning calorimetry (DSC). This technique identifies phase transitions as a function of a heating process (melting, crystallization, decomposition, and glass transition temperatures). Another technique is thermogravimetry (TGA), which measures the loss of mass as a function of the temperature, due to loss of water [44] or volatile samples [124], respectively. The most common rate used is 10 °C/min, but the smaller heating ramps of 5 °C/min [68,95,100] and 2 °C/min in several articles have also been used (see Table 9). It is well-known that many transitions, such as crystallization, decomposition, evaporation, etc., are kinetic events, as functions of time and temperature. Therefore, the transition will shift to a higher temperature when heated at a higher rate. Another transition that can also be affected by the heating speed is the
glass transition temperature; its shift is the result of some events. First, the temperature of the center of the sample lags the temperature of the surface. The temperature lag increases with the heating rate and causes the glass transition to shift to a slightly higher temperature. Secondly, the glass transition is associated with a change in molecular mobility, and this mobility has a small time-dependent or kinetic contribution [156].

Table 9. Overview of thermal characterization (DSC) of amorphous samples obtained by ball milling.

| #   | Sample                                      | Molar Ratio/Composition | Glass Transition Temperature (Tg)/(°C) | Milling Temperature | Conditions | Ref. |
|-----|---------------------------------------------|-------------------------|----------------------------------------|---------------------|------------|------|
| 2A  | Furosemide-arginine                          | 1:1                     | 127 ± 0.5                              |                     |            |      |
|     | Furosemide-citrulline                        | 1:1                     | 77.1 ± 5.6                             |                     |            |      |
|     | Nitrofurantoin-arginine                      | 1:1                     | 139.1 ± 0.2                            |                     |            |      |
|     | Nitrofurantoin-citrulline                    | 1:1                     | 49.3 ± 2.1/108.5 ± 0.3                 | 5 °C               | 2 °C/min, −10 °C to 180 °C, 50 mL./min | [85] |
|     | Cimetidine-arginine                           | 1:1                     | 40.4 ± 3.1                             |                     |            |      |
|     | Cimetidine-citrulline                         | 1:1                     | 39.5 ± 1.5                             |                     |            |      |
|     | Mebendazole-arginine                          | 1:1                     | 53.5 ± 3.3/112.2 ± 0.4                 |                     |            |      |
|     | Mebendazole-citrulline                        | 1:1                     | 43.6 ± 1.2/112.1 ± 0.2                 |                     |            |      |
| 3A  | Sulfathiazole-polyvinylpyrrolidone            | STZ/PVP Xpvp = 0.4      | 173.2                                  | Room temperature    | 10 °C/min  | [86] |
|     | Sulfadimidine-polyvinylpyrrolidone            | SDM/PVP Xpvp = 0.6      | 146.7                                  |                     |            |      |
| 4A  | Naproxen-cimetidine                           | 1:1                     | 34.5                                   | 4 ± 2 °C            | 10 K min⁻¹ | [87] |
|     |                                            | 2:1                     | 31.5                                   |                     |            |      |
|     |                                            | 1:2                     | 40.2                                   |                     |            |      |
| 5A  | γ-indomethacin–ranitidine hydrochloride       | 1:1                     | 32.5                                   | 4 ± 2 °C            | 10 K per min from 0 to 160 °C | [28] |
|     |                                            | 2:1                     | 34.3                                   |                     |            |      |
|     |                                            | 1:2                     | 29.3                                   |                     |            |      |
| 6A  | γ-indomethacin                               | N/A                     | 39.23                                  | 4 ± 2 °C            | 10 K min⁻¹ from 0 to 180 °C under nitrogen gas flow 50 mL min⁻¹ | [88] |
|     | α-indomethacin                               | N/A                     | 37.92                                  |                     |            |      |
| 7A  | Tadafil                                      | N/A                     | 147                                    | Cryogenic temperature (liquid nitrogen) | 10 °C/min under nitrogen atmosphere (60 mL./min) | [26] |
| 8A  | Glibenclamide                                | N/A                     | 65                                     | Cryogenic temperature (samples immersed in liquid nitrogen) | 10 K/min from 20 to 190 °C | [89] |
| 9A  | Trehalose dihydrate                          | N/A                     | 21                                     | Cryogenic temperature (samples immersed in liquid nitrogen) | 10 °C/min from 0 to 150 °C | [90] |
| 10A | Atenolol-hydrochlorothiazide                 | 1:1                     | 311.44                                 |                      |            |      |
|     |                                            | 1:2                     | 315.82                                 |                      |            |      |
|     |                                            | 2:1                     | Not determined due to fast recrystallization |                      |            |      |
| 11A | Indomethacin-tryptophan                      | 1:1                     | Tg ranges from 120 to 45 °C, decreasing as mol% of Ind increases | 6 °C               | 2 K/min from −20 to 180 °C | [92] |
|     | Furosemide-tryptophan                        | 1:1                     | Tg ranges from 138 to 80 °C, decreasing as mol% of Fur increases |                     |            |      |
| 12A | Dexamethasone                                | N/A                     | 115 < Tg < 120                         | Room temperature    | 0.663 °C and 50 S, “Heat only” conditions | [27] |
| 13A | α-lactose                                    | N/A                     | 70                                     | 30 ± 5% relative humidity and 22 ± 3 °C | From 0 to 240°, 10 °C/min under N2 flow of 50 mL/min | [93] |
Table 9. Cont.

| #    | Sample                                           | Molar Ratio/Composition | Glass Transition Temperature (Tg/°C) | Milling Temperature | Conditions                                                                 | Ref. |
|------|--------------------------------------------------|-------------------------|--------------------------------------|---------------------|------------------------------------------------------------------------------|------|
| 14A  | α-D-glucose                                      | N/A                     | 38                                   | −15 °C and 0% relative humidity | 5 °C/min, flushed with highly pure nitrogen gas                              | [68] |
|      | Mebendazole-ASPA                                | 1:1                     | 91                                   | 5 °C, cold room       | −10 °C to 180 °C, 2 °C/min, nitrogen flow was 50 mL/min                     | [94] |
|      | Piroxicam-ASPA                                   | 1:1                     | 76                                   |                     |                                                                              |      |
| 16A  | α-D-glucose                                      | N/A                     | 38                                   | −15 °C and 0% relative humidity | 5 °C/min                                                                     | [95] |
|      | β-D-glucose                                      | N/A                     | 39                                   |                     |                                                                              |      |
| 17A  | Carvedilol, carbamazepine, furosemide, indomethacin, mebendazole-amino acids | 1:1                     | A single Tg for each formulation     | Cold room (+6 °C)     | Nitrogen flow of 50 mL/min, 2 °C/min heated to 180 °C                       | [31] |
| 18A  | Indomethacin-lysine                              | 1:1                     | 100 (DMB)                            | Cold room (+6 °C)     | Nitrogen flow of 50 mL/min, 2 °C/min heated to 180 °C                       | [96] |
| 19A  | Carvedilol, carbamazepine, furosemide, indomethacin, mebendazole-amino acids | Xmeb = 0.1              | 53.5                                 | Room temperature      | −5 °C to 210 °C at 10 °C/min                                                 | [97] |
|      | Pioglitazona-tryptophan                          | Xpgz = 0.1, 150 min     | 44.9                                 |                     |                                                                              |      |
| 22A  | (S)-naproxen-L-arginine                          | 1:1                     | 91.9 ± 0.2                           | 6 °C                 | Nitrogen flow of 50 mL/min, 2 °C/min from −10 °C to 180 °C                  | [99] |
| 23A  | Griseofulvin-tryptophan                          | 1:1                     | 113.46                               | NR                  | 25 to 300 °C, 5 °C/min                                                       | [100]|
| 24A  | Naproxen-tryptophan-proline                      | 1:1                     | 55.1 ± 3.1                           | 6 °C                 | Nitrogen flow of 20 mL/min, 10 K/min from −20 to 170 °C                     | [101]|
|      | Naproxen-tryptophan                              | 1:1                     | 58.2 ± 0.5                           | 6 °C                 |                                                                              |      |
|      | Tryptophan-proline                               | 1:1                     | 67.2 ± 6.8                           |                     |                                                                              |      |
| 25A  | Mebendazole-tryptophanphenylalanine              | 1:1                     | 107.5 ± 0.2                          | 5 °C                 | 2 °C/min, heating to 180 °C                                                  | [102]|
|      | Mebendazole-phenylalaninetryptophan              | 1:1                     | 104.6 ± 0.2                          |                     |                                                                              |      |
|      | Mebendazole-aspartatetryptosine                  | 1:1                     | 61.2 ± 0.9                           |                     |                                                                              |      |
|      | Mebendazole-histidinetelycine                    | 1:1                     | 34.9 ± 1.2/89 ± 0.6                  | 5 °C                 |                                                                              |      |
|      | Mebendazole-proline tetryptophan                 | 1:1                     | 6.5 ± 0.2                            |                     |                                                                              |      |
|      | Mebendazole-tryptophan                           | 1:1                     | 128.7 ± 0.2                          |                     |                                                                              |      |
|      | Mebendazole-proline                              | 1:1                     | 96.9 ± 0.1                           |                     |                                                                              |      |
|      | Mebendazole-proline phenylalanine                | 1:1                     | 56.3 ± 0.2                           |                     |                                                                              |      |
|      | Mebendazole-tryptophanphenylalanine              | 1:1                     | 119 ± 0.1                            |                     |                                                                              |      |
| 27A  | Indomethacin-arginine                            | 1:1                     | 117 ± 4                              | 6 °C                 |                                                                              | [104]|
| 29A  | Naproxen-NAP(Na)                                 | 2:1                     | 55.8                                 | 4 °C                 | 2 °C/min, 0.2120 °C with a period of 40 s                                   | [106]|
|      |                                                 | 1:1                     | 40                                   | 4 °C                 |                                                                              |      |
|      |                                                 | 1:2                     | NR                                   |                     |                                                                              |      |
| 31A  | Indomethacin-arginine                            | 1:1                     | 62.9 ± 0.8                           | NR                  | Nitrogen gas flow of 50 mL/min, 10 °C/min to 180 °C                         | [36] |
|      | Indomethacin-phenylalanine                       | 1:1                     | 55.3 ± 0.4                           | NR                  |                                                                              |      |
|      | Indomethacin-tryptophan                          | 1:1                     | 62.7 ± 7.0                           | NR                  |                                                                              |      |
| 32A  | Glibenclamide-serine                             | 1:1                     | 70.1 ± 1.3                           | 6 °C                 | Nitrogen flow of 50 mL/min, 10 °C/min, from −50 °C to 280 °C (depending on the sample) | [108]|
|      | Glibenclamide-threonine                          | 1:1                     | 58.4 ± 1.3                           |                     |                                                                              |      |
Table 9. Cont.

| #   | Sample                        | Molar Ratio/Composition | Glass Transition Temperature (Tg/°C) | Milling Temperature | Conditions                                                                 | Ref. |
|-----|-------------------------------|-------------------------|-------------------------------------|---------------------|----------------------------------------------------------------------------|------|
| 33A | Indomethacin-arginine         | 1:1                     | 36.7 ± 0.8                          |                     |                                                                             | [98] |
|     | Indomethacin-phenylalanine    | 1:1                     | 64.1 ± 1.4                          |                     |                                                                             |      |
|     | Indomethacin-tryptophan       | 1:1                     | 47.8 ± 2.9                          |                     |                                                                             |      |
|     | Indomethacin-phenylalanine-tryptophan | 1:1:1                 | 68.7 ± 2.6                          | 6 °C                | Nitrogen gas flow, 20 mL/min, from −20 to 180 °C, 10 K/min                |      |
|     | Indomethacin-arginine-phenylalanine | 1:1:1                 | 63.1 ± 0.8                          |                     |                                                                             |      |
|     | Carbamazepine-tryptophan      | 1:1                     | 81 ± 0.6                            |                     |                                                                             |      |
|     | Carbamazepine-phenylalanine-tryptophan | 1:1:1                 | 75.1 ± 1.1                          |                     | Nitrogen gas flow, 20 mL/min, from −20 to 200 °C, 10 K/min               |      |
|     | Carbamazepine-arginine-tryptophan | 1:1:1                 | 65.4 ± 1.1                          |                     |                                                                             |      |
| 35A | Carbamazepine-citric acid     | 1:1                     | 38.8 ± 2.7                          |                     |                                                                             | [110]|
|     | Citric acid-arginine          | 1:1                     | 56.2 ± 0.7                          |                     |                                                                             |      |
|     | Citric acid-arginine          | 1:2                     | 106 ± 0.3                           |                     |                                                                             |      |
|     | Citric acid-arginine          | 1:3                     | 130.5 ± 0.1                         |                     |                                                                             |      |
|     | Citric acid-arginine          | 1:4                     | 119 ± 0.1                           |                     |                                                                             |      |
|     | Carbamazepine-citric acid-arginine | 1:1:1                 | 77.8 ± 1.8                          | 4 °C                | Nitrogen gas at 50 mL/min, 2 °C/min from 0 to 150 °C, 0.212 °C with a period of 40 s |      |
|     | Carbamazepine-citric acid-arginine | 1:1:2                 | 105.3 ± 0.2                         |                     |                                                                             |      |
|     | Carbamazepine-citric acid-arginine | 1:1:3                 | 127.8 ± 0.8                         |                     |                                                                             |      |
| 36A | Glibenclamide-quercetin       | 1:1                     | 85.97 ± 0.29                        |                     | Cryomilled                                                                | [111]|
| 37A | Mebendazole-glutamate-arginine (crystalline salt) | 1:1:1                 | 37.8                                |                     | Cold rooms (5 °C)                                                         | [112]|
|     | Mebendazole-glutamate-arginine (amorphous salt) | 1:1:1                 | 37.3                                |                     | Nitrogen gas flow of 50 mL/min, 2 °C/min, 0.212 °C (amplitude), 40 s (period) |      |
|     | Meb-glutamate-arginine        | 1:1                     | 36.5/77                             |                     |                                                                             |      |
|     | Meb-arginine-glutamate        | 1:1                     | 36.3/76.3                           |                     |                                                                             |      |
| 42A | Candesartan cilexetil-hydrochlorothiazide | NA                    | 110                                 |                     | Nitrogen gas flow, 100 mL/min, 10 °C/min, from 30 to 300 °C               | [116]|

Tables 9–11 show all the thermal characterization and phase transitions of co-amorphous, co-crystals, and polymorphs. The following sections discuss specific results for each kind of formulation.

(f) Thermal analysis of ball-milled co-amorphous systems

After analyzing the thermal characterization results of the amorphous and co-amorphous samples obtained by milling (shown in Table 9), it can be concluded that the determination of glass transition temperature (Tg) is a very useful tool to reach conclusions of amorphization of the material. For binary systems, detecting a single Tg is a clear indication of a homogeneous, single-phase, co-amorphous mixture [94]. Most of the co-amorphous system reported a single Tg, except Wu et al. [102], who prepared a total of nine co-amorphous systems and found two Tgs in the mebendazole-histidine-glycine ternary system; the rest showed only one Tg.
Several articles report the values of Tg at different molar ratios, namely 1:1, 1:2, and 2:1. In some cases, the determination of Tg is not possible, due to fast recrystallization or because it is not reported, but the rest of the articles reported the value of Tg at each molar ratio. In most cases, Tg’s value at 1:1 ratio tends to be between the values at ratios of 1:2 and 2:1. When the composition is different than 1:1, the newly observed Tg tends to be closer to the Tg of the component present in excess within the mix [87,157]. This is because the excess components in a mixture show a tendency to recrystallize [158]. These shifts in the value of Tg give clear information regarding the development of new interactions of the components in the sample, and this is where the Gordon–Taylor equation is very relevant. The theoretical Tg for a co-amorphous system containing two amorphous components can be calculated with this equation [159]

\[
T_{g1,2} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + Kw_2}
\]  

(2)
where $T_{g1,2}$ is the glass transition temperature of the co-amorphous mixture, $w_1$, $w_2$, $T_{g1}$, and $T_{g2}$ are the weight fractions and glass transition temperatures for the two amorphous components, and $K$ is a constant expressed as:

$$K = \frac{T_{g1} \times \rho_{g1}}{T_{g2} \times \rho_{g2}}$$

where $\rho_1$ and $\rho_2$ are the densities of each of the two components [92].

The Gordon–Taylor equation assumes no interaction between the molecules in the mixture; therefore, large deviations could suggest that the two components interact at the molecular level [87]. A negative deviation from the predicted value of $T_g$ by the Gordon–Taylor equation indicates a non-ideal mixing [158,160,161]. In this sense, free volume additivity, interactions between components, and loss of hydrogen bonding during mixing could account for this non-ideal mixing and negative deviations [160]. On the other hand, it has been mentioned that, when the $T_g$s of the co-amorphous systems are higher than the $T_g$s (a positive deviation) calculated by the Gordon–Taylor equation, it suggests strong molecular interactions between the components [92,96]; such interactions can be hydrogen bonding [162], $\pi$–$\pi$ interactions [98], and salt formation [163] between the drug and co-former, thus leading, again, to a rise in the value of the experimental $T_g$ over the theoretical $T_g$ [94]. This deviation between theoretical and experimental $T_g$ strongly depends on the drug–drug or drug–co-former selected for study. It is worth mentioning that Kasten et al. [31] concluded that the highest increase in $T_g$s occurred in the acidic drug basic AAs combinations (See Table 9), due to interactions resulting in salt formation. As was mentioned in Section 3.2, amorphization for milling requires to be performed at temperatures far below from the glass transition temperature; as shown in the data from Table 9, all reported experimental conditions agreed with this statement.

(g) Phase transitions reported for co-crystals prepared by milling

After analyzing the data presented in Table 10, it was concluded that DSC can identify the melting point of co-crystals, as it is, in general, remarkably different from the pure melting temperatures of APIs and pure co-former [44]. Identifying new endothermic peaks between the melting points of both components indicates the formation of the co-crystal phase [121,124,127].

According to Stoler et al. [70], identifying a eutectic mixture in a phase diagram will result in a classic V shape (where the minimum point represents the eutectic point). By contrast, the binary-phase diagram for a co-crystal exhibits two eutectic points and a region of co-crystal at the maximum between the two eutectic points, resulting in a W-shaped phase diagram for co-crystals [71,72,164] (See Figure 2 for a representation of these diagrams).

In conclusion, for co-crystals ball-milled samples, endothermic peaks usually are located between the melting points of the parent compounds to proof the co-crystal formation (See Table 10); except, Nugrahani et al. [165] and Macfionnghaile et al. [119] found values of $T_m$ of the co-crystal lower than the parent drug, and Zhao et al. [44] found two endothermic peaks in the sample analyzed.

(h) Phase transitions of polymorphs resulting from mechanical activation

After reviewing the results of the thermal analysis presented in Table 11, it can be concluded that DSC is a valuable technique to identify phase transitions. With DSC, it is also possible to observe reminiscence of residual solvents [79] and melting temperature ($T_m$) to identify polymorphs. Between two polymorphs, a higher melting point would indicate a more stable form of the drug.
Table 11. Overview of thermal characterization (DSC) of drug polymorphs obtained by ball milling.

| #  | Sample                          | Polymorph Identified | Transition Temperature (°C) | Milling Temperature Conditions and Milling Time | Ref.       |
|----|--------------------------------|----------------------|-----------------------------|-----------------------------------------------|-----------|
| 1P | Ranitidine hydrochloride        | Form 1               | Tm = 142.73                 | Room temperature 100 mL/min                   | [166]     |
|    |                                | Form 2               | Tm = 145.01                 | 12 ± 3 °C and 35 °C, 10 K/min                 |           |
| 2P | Chlorhexidine dihydrochloride   | Form 2               | Te2 = 124                   | Room temperature                              |           |
|    |                                | Form 3               | Te3 = 157                   | 5 °C/min                                       | [140]     |
|    |                                | Form 3               | Tm3 = 256                   | Room temperature 5 °C/min                     |           |
| 3P | Γ-sorbitol                     | Form A               | Decrease in melting temperature (value not reported) | Room temperature | [34] |
| 4P | Rivastigmine (RHT form II)     | Form II              | Tm1 = 97.5, Tm2 = 124.5     | Room temperature 10 °C/min from 0 to 150 °C   | [141]     |
|    |                                |                      | Exo peak = 105.5            |                                               |           |
|    |                                | Form I               | Tm = 123.5                  |                                               |           |
| 6P | Dexamethasone                   | Form A               | Tm = 242                    | Room temperature                              | [27]      |
|    |                                | Form B               | Tm = 250                    | 5 °C/min                                       |           |
| 7P | Sofosbuvir (anhydrous form I)  | Form A               | Tm = 117.90                 | Room temperature                              |           |
|    |                                | Form B               | Tm = 124.83                 | 0 to 300 °C, 5 °C/min                          | [79]      |
|    |                                | Form V               | Tm = 71.54                  |                                               |           |
| 8P | Sulindac (form II)             | II → I               | Endo peak = 160             | Room temperature                              |           |
|    |                                |                      | 5 °C/min                     |                                               | [69]      |
| 9P | Γ-sorbitol                     | Form A               | Tm = 98.5                   | Room temperature with dry nitrogen atmosphere |           |
|    |                                |                      | 5 °C/min                     |                                               | [75]      |
|    |                                | A-form               | Tm = 85                     |                                               |           |
| 12P | Sulfamerazine                 | Form I               | Tm = 236                    | Room temperature                              |           |
|    |                                | Form II              | Tm = 212–214                | 100 mL/min                                    | [166]     |

Other transitions, such as crystallization temperature (Tc) and other endothermic signals, are also reported (along with the articles) and summarized in Table 11. For example, Elisei et al. (Elisei et al., 2018) determined two different crystallization temperatures, one for form 2 (Tc = 124 °C) and another for form 3 (Tc = 157 °C). Finally, a melting temperature of form 3 (Tm = 256 °C) from chlorohexidine dihydrochloride polymorph. In conclusion, endothermic peaks, such as melting temperatures, are very important because higher values lead to more stable polymorphic forms, and lower values lead to metastable forms.

As mentioned in Section 3.2, crystallization and polymorphic transformations occurred during the milling process at temperatures above the glass transition temperatures; however, most of the studies of co-crystals or polymorphs do not report Tg values of the materials.

Table 10. Overview of thermal characterization (DSC) of drug co-crystals obtained by ball milling.

| #  | Sample | Polymorph Identified | Tm Parent | Tm Co-Crystal | Ref.       |
|----|--------|----------------------|-----------|---------------|-----------|
| 14 | Ciprofloxacin-nicotinic acid | 254.8 | 235.1 | 241 | [124] |
| 15 | Brexpiprazol-catechol | 184.8 | 106.3 | 161.3 | [120] |
| 16 | Acetazolamide (polymorph I)-4-aminobenzoic acid | 167 | 188.5 | 163.4 | [133] |
| 17 | Chlorothiazide-DL-proline | NR | NR | 212.9 | [129] |
| 18 | Praziquantel-F-127 4B (20:1) | 140.23 | 56.22 | 133.06 | [130] |
| 19 | Itraconazole-4-aminobenzoic acid | * | 161.2 | 168.2 | [136] |
| 20 | Ibuprofen-nicotinamide | NR | NR | 80.5 | [134] |
| 21 | Sofosbuvir | Form II | 236.1 | Room temperature 0 to 160 °C, Room temperature 100 mL/min | [166] |
| 22 | Sulindac (form II) | II → I | Endo peak = 160 | Room temperature 5 °C/min | [69] |
| 23 | Dexamethasone | Form A | Tm = 242 | Room temperature | [27] |
| 24 | Chlorhexidine dihydrochloride | Form 2 | Te2 = 124 | Room temperature | [140] |
| 25 | Ranitidine hydrochloride | Form 1 | Tm = 142.73 | Room temperature 100 mL/min | [166] |
4.4. Identification of Amorphous and Crystalline Phases by Powder X-ray Diffraction (PXRD)

X-ray diffraction patterns show specific features, depending on the sample analyzed, and allow identification of amorphous and co-amorphous systems, co-crystals, and polymorphs. In this sense, a diffused halo is a clear indicator of the amorphous state (See Figure 3). In addition, XRD allows for identifying specific peaks in co-crystals, differentiation between polymorphs, and degree of crystallinity. In the following, Tables 12 and 13, the diffraction peaks were directly taken from the articles; when values were not reported, the diffractograms were analyzed in WebPlotDigitizer-3.8 to obtain the accurate values. The samples are marked with an asterisk (*) when data were obtained using this program.

XRD is a technique that can also be useful to identify changes in the crystal system and space groups. Anyway, it allows for the identification of specific peaks that correspond to a particular co-crystal form. From Table 12, it was observed that peaks might vary slightly, depending on the molar ratio [121], and they might even be solvent-dependent [124]. It is worth mentioning that a co-crystal with two polymorphic forms was obtained by Stolar et al. [66] upon the use of mechanochemical preparation (See Row 1 Table 12), but these results will not be further discussed, as they exceed the objectives set out in this review.

Finally, Table 12 also shows that all the articles that reported measurement conditions used a voltage of 40 kV, and the main current used was 40 mA, with step sizes ranging from 0.01 to 0.4, when reported.

A similar analysis can be performed for polymorphs. Each polymorph of a drug shows characteristic diffraction peaks, which enable the accurate identification of the form. It is important to know that milling might cause the disappearance of certain peaks, and new peaks might grow and increase in intensity; this is a clear indicator of the presence of a certain form of the drug (see Table 13).

Besides the information previously discussed, this technique allows analysis of the stability over time of pharmaceutical formulations, which will be discussed below.

Figure 3. Example of diffractogram of the crystalline pure drug (irbesartan and glimepiride) and co-amorphous form of the binary system.
Table 12. Overview of identification of diffraction peaks and measurement conditions for co-crystals.

| #  | Sample                                | Co-Crystal          | Characteristic Peaks (°2θ) | Conditions: Current (mA), Voltage (kV), etc. | Ref. |
|---|---------------------------------------|---------------------|---------------------------|-----------------------------------------------|------|
| 1C| Nicotinamide-L-(+)-ascorbic acid      | Form I polymorph    | 1.2, 1.5, 1.9, 2.1, 2.8, 3.2, 3.3 | 7.5 mA, 40 kV                                 | [66] |
|   |                                       | Form II polymorph   | 1.5, 1.8, 2.1, 2.7, 3.1, 3.2 |                                               |      |
| 2C| Salicylic acid-2-pyridone             | sal2hyp             | 7.8, 11.02, 15.2, 15.8, 16.7, 24.1, 26.8, 28.7 |                                               | [117]|
|   | Salicylic acid-3-hydroxypyridinone    | sal3hyp             | 9.2, 20.3, 23.2, 27.5, 31.6 |                                               |      |
|   | Salicylic acid-4-pyridone             | sal4hyp             | 1.6, 1.9, 2.0, 2.1, 2.8, 3   |                                               |      |
| 3C| Ciprofloxacin-thymol                  | N/A                 | 5.3, 5.7, 7.8, 11.4, 13.2, 15.7, 17.51, 19.4, 20.9 | 40 kV, 40 mA, step size 0.0130° | [118]|
| 4C| Urea-caffeine                         | N/A                 | 8.64, 10.82, 13.89, 24.30, 25.08, 25.46 | 35 kV, 25 mA                                 | [119]|
| 5C| Brexpiprazol-catechol                 | N/A                 | 8.42, 9.94, 18.47, 22.25, 22.53, 23.98, 24.3 | 40 kV, 30 mA, step 0.03° | [121]|
|   | Brexpiprazol-succinic acid            | N/A                 | 9.2, 12.9, 16.7, 20.2, 25.9, 27.3, 28.7, 29.4, 33.1, 35.0 | 40 kV, 40 mA | [122]|
| 6C| Ciprofloxacin-nicotinic acid          | CIP-NCA/EtOH (1:1)  | 9.2, 11.5, 18.5, 22.9, 23.4, 26.4, 28.5, 29.4 | 40 kV, 40 mA, 5–50°, step 0.04°, speed 4°/min | [124]|
|   | Ciprofloxacin-isonicotinic acid       | CIP-INCA/EtOH (1:1) | 5.4, 10.6, 19.2, 21.4, 28.4 | 40 kV, 15 mA, 5–50°, step 0.04°, speed 4°/min | [127]|
| 13C| Acetazolamide-4-aminobenzoic acid      | N/A                 | 6.4, 10.1, 12.1, 12.9, 13.4, 14.1, 15.6, 16.7, 17.2, 17.6, 18.2, 18.3, 19.6, 20.1, 21.4, 22, 23.3, 24.9, 25.6, 26.2, 26.6, 27.8, 29.1 | Ambient conditions | [67]|
| 15C| β-Lapachone-resorcinol                | N/A                 | 9.9, 10.5, 11.9, 12.9, 16.8, 18.1, 19.1, 21.4, 21.8, 24.9, 28.8 | 40 mA, 40 kV, step size 0.01°, collection time 18 h | [125]|
| 16C| Norfloxacin-nicotinic acid            | (with EtOH)         | 5.4, 14.5, 25.4 | Room temperature, 40 kV, 40 mA | [128]|
| 17C| Chlorothiazide-DL-proline             | (w/acetonitrile-water) | 7.3, 20.1, 22.8, 24.12, 25.01 | Ambient temperature, 40 kV, 100 mA, 8°/min | [129]|
|   | Chlorothiazide-DL-proline hydrate     | (w/acetonitrile-water) | 8.02, 11.42, 16.4, 23.47, 23.83, 24.95, 25.3 | Ambient conditions | [67]|
|   | Chlorothiazide-D-proline hydrate      | (w/acetonitrile-water) | 8.2, 11.7, 16.2, 16.7, 17.5, 24.03, 25.2, 26.5, 29.2, 30.9 | Ambient conditions | [67]|
| 18C| Praziquantel-F-127 2B (201)           | N/A                 | 8.06, 15.2, 16.4, 16.9, 19.9 | 40 mA, 40 kV, scan rate 0.02°/s | [130]|
|   | Praziquantel-F-127 4B (10:2)          | N/A                 | 6.08, 7.9, 11.9, 12.5, 15.1, 18.8, 19.8, 22.8, 25.3 | 40 mA, 40 kV, scan rate 0.02°/s | [130]|
| 20C| Ketoconazole-fumaric acid             | N/A                 | 8.03, 12.2, 16.9, 19.3, 20.3, 21.6, 23.9, 25.9, 28.8 | 40 kV, 40 mA, step size 0.02°, counting time set 0.2 s/step | [132]|
|   | Ketoconazole-succinic acid            | N/A                 | 6.7, 7.9, 12.1, 17.1, 17.7, 19.3, 20.1, 21.2, 23.3, 23.8, 24.3 | 40 kV, 40 mA, step size 0.02°, counting time set 0.2 s/step | [132]|
| 21C| Itraconazole-4-hydroxybenzamide form 1 (1:2) | N/A                 | 7.3, 9.4, 9.7, 10.3, 11.1, 12.3, 12.7, 16.2, 16.6, 19.5, 20.4, 21.6, 26.2, 26.3 | Ambient conditions, rotated at 15 rpm | [133]|
|   | Itraconazole-4-hydroxybenzamide form 2 (1:2) | N/A                 | 5.7, 11.4, 12.9, 18.7, 19.04, 20.1, 23.3, 23.8, 25.2 | Ambient conditions, rotated at 15 rpm | [133]|
|   | Itraconazole-4-aminozinc acid (1:1)   | N/A                 | 6.1, 10.8, 11.4, 11.9, 13.5, 14.6, 18.8, 19.2, 20.4, 21.2, 21.5, 22, 25.4, 25.5 | Ambient conditions, rotated at 15 rpm | [133]|
| 23C| Pyrazinamide-4-aminosalicylic acid    | N/A                 | 5.95, 11.91, 13.06, 13.54, 28.25 | NR | [135]|
| 24C| Theophylline-4-aminobenzoic acid      | N/A                 | 12.3, 14.5, 25.8, 27.5, 28.6 | 40 kV, 40 mV, step size 0.026° and step time of 56 s | [136]|
| 25C| Betulin-terephthalic acid             | (w/acetone)         | 5.08, 8.6, 10.2, 12.8, 14.1, 14.7, 16, 18.8, 21.3 | Range from 5 to 70° | [137]|
|   | Betulin-Terephthalic acid             | (w/isopropanol)     | 5.1, 8.7, 9.4, 10.2, 12.9, 14.2, 14.6, 16.1, 17.3, 17.8, 18.9, 19.3 | Range from 5 to 70° | [137]|
Table 13. Overview of identification of diffraction peaks for polymorphs.

| #  | Sample                        | Polymorph Identification | Characteristic Peaks (° 2θ) | Ref. |
|----|-------------------------------|--------------------------|-----------------------------|------|
| 1P | Ranitidine hydrochloride *    | Form 1                   | 17, 21.8, 24.9              | [74] |
|    |                               | Form 2                   | 20.40, 23.7                 |      |
| 2P | Chlorhexidine dihydrochloride * | Form 1 → initial spectrum | 13.9, 18.5, 23.7            | [140]|
|    |                               | Form 2 → few peaks       | 5.2                         |      |
|    |                               | Form 3 → many Bragg peaks| 14.9, 28.3                  |      |
| 3P | γ-Sorbitol *                  | A phase → Sharp peaks, increased milling time | 16.6, 30.9 | [34] |
|    |                               | γ phase                  | 11.6, 25.5                  |      |
| 4P | Rivastigmine                   | Form II                  | 9.5, 11.3, 14.2, 15.5, 19.1, 20 | [141]|
|    |                               | Form I → Broadening of peaks | 5.1, 14.7, 16.5, 17.6, 18.6, 20.4, 21.1 |      |
| 5P | α-Aminobenzoic acid FI        | FI                       | 10.7, 13.7, 14.35, 16.4, 18.6, 23.5, 24.3, 24.9, 26.2, 27.6, 30.5 | [54] |
|    |                               | FII                      | 11.2, 15.4, 22.2, 26.7      |      |
|    | m-Aminobenzoic acid (FIII form) | FI                       | 8.6, 17.2, 24.9             |      |
|    |                               | FIII                     | 8.3, 16.8, 17.9, 23.7, 23.7, 24.2, 25.9, 26.6, 27.8 |      |
| 6P | Dexamethasone *               | Form A                   | 7.9, 13.5, 16.0, 17.6       | [27] |
|    |                               | Form B                   | 7.5, 16.8, 18.4             |      |
| 7P | Sofosbuvir *                  | Form I                   | 5.3, 7.6, 9.0, 9.8, 10.3    | [79] |
|    |                               | Form A                   | 6.2, 8.4, 10.5, 12.8, 17.4, 17.9, 18.2, 20.3, 21.1 |      |
|    |                               | Form B                   | 7.9, 10.3, 12.3, 16.7, 17.1, 19.3, 20, 20.9 |      |
|    |                               | Form V                   | 5.6, 6.9, 7.5, 10.8, 13.8, 16.4, 19.7, 25.4 |      |
| 8P | Sulindac *                    | Form I                   | 10.8, 17.6                  | [69] |
|    |                               | Form II                  | 9.3, 16.1                   |      |
| 9P | Γ-sorbitol *                  | Γ-form                   | 11.7, 25.6                  | [75] |
|    |                               | A-Form                   | 16.7, 31.1                  |      |
| 12P | Sulfamerazine                 | I                        | 12.6, 14.8, 16.3, 17.4, 20.5, 22.7, 23.6, 24.6, 31.2, 32.7 | [166]|
|    |                               | II                       | 14.5, 17.0, 19.2, 21.5, 26.6, 27.4, 27.9 |      |

(i) Measurement of structural stability on co-amorphous systems during storage by XRD

It is well-known that amorphous samples are not necessarily stable and can recrystallize upon environmental conditions such as high humidity and temperature modification. Table 14 summarizes the information found on articles regarding structural stability, which has been measured under different temperatures ranging from 4 °C to 40 °C, under dry (silica gel and P₂O₅) and other humidity conditions (5, 10, and 75% RH) and storage days from 2 to 730 days observing if recrystallization occurred.

More than half of the articles studied structural stability at 25 °C and 40 °C, whereas fewer articles kept the samples at 4 °C or below for further analysis. This stability may depend on the properties of each drug alone, as well as the storage under dry conditions. Note that highly unstable compounds recrystallize immediately after the end of the milling process, even at very low temperatures, such as −15 °C, and a relatively long milling time (14 h) [68]. The reason is that the amorphous state of single drugs is usually less stable (see trehalose dihydrate and α-D-glucose in Table 14) than a co-amorphous system. Therefore, they tend to recrystallize. Nonetheless, other individual drugs studied, such as tadalafil [26] and glibenclamide [89], did not crystallize after 365 and 210 days of storage and 25 °C, respectively. A low percentage of relative humidity rendered amorphous samples for more extended periods.

Badal Tejedor et al. suggest that amorphization is a phenomenon that begins at the surface and propagates to the bulk, thus disrupting the crystalline structure of the material, where additional changes clearly occur at the surface during prolonged milling times [93]. They noticed that other factors can affect the amorphous state’s physical stability
once amorphization is reached. These are: (1) remanence of nuclei during milling [167]; (2) different local order in the milled material changes nucleation and growth properties of the crystalline form [95]; and (3) larger specific surface of the milled material can also promote crystallization because the molecular mobility is higher at the surface than in bulk [168].

Table 14. Overview of structural stability of amorphous systems upon storage in diverse conditions.

| #  | Sample                                                                 | XRD Interpretation                             | Storage Time (Days) | Storage Conditions *                                      | Ref.     |
|----|-------------------------------------------------------------------------|-------------------------------------------------|---------------------|----------------------------------------------------------|----------|
| 2A | Furosemide-arginine, furosemide-citrulline, nitrofurantoin-arginine, nitrofurantoin-citrulline (1:1) | Remained amorphous                             | 450                 | 25 °C, (dry conditions, silica gel)                      | [85]     |
|    | Furosemide-arginine, furosemide-citrulline, nitrofurantoin-arginine     | Remained amorphous                             | 450                 | 40 °C, (dry conditions, silica gel)                      |          |
|    | Nitrofurantoin-citrulline                                              | Recrystallization of Nitrofurantoin            | 450                 | 40 °C, (dry conditions, silica gel)                      |          |
| 3A | Sulfathiazole-polyvinylpyrrolidone, sulfadimidine-polyvinylpyrrolidone   | Diffused halo → amorphous state                | 365                 | 4 °C with desiccant                                      | [86]     |
| 4A | Naproxen-cimetidine (1:1)                                              | Halo, most stable sample                       | 186                 | 4 °C, 25 °C and 40 °C, dry conditions (silica gel)       | [87]     |
|    | Naproxen-cimetidine (2:1)                                              | Halo, stable                                   | 33                  | 4 °C, dry conditions (silica gel)                        |          |
|    | Naproxen-cimetidine (2:1)                                              | Crystalline naproxen (in excess) peaks         | 33                  | 25 °C and 40 °C, dry conditions (silica gel)             |          |
|    | Naproxen-cimetidine (1:2)                                              | Traces of crystalline cimetidine              | 33                  | 4 °C, 25 °C and 40 °C, dry conditions (silica gel)       |          |
| 5A | γ-indomethacin-ranitidine hydrochloride (1:1)                          | Halo, highest stability                        | 30                  | 4 °C and 25 °C, dry conditions (silica gel)              | [28]     |
|    | γ-indomethacin-ranitidine hydrochloride (2:1)                          | Small crystalline peaks of indomethacin (indo in excess) peaks | 30                  | 25 °C and 40 °C, dry conditions (silica gel)             |          |
|    | γ-indomethacin-ranitidine hydrochloride (1:2)                          | Progressive increase in peak intensity as temperature increased. | 30                  | 25 °C and 40 °C, dry conditions (silica gel)             |          |
| 6A | γ-indomethacin                                                         | γ-form, crystallized                           | <1                  | 22 °C over P₂O₅                                          | [88]     |
|    | α-indomethacin                                                         | α-form crystallized to γ-form                 | 4                   |                                                          |          |
| 7A | Tadalafil                                                              | Amorphous                                     | 365                 | 4 °C with desiccant                                      | [26]     |
| 8A | Glibenclamide (GCM)                                                    | Broad halo, amorphous state                   | 210                 | 25 °C, 10% RH, dry conditions                            | [89]     |
| 9A | Trehalose dihydrate                                                    | Recrystallised material is trehalose dihydrate | 2                   | 25 °C                                                   | [90]     |
| 10A| Atenolol-hydrochlorothiazide (1:1)                                     | Amorphous, stable                             | 30                  | 4 °C and 25 °C, in desiccator                            | [91]     |
|    | Atenolol-hydrochlorothiazide (1:2)                                     | Amorphous, stable                             | 30                  | 4 °C, in desiccator                                      |          |
|    | Atenolol-hydrochlorothiazide (1:2)                                     | Traces of crystals                            | 30                  | 25 °C, in desiccator                                     |          |
| 12A| Dexamethasone                                                          | Form A converts to form B                     | 7                   | 150 °C                                                  | [27]     |
| 14A| α-D-glucose                                                            | Absence of Bragg peaks → amorphization        |                      |                                                          | [68]     |
|    |                                                                      | Well-defined Bragg peaks → crystalline state  |                      |                                                          |          |
|    |                                                                      | Immediate analysis after 14 hrs of milling     | −15 °C              |                                                          |          |
|    |                                                                      | Immediate analysis after 14 hrs of milling     | 25 °C               |                                                          |          |
| 15A| Mebendazole-ASPA                                                       | Amorphous                                     | 120 days            | 25 °C and 40 °C (silica gel)                            | [94]     |
|    | Tadalafil-ASPA                                                         | Amorphous                                     | 120 days            | 25 °C and 40 °C (silica gel)                            |          |
|    | Piroxicam-ASPA                                                         | Amorphous                                     | 120 days            | 25 °C and 40 °C (silica gel)                            |          |
| 16A| β-D-Glucose                                                            | Bragg peaks restore immediately after the end of the milling process | 1 h                 | 25 °C                                                   | [95]     |
| # | Sample | XRD Interpretation | Storage Time (Days) | Storage Conditions * | Ref. |
|---|---|---|---|---|---|
| 17A | Carvedilol, carbamazepine, furosemide, indomethacin, mebendazole-amino acids | Recrystallization → Meb-Lys, Meb-Ile, Meb-Leu, Car-Val, Sim-Lys, Ind-Ile, Ind-Leu | 140 | 25 °C, 5% RH (P₂O₅) | [31] |
| 17A | | Recrystallization peaks → Fur-Met, Fur-Val, Ind-Leu | 140–365 | | |
| 17A | | Amorphous → Arg-Fur, Arg-Ind, His-Fur, Lys-Fur, Lys-Ind, Car-Ile, Car-Leu, Car-Met, Car-Phe, Car-Trp, Meb-Met, Meb-Phe, Meb-Trp, Sim-Phe, Cbz-Trp, Sim-Trp | 365–730 | | |
| 18A | Indomethacin-lysine | Amorphous halo | 252 days | DMB, 25 °C (P₂O₅) and 40 °C (silica gel), dry conditions | [96] |
| 18A | | Recrystallization → within 25 days it turned into same crystalline form of LAG | 10 days | DMB, 25 °C, 75% RH | |
| 18A | | Crystalline form | 252 days | LAG, 25° and 40 °C | |
| 23A | Griseofulvin-tryptophan | Amorphous state, no recrystalization detected | 365 | Silica gel (13–32% RH), vacuum, 23–28 °C | [100] |
| 25A | Mebendazole-tryptophan-phenylalanine | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-tryptophanphenylalanine | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-phenylalanine-tryptophan | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-aspartate-tyrosine | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-histidine-glycine | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-proline-tryptophan | Remained amorphous | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | Mebendazole-proline | Recrystallized | 90 | 40 °C, 2% RH (silica gel) | [102] |
| 25A | All samples | Remained amorphous | 90 | 25 °C, 2% RH (silica gel) | |
| 29A | Naproxen-NAP(Na) (2:1) | Recrystallization peaks are visible | 7 | 40 °C, silica gel | [106] |
| 29A | Naproxen-NAP(Na) (1:1) | Remained amorphous | 60 | | |
| 32A | Simvastatin-lysine | Amorphous | 150 | 4 °C and 0% RH | |
| 32A | | Recrystallization | 90 | 4 °C and 0% RH | |
| 32A | | Recrystallization | 56 | Ambient temperature and 60% RH | |
| 32A | Glibenclamide-threonine | Recrystallization | 40 | 40 °C and 0% RH | [108] |
| 32A | Glibenclamide-serine-threonine | Recrystallization | 90 | 40 °C and 0% RH | [108] |
| 32A | Glibenclamide-serine | Amorphous | 180 | | |
| 32A | Glibenclamide-serine | Amorphous | 180 | | |
| 32A | Glibenclamide-threonine | Recrystallization | 44 | 4 °C and 0% RH | |
| 32A | Glibenclamide-serine-threonine | Recrystallization | 90 | | |
| 32A | Glibenclamide-serine | Recrystallization | 150 | Ambient temperature and 60% RH | |
| 32A | Glibenclamide-threonine | Recrystallization | 26 | | |
| 33A | Indomethacin, carbamazepine, L-arginine, L-phenylalanine, L-tryptophan and L-tyrosine | Remained amorphous (halo) | 180 | 40 °C, dry conditions (silica gel) | [169] |
| 35A | Carbamazepine-arginine (1:1, 1:2, 1:3, 1:4) carbamazepine-Citr acid-arginine (1:1:1, 1:1:2, 1:1:3) | Amorphous | 60 | 40 °C, silica gel | [110] |
In this sense, several authors prepared the amorphous systems at different molar ratios (see Table 14), and it was clearly observed that the 1:1 preparation allows for the obtention of the structurally most stable ball-milled mixtures from 30 to 186 days, compared to 2:1 and 1:2 molar ratios.

It has been argued that recrystallization prevails at high temperatures, while amorphization prevails at low temperatures due to low molecular mobility [95] in amorphous systems. For preparations that involve molar ratios different than 1:1, the amorphous state is maintained at low temperatures (4 °C). However, as the temperature rises in the sample, recrystallization occurs in the form of a progressive increase in peak intensity, where the excess compound is the one that recrystallizes first [28,87,91]. This observation is

Table 14. Cont.

| # | Sample                                                                 | XRD Interpretation          | Storage Time (Days) | Storage Conditions *                                                                 | Ref. |
|---|------------------------------------------------------------------------|------------------------------|---------------------|-------------------------------------------------------------------------------------|------|
| 36A | Mebendazole (Meb)-glutamate-arginine (crystalline salt), meb-arginine-glutamate (amorphous salt), meb-glutamatearginine, meb-arginineglutamate (dipeptide) | Remained amorphous           | 180                 | 25 °C, dry conditions (silica gel), 2% RH                                            | [112]|
|    | Meb-glutamate-arginine meb-arginine-glutamate                          | Recrystallization            | 180                 | 40 °C, dry conditions (silica gel), 2% RH                                            |      |
|    | Meb-glutamatearginine meb-arginineglutamate                            | Remained amorphous           | 180                 |                                                                                     |      |
| 38A | Glibenclamide-serine glibenclamide-arginine                            | Samples after storage were similar to the patterns exhibited before the test | 180                 | 40 °C and 75% RH                                                                   | [170]|
| 39A | Rutin-naringin hydrate (all molar ratios), rutin-hesperidin (all molar ratios), rutin-methionine (1:1), rutin-queercetin dihydrate (1:1, 2:1) | Remained amorphous           | 12 h                 | Dry and wet conditions                                                              | [114]|
|    | Rutin-methionine (1:2 and 2:1)                                          | Small peaks                  | 12 h                 | Dry conditions                                                                     |      |
|    | Rutin-queercetin dihydrate (1:2)                                        | Small peaks                  | 12 h                 | Dry and wet conditions                                                              |      |
| 40A | Gliclazide (Glz)-nifedipine                                             | Crystallized to a physical mixture | 3                  | Ambient temperature, 56% RH                                                         | [38] |
|    | Glz-indapamide, Glz-triamterene, Glz-hydrochlorothiazide                | Remained amorphous           | 180                 |                                                                                     |      |
|    | Glz-chlorothiazide                                                      | Recrystallized               | 30                  | Ambient temperature, 98% RH                                                         |      |
|    | Glz-indapamide, Glz-triamterene, Glz-hydrochlorothiazide                | Remained amorphous           | 120                 |                                                                                     |      |
|    | Glz-hydrochlorothiazide                                                | New peaks                    | 30                  |                                                                                     |      |
|    | Glz-triamterene                                                        | Small peaks                  | 120                 |                                                                                     |      |
|    | Glz-benzamidine                                                        | New pattern assigned to the salt | 30                 |                                                                                     |      |
| 42C | Cilexetil-hydrochlorothiazide                                          | Recrystallization            | 30                  | 4 °C, 0% RH                                                                         | [116]|
|    | Cilexetil-hydrochlorothiazide-hydroxypropylmethylcellulose acetate succinate type M (HPMCAS) |                          | 60                  |                                                                                     |      |
| 43C | Cilexetil-hydrochlorothiazide                                          | Small reflections            | 15                  | 40 °C, 75% RH                                                                        |      |
|    | Cilexetil-hydrochlorothiazide-HPMCAS (CH50)                              |                             | 90                  |                                                                                     |      |
|    | Cilexetil-hydrochlorothiazide-HPMCAS (CH70)                              |                             | 30                  |                                                                                     |      |
|    | Glibenclamide-queercetin                                               | Remained amorphous           | 120                 | 4 °C, 0% RH                                                                         | [111]|
|    |                                                                           | Recrystallization            | 390                 | Room temperature, 60% RH                                                            |      |
|    |                                                                           |                             | 120                 | 40 °C, 0% RH                                                                         |      |

* Acronyms: DMB: dry ball milling, LAG: liquid-assisted grinding, RH: relative humidity.
supported by thermal behavior, as the samples shift the Tg towards the compound present in excess (See Table 9).

Finally, it is important to mention the results obtained by Kasten et al. (2017), as they analyzed two methods of preparation: DMB and LAG. Interestingly, DMB, whether at 25 or 40 °C, under dry conditions, resulted in a stable amorphous form for 252 days of the amorphous salts prepared. On the other hand, increasing relative humidity at 75% and maintaining the temperature at 25 °C caused recrystallization in the sample after 10 days; surprisingly, not into the crystalline form of the initial compounds, instead they transform into LAG peaks of the crystalline salt. This article is relevant for developing novel drugs because it indicates that although recrystallization of the DBM sample might occur, the recrystallization process will not lead to the initial material. Instead, a crystalline salt will be obtained (the same salt as the one prepared by LAG process). This means enhanced solubility over the crystalline drug will be obtained, even after recrystallization. To put this in perspective, 14-fold (crystalline salt), compared to 90-fold, of the co-amorphous salt.

(j) Measurement of structural stability on co-crystals after milling by XRD

Co-crystals have been little studied, compared to amorphous systems. Only a few articles have subjected the samples to stability tests. The reports showed that the storage time ranged from hours to 180 days, where relative humidity conditions higher than 80% caused the partial dissociation of co-crystals [165] (for further details, see Table 15). More articles are needed to reach conclusions regarding the structural stability of co-crystals, but these drug formulations are stable at high relative humidity values (75% RH) and relatively high temperatures (40 °C).

Table 15. Overview of structural stability of co-crystals upon storage in diverse conditions.

| # | Co-Crystal                  | XRD Interpretation                      | Storage Time (Days) | Storage Conditions * | Ref.  |
|---|-----------------------------|-----------------------------------------|---------------------|----------------------|-------|
| 1C | Nicotinamide-L-(+)-ascorbic acid | Without changes in peaks → chemically stable | 180                 | At shelf             | [66]  |
| 3C | Ciprofloxacin-thymol         | Stable, no changes of crystalline phase  | 50                  | Open air             | [118] |
| 4C | Urea-caffeine                | Formation of co-crystal                 | Within hours        | 25 °C, 30% RH       | [119] |
| 7C | Paracetamol-trimethylglycine | Physically stable                       | 90                  | 40 and 75% RH       | [44]  |

* Acronym: RH: relative humidity.

(k) Structural stability on polymorphs after mechanical activation by XRD

The structural stability of polymorphs has been little studied, as well. Only a few articles were found that performed structural stability tests (see Table 16). The range of temperatures was wide, from 25 °C and heating up to 150 °C, where only Kamali et al. [54] reported humidity with a value of 85% RH. The storage time varied from immediate analysis to 150 days, which allowed for studying the transformations from one polymorph to another. In principle, these changes between forms happen due to the metastable states of the drugs because the system looks for the state with the lowest energy and, therefore, changes into a more stable crystalline form.

These results conclude that a wide field in co-crystals and polymorphs, regarding the structural stability of systems, is yet to be studied and understood. It would be worth researching, in more detail, the shelf life of co-crystals and polymorphs with improved solubility and higher stability. These drug formulations could be used in the pharmaceutical industry, due to their superior properties and therapeutic effects.
Table 16. Overview of structural stability of polymorphs upon storage in diverse conditions.

| #  | Sample                  | Polymorph Identification                          | XRD Interpretation                  | Storage Time (Days) | Storage Conditions               | Ref.  |
|----|-------------------------|---------------------------------------------------|-------------------------------------|---------------------|----------------------------------|-------|
| 5P | o-aminobenzoic acid     | Polymorphs: I, II, III, and IV                     | FII → reappearance of FII           | 9                   | 25 °C, 40% and 85% RH            | [54]  |
|    |                         |                                                   | FII → reappearance of FIII          | 150                 | 25 °C, 85% RH                   |       |
|    |                         |                                                   | FII → FIII                          | 150                 | 25 °C, 85% RH                   |       |
|    | m-aminobenzoic acid     | Polymorphs: I, II, III, IV, and V                  | FIV                                 | 150                 | 25 °C, 85% RH                   |       |
|    |                         |                                                   | FI → reappearance of FIII           | 3                   | 25 °C, 85% RH                   |       |
|    | p-aminobenzoic acid     | Polymorphs: α and β                               | β polymorph                          | 150                 | 25 °C, 85% RH                   |       |
| 6P | Dexamethasone           | Form A                                            | Broaden Bragg peaks, characteristic of form A | Immediate          | Freshly milled samples          | [27]  |
|    |                         | Form B                                            | Predominantly peaks of form B, peaks of form A decrease | 7                  | Heating up to 150 °C            |       |
| 7P | Sofosbuvir              | Form V                                            | V → transformation to A             | 120                 | NR                              | [79]  |

Acronym: RH: Relative humidity.

5. Characterization by Microscopy

Finally, other techniques, although rarely mentioned, are also important for the characterization of drug formulations prepared by milling. For instance, scanning electron microscopy is a well-known technique for analyzing the morphologies of the particles. For pharmaceutical compounds, shape, size, and agglomeration are important characteristics for evaluation. According to Badal Tejedor et al. [93], topographical changes at the particle surface after short and longer milling times suggest changes of the particles’ mechanical properties. It would be worth investigating how size and shape affect the stability and behavior of the compound. Amaro et al. used SEM to analyze polymorphs of rivastigmine hydrogen and found different morphologies for forms I (plate-like shape) and II (elongated tetrahedral/needle-like shape). This technique is useful for reinforcing the information obtained from other techniques for the identification of polymorphs [141].

Another common technique for studying the surface mechanical properties, topography, and energy dissipation [171] of a sample is atomic force microscopy (AFM). Badal Tejedor et al. [93] have concluded that crystalline materials show less deformation under an applied pressure with low energy dissipation in AFM, contrary to an amorphous material, which will be more viscous and show higher dissipation, possibly due to the disorder of the atoms in the structure. The presence of both low and high dissipation values across the map would indicate a partially induced surface amorphization [93].

Finally, ultraperformance liquid chromatography (UPLC) is a little used method, but it used to observe the purity of the sample. In this sense, impurities would be present as major or minor intensity peaks in a chromatogram [89], depending on the drug formulation analyzed.

6. Concluding Remarks and Future Works

This review focused on characterization results, in order to study different drug formulations, i.e., co-amorphs, co-crystals, and polymorphs, upon milling.

The analyses of experimental milling conditions showed that, in most cases, the milling method is in dry conditions and low or cryogenic temperatures for co-amorphous. Processing times for this kind of formulation ranged from 60 to 180 min. While, for co-crystals, the grinding time reported was shorter, around 30 min, and required solvent-assisted milling at room temperature. For polymorphs, prolonged periods, longer than one hour, were needed to induce structural rearrangement; milling was performed at room temperature in most cases to obtain a polymorph. It is important to note that this information regarding milling times is just an observation of the range of minimum and maximum periods of milling, based on the experimental data reported in the tables. However, parameters such as time, temperature, frequency, and the number of balls are inherent to the material or system, so the effect of milling parameters on the structure change is multifactorial.
Co-amorphous and co-crystal systems that were successfully prepared by milling with enhanced solubility have been widely studied, thus demonstrating the potential of ball milling as a preparation method for drug formulations. Despite the achievements in increases in its solubility, future work is still needed to improve the stability of co-amorphous; additionally, a wide field, regarding the shelf life of polymorphs and co-crystals, is yet to be researched and understood.

Finally, although scaling ball milling to industrial capacities is still a challenge to address, this preparation method represents a non-thermal and advantageous alternative, as it results in drug formulations with enhanced properties.

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