Better and greener: sustainable pharmaceutical manufacturing technologies for highly bioavailable solid dosage forms

Serena Bertoni[1] · Dritan Hasa[2] · Beatrice Albertini[1] · Beatrice Perissutti[2] · Mario Grassi[3] · Dario Voinovich[2] · Nadia Passerini[1]

Accepted: 29 November 2021

Abstract
In the last decades, Green Chemistry has been gaining widespread attention within the pharmaceutical field. It is thus very important to bring more sustainable approaches into the design and manufacture of effective oral drug delivery systems. This review focuses on spray congealing and mechanochemical activation, two technologies endorsing different principles of green chemistry, and at the same time, addressing some of the challenges related to the transformation of poorly water-soluble drugs in highly bioavailable solid dosage forms. We therefore present an overview of the basic principles, equipment, and application of these particle-engineering technologies, with specific attention to case studies carried out by the groups working in Italian Universities.

Keywords Spray chilling · Mechanochemistry · Microparticles · Bioavailability enhancement · Polymers · Low melting carriers · Solid dispersions

Introduction

Oral delivery is the preferred route of administration for most pharmaceutical drug products. Yet, many of the discovered new chemical entities are characterized by large hydrophobic structures and show unfavorable pharmacokinetic properties due to poor solubility and/or poor membrane permeability. It is indeed reported that up to 70% of new drug candidates under development have poor solubility issues [1]. Biopharmaceutical classification system (BCS) class II drugs [2] are especially characterized by high permeability and low water solubility, and therefore, their bioavailability is typically limited by the slow drug dissolution and low drug concentration achieved in the gastrointestinal fluids. Unfortunately, the absence of a suitable strategy for formulation development of the compound could result in failure during preclinical or clinical testing, as the poor bioavailability of the compound might prevent the desired therapeutic effect.

In the last decades, a great part of the research in the field of pharmaceutical technology has focused on the development of new strategies for improving the bioavailability of orally administered drugs. A large amount of published literature explores the excipient effects on drug bioavailability, formulation strategies, and approaches aiming to improve their solubility and dissolution rate. The formulation approaches for addressing the issue of poorly water-soluble drugs can be grouped in three main areas, on the basis of their working principle:

- Approaches aiming at reducing drug particle size (e.g., nanocrystals)
- Approaches aiming at improving drug solubilization in the gastrointestinal fluids (e.g., lipid-based formulations, surfactants, and complexing agents)
- Approaches aiming at modifying drug solid state (e.g., amorphous solid dispersions, co-crystals, and polymorphs)

Serena Bertoni and Dritan Hasa contributed equally to the work

✉ Nadia Passerini
nadia.passerini@unibo.it

[1] Department of Pharmacy and Biotechnology, Alma Mater Studiorum—University of Bologna, Via S. Donato 19/2, 40127 Bologna, Italy

[2] Department of Chemical and Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy

[3] Department of Engineering and Architecture, University of Trieste, Via Alfonso Valerio, 6/1, 34127 Trieste, Italy

The numerous formulation strategies cited above and developed in academic laboratories, however, have often poor clinical translation potential. Batches of milligrams or few grams are usually produced in research laboratories, while grams or kilograms are necessary for pre-clinical and clinical studies. Multiple manufacturing steps, high production costs, low batch-to-batch reproducibility, and the use of toxic solvents make the production of large-scale batches under good manufacturing practice (GMP) conditions difficult [3, 4]. Due to the gap between academic and industrial production settings, most of the formulation strategies of poorly water-soluble drugs are therefore not feasible for clinical applications [4].

Additionally, similar to other manufacturing processes, also in the case of pharmaceutical formulation, a large amount of waste is generated, which represents a significant percentage of the total amount of hazardous waste generated by the chemical and pharmaceutical companies in general [5]. This is the reason why in the past 2 decades, Green Chemistry has progressively gained widespread acceptance in the scientific community [6]. In this context, environmentally friendly manufacturing technologies characterized by reproducible processes and simple scale-up production to an industrial scale are receiving great attention. Such methods reduce or avoid totally the use of toxic solvents and offer high product yield, thus limiting the production costs.

This review focuses on two sustainable pharmaceutical manufacturing methods, namely spray congealing and mechanochemistry, which are receiving increasing attention for formulation of poorly bioavailable drugs, with particular attention to the studies carried out by research groups working at the Italian University.

Spray congealing

The process of spray congealing (SC), also called spray chilling or spray cooling, was first mentioned in the early sixties to refer to the process of atomization of a melt material for the manufacture of solid particles [7]. The application of spray congealing for pharmaceutical production has been initially related to the development of sustained release and taste masking formulations [8, 9]. Successively, by properly choosing the main carrier and other additives, SC has been employed for the development of more differentiated delivery systems, including formulations for improving dissolution rate and drug stability.

In the process, the active compound is added to the molten excipient obtaining a solution or a suspension; the fluid is then atomized in the spray congealing apparatus and, for this reason, it is also named as melt spray congealing. The product obtained has been defined in various ways, such as "micropellets" [10], "granules" [11], "spray congealed solid dispersion" [12], "microspheres," and "microparticles" [13]. Specifically, the free-flowing powder collected as SC product consists on individual solidified droplets of the congealed material. Waxes, glycerides, fatty acids, polyethylenglycols, and other materials which are solids at room temperature and melt in the temperature range 40–90 °C can be used as carriers for SC. Although this feature might sometimes limit the formulation of actives by SC, the marketing of new multifunctional lipid-based materials over the last decade has expanded the array of carriers suitable for melting-based processes such as SC. Thus, an increased number of APIs not previously thought to be applicable for this technology can now be formulated into spray congealed microparticles with tunable properties.

The particles obtained are characterized by a dense matrix with the excipient occupying most particle volume and the active substance randomly distributed within. The spherical shape of the congealed particles often results in good flowability. The dimensions are variable and depend on the type of SC system used, but generally varied from tens to hundreds of micrometers. The behavior of the final congealed product depends only in part on the properties of the active ingredient (solubility, hydrophobicity, etc.) and mostly on the selection of suitable formulation parameters, which is, in fact, on fundamental importance in order to achieve the desired properties. Specifically, the type of carrier, the microparticle size, and the drug content are the most important aspects to determine the biopharmaceutical outcome of the spray congealed systems.

Nowadays, the main industrial applications of this technology are limited to food and supplement products as well as on veterinary medicinal products. The application of spray congealing technology on pharmaceuticals for human use still represents a market niche. Nevertheless, pharmaceutical companies such as Hovione (Portugal), ProCepT (Belgium), GEA Group (Germany), and Lonza (Switzerland) have recently started to develop pharmaceutical products based on SC technology. In the academic field, the research groups currently working on this technology are mainly the Chan Lai Wah's one at the University of Singapore (Singapore) [14], Favaro-Trindade's group at the Universidade de Sao Paulo (Brazil) [15], and our group at the University of Bologna (Italy).

Spray congealing: equipment and process parameters

Different equipment has been employed for microparticle production by SC. Most of them were laboratory spray dryers suitably adapted for the SC purpose. Different from spray drying, where a solution of drug and/or excipients in a solvent is used, a melted fluid should be atomized in SC. The higher viscosity of the molten material compared to an

aqueous-based or organic solvent-based solution led to the necessity of employing equipment with specific features. All SC apparatus have common elements: the feeding device; the atomization device; the cooling chamber and the collection system.

SC process involves three main steps, schematized in Fig. 1. The first step is the preparation of the molten mixture and consists in the carrier melting and addition of the active substance to be loaded in the microparticles. In this step, the temperature and the mixing play important roles. According to the properties of the drug substance and of the specific carrier chosen, the API can either solubilize into the molten excipient, forming a solution, or remained as a suspended powder. In the former case, it is important to consider that the solution of drug and excipient can present different physicochemical properties compared to the pure molten excipient. For example, the solution might have a different solidification temperature and thermal capacity, thus affecting the solidification stage. In case of suspended drug, specific attention should be placed on the viscosity of the mixture, as generally suspensions present significantly higher viscosities compared to pure molten carriers. The main limitation regarding the active pharmaceutical ingredients (APIs) suitable for CS process is the temperature sensitivity, as the drug must be stable at the temperature required to melt the matrix material. Nevertheless, it should be mentioned that the working temperatures employed in SC are generally modest (in the range 50–90 °C), compared to other melting based-technologies, such as hot melt extrusion, which employed temperatures higher than 100 °C [16], and therefore, most APIs can be easily processed by SC.

The second step, the actual spray congealing process, includes feeding, atomization, and solidification of the droplets. First, the molten mixture is fed into the atomization device, during which the fluid should be maintained heated and agitated. The temperature is generally kept at least 10 °C above the melting point of the carrier. Moreover, the molten carrier is stirred to prevent sedimentation and/or solidification. The feeding device generally consists on a container or tank placed above the atomizer, so that the fluid is facilitated to escape by gravity or by aid of a screw pump. The feeding occurs at a constant rate of about hundreds of ml min^{-1}. The feeding stage is followed by the atomization of the molten mixture, consisting on continuous division of the fluid into a spray of small droplets. The optimization of the process parameters, according to the selected atomizer, contributes to determine the process outcome. Moreover, depending on the batch size and feeding speed, the atomization step of a lab-scale SC process can last from few seconds to several minutes. Finally, the liquid droplets solidify in the cooling chamber, which can be of different shapes and sizes. Nevertheless, the higher the cooling chamber, the longer time has the droplets to solidify during the falling to the bottom. The temperature can be maintained at 25 °C or cooled down to lower values; either way, the cooling chamber should be maintained at a temperature below the carrier melting point. Moreover, the solidification in a "fluidized mode" by employing either in co-current and/or counter-current gas flow rate can be useful to increase residence time, improve the solidification efficacy, and thus better powder properties [14]. The actual solidification process is rapid. Specifically, the events occurring at the micro- and macro-structural levels during the solidification stage are fundamental to define the morphological features of the congealed microparticles. For example, a slow crystallization kinetic of the main excipient can negatively influence the shape and surface morphology of the obtained microparticles, or determine their aggregation [17]. Fast crystallizing excipients (e.g., waxes or high melting point triglycerides) have been shown to generate individual and not aggregated particles [18]. Nevertheless, both the atomization and the cooling chamber parameters should be set in order to assure the complete solidification

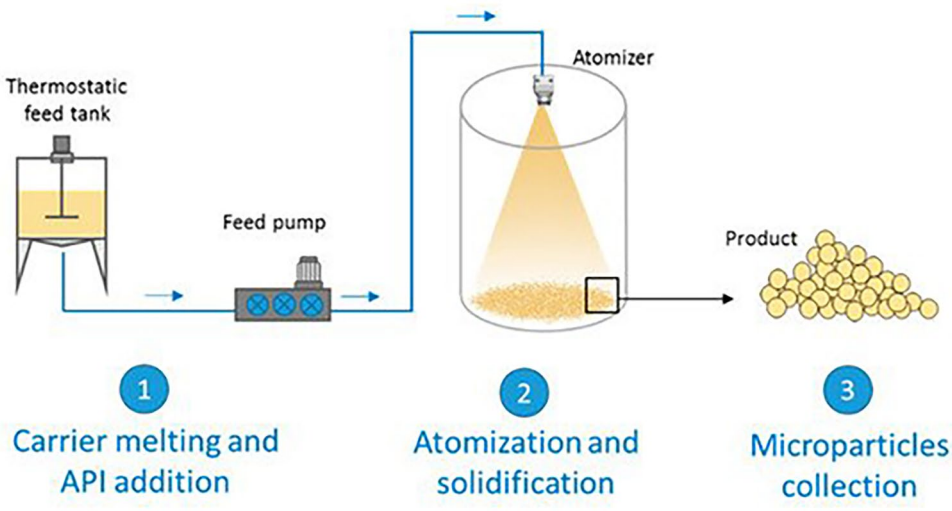

Fig. 1 Scheme of the main steps of spray congealing process. Reproduced from [19] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

of the molten droplets, thus producing a free-flowing solid powder. In addition, the congealing step might affect the solid-state properties and thus the biopharmaceutical characteristics of the APIs. The lower the temperature of the collecting chamber, the higher is the cooling rate influencing the crystallization of both the APIs and the excipients [23].

The last step consists in the collection of the product. The microparticles collected are generally ready-to-use and do not need any further processing steps (e.g., drying and spheronization).

The performance of the spray congealing process mainly depends on the atomization efficiency of the molten fluid [20]. Thus, the most important step of spray congealing technology is the *atomization phase*. In principle, the same types of atomizers can be employed for both SC and spray drying. However, a specific atomizer may have a different performance in the two processes, due to the fact that the fluid to be atomized in SC is generally more viscous than a water-based or organic-based solution employed in spray drying. Moreover, although the atomizer structure and working mechanism are the same, in SC, the atomizer should necessarily be heated to avoid solidification of the carrier mixture and clogging of the nozzle. Therefore, an important part of our research has been focused on the development of atomizers specifically designed for the SC process. Depending on the mechanism of atomization, atomizers can be classified in different types: *rotary*, *ultrasonic*, *and pneumatic atomizers*.

Rotary (or centrifugal) atomizers utilize high-speed rotating disks; thus, centrifugal energy is employed to shatter the fluid. This type of atomizer can be applied to a wide variety of feed rates and viscosities, allowing a relatively homogeneous particle size distribution of the droplets [12]. Specifically, the particle size can be controlled by varying the disk rotation speed, with higher speeds yielding smaller particles. However, the spray pattern is wide and short, so requiring wide cooling chambers [13–15]. *Ultrasonic atomizers* exploit high-frequency vibration (above 20 kHz) to generate capillary waves or cavitation on the fluid surface in order to produce droplets [16]. Compared to other mechanisms of atomization, ultrasound-based devices are more energetically efficient, as most energy employed is transmitted to the fluid and transformed into surface energy (85% efficiency), while only a small part of the energy employed is converted to heat [17]. This type of atomizer generally includes an ultrasound piezoelectric generator, a system allowing the regulation of the amplitude of the ultrasound wave and a vibrating surface (e.g., sonotrode), on which the fluid is poured and atomization occurs. According to the frequency and the amplitude of the ultrasound generator, different droplet sizes can be obtained. As for rotary atomizers, the ultrasonic ones avoid any risks of clogging, but they could not efficiently atomize more viscous fluids, such as suspensions. One of the first study performed by our group on SC technology employed an ultrasonic atomizer developed by Saitec s.r.l. (Bologna, Italy), the owner of the related patent, for the production of lipid-based microparticles contained theophylline and fenbufen as model drugs and stearic acid, carnauba wax, Cutina HR®, and Compritol 888 ATO® as low melting excipients [17]. Subsequently, a differently designed ultrasonic apparatus was employed for SC process, showing to be suitable for the production of non-aggregated spherical microparticles containing 10% w/w of praziquantel [18]. The schematic representations of these two ultrasonic atomizers are shown in Fig. 2A, B. The most commonly employed atomizers are the *pneumatic nozzles*, also called two-fluid nozzles, which can either be internal or external mixing. In the former, the molten mixture is mixed with air inside the atomization device, while in external-mixing nozzles, the molten fluid and the atomization air come in contact outside the nozzle. Common drawbacks related with pneumatic devices used for SC regard nozzle clogging, inefficient atomization when highly viscous fluids are employed and difficulty to achieve high drug loadings (higher than 20–30% w/w). In order to overcome these limitations, a new type of two-fluid atomizer, called Wide Pneumatic Nozzle (WPN), was developed by our research group [15] and has been applied for over 10 years in many studies [19–21]. This atomization device, specifically designed for SC application, is an external-mixing pneumatic atomizer with special features (Fig. 2C). First, the internal diameter of the orifice is larger (4.5 mm) than the usual, favoring the feeding of highly viscous fluids. Secondly, the molten fluid is moved along the orifice by the Venturi effect, while the atomization air is delivered in a radial direction with respect to the molten fluid. At the orifice end, the air mixes with the fluid stream and the atomization takes place. Due to these characteristics, WPN atomizer is able to atomize complex, highly viscous, multicomponent liquids generating not aggregated, perfectly spherical microparticles [15].

The process parameters should be selected in the different atomization devices (e.g., air pressure/disc speed/ultrasound vibration intensity) according to the properties of the molten fluid and to the desired product characteristics. For example, one advantage of the centrifugal atomizer is that the rotational speed can be easily adjusted to finely regulate the average drop size. Generally, the higher energy input leads to smaller droplets, e.g., the higher the atomization air pressure or the disc speed, the finest the spray and thus the dimensions of the obtained particles. Next to the atomizer working parameters, three properties of the fluid influence the process of atomization: the liquid density, viscosity, and surface tension. Among the various formulation variables of spray congealing process, the *viscosity* of the molten mixture can be considered the most critical parameter. The viscosity of the carrier depends on numerous factors, including the property

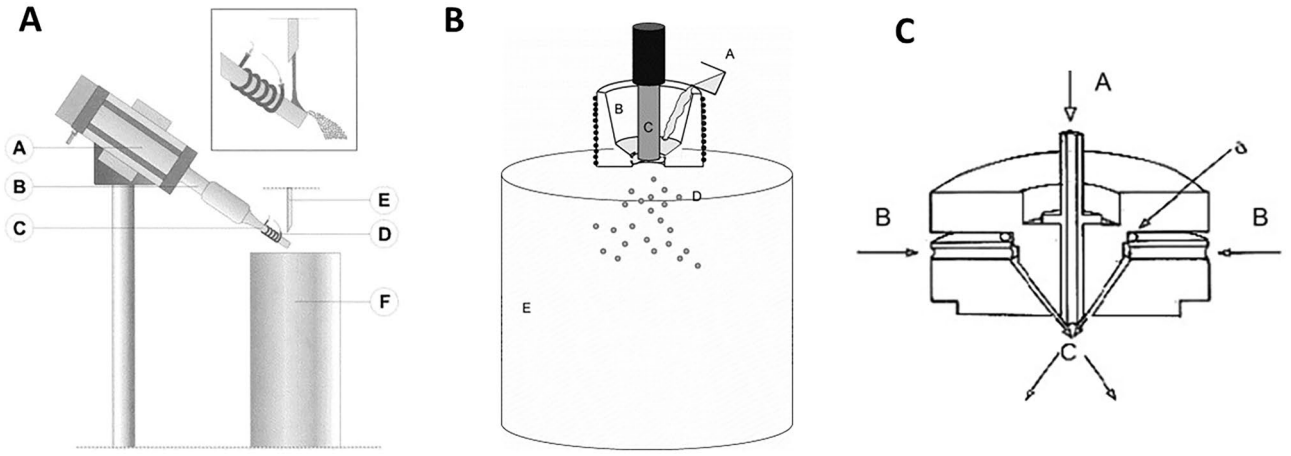

Fig. 2 Schematic representation of **A** ultrasonic atomizer developed by Saitec s.r.l. (not in scale): (A) US generator, (B) booster, (C) sonotrode, (D) inductive coil, (E) supply funnel, (F) cylindrical chamber (collector) [18]; **B** ultrasonic atomizer (type UIP 250, Hielscher, Berlin, Germany, not in scale): (A) drug + molten carrier, (B) thermostated reservoir, (C) sonotrode (atomizer), (D) molten droplets, (E) solidifying chamber [21]; and **C** Wide Pneumatic Nozzle (WPN) atomizer developed by our research group: (A) Material aspiration (feeding), (B) air inlet, (C) atomization of the fluid, (α) o-ring [22]

of the molten material, the amount and physical state (e.g., suspended as solid powder or partially/totally solubilized) of the drug, and the presence of additives. Specifically, powder substances that are dispersed in the molten mixture tend to significantly increase the viscosity of the sprayed mixture [23]. Both viscosity and surface tension vary with temperature; therefore, the temperature of the molten carrier is also of fundamental importance [24].

Spray congealing: the choice of the carrier

All materials employed as carriers are nontoxic, biodegradable, biocompatible, and of generally regarded as safe (GRAS) status. It should be noted that the lipids such as triglycerides, fatty alcohols, and waxes, although very commonly used in spray congealing, find application for API protection, taste masking, and sustained/prolonged release formulations, and thus will not be treated in this review.

Partial glycerides, consisting in mono- and/or di-glycerides, often with a fraction of triglycerides present as well, with HLB values between 2 and 4, are mostly water insoluble and therefore the drug release in aqueous media tends to be controlled. It should be considered, however, that the complex milieu of the gastrointestinal content, including the digestive lipases, bile salts, and digested food has a significant impact on the release behavior from microparticles based on partial glycerides [25]. In addition to the degree of substitution of the glycerides, the fatty acid chain length plays an important role in the digestion phase. In fact, lipids with shorter chain length (i.e., glyceryl trimyristate, C14) showed a fast degradation, and the active was promptly released in the intestine [26]. Therefore, the release observed in vitro in simple dissolution media can be underestimated compared to the behavior in vivo. Moreover, these excipients are able to increase the absorption of lipophilic drugs through the gastrointestinal membrane by enhancing the drug transport to the systemic circulation via the intestinal lymphatic system [27], which might be an important mechanism for bioavailability enhancement of poorly permeable drugs, such as them belonging to BCS class III and IV.

Polyoxylglycerides are obtained by reacting glycerides with polyoxyethylene glycols (PEG). PEG esters are amphiphilic as the PEG part is hydrophilic and the fatty acid is lipophilic, thus behaving as a surfactant. By varying the molecular weight of the PEG, the fatty acid length, and the amount of glyceride fraction, materials with different HLB values can be produced. Compritol ATO 5, for example, is mainly composed of esters of behenic acid and PEG and its HLB value is 5. Gelucire® is Gattefossé's brand of semi-solid lipid-based excipients originally designed for hard gelatin capsule molding [28]. Gelucires with high HLB are based on esters of long chain fatty acids and PEG; they represent the most utilized carrier to improve the drug dissolution rate by SC technology. Among the different hydrophilic Gelucire, Gelucire®48/16 contains only PEG esters, beside a small fraction of free PEG, and is water soluble. Differently, Gelucire®44/14 and Gelucire®50/13 are mixtures of PEG esters, mono-, di-, and triglycerides and are "water dispersible" surfactants.

Polyethylene glycols (PEGs) and *poloxamers* are the two most commonly used hydrophilic carriers in the preparation of solid dispersion of poorly water soluble, because of their low toxicity and low costs. Solid PEGs with molecular weight of 1500–6000 g/mol with melting point ranging

from ca. 55 to 65 °C are used in SC technology. Poloxamers are surface active materials with a structure of ABA-type triblock copolymers composed of polyoxyethylene (A) and polyoxypropylene (B) units, and exhibit amphiphilic nature and high solubilizing capacity. Poloxamers have been applied for the production spray congealed systems [29, 30] although their application as main carrier material may be limited by their high viscosity at the molten state and their high thermal capacity.

Finally, SC offers the possibility to combine two or more classes of carriers in order to obtain the desired properties. A positive effect on dissolution rate of the BCS class II drugs olanzapine [31] and glibenclamide [32] was observed by combining Gelucire® with other hydrophilic excipients, such as PEG or poloxamers.

Application of SC for oral bioavailability enhancement

As previously mentioned, the first studies employed the SC technology to obtain controlled release and taste-masking systems, using the ultrasonic atomizer represented in Fig. 2A [18]. The application for enhancing the bioavailability of a BCS class II drug is more recent. The first example date back in 2002 and focused on carbamazepine (CBZ) [33]- and indomethacin [34]-loaded systems. Both carbamazepine and indomethacin SC microparticles were obtained using the optimized ultrasonic atomizer (see Fig. 2B), employing Gelucire®50/13 or different PEGs (4000, 5500, and 6000) as hydrophilic carriers. Our results suggested that SC could be a useful process to obtain solid dispersion in the form of microparticles with increased drug dissolution properties. Subsequently, the same devise was utilized to successfully produce 5, 20, and 30% praziquantel-loaded microparticles, selecting Gelucire®50/13 as carrier [21]. The microparticles were non-aggregated, with good encapsulation efficiency and increased dissolution profiles with respect to row drug. Solid-state characterization evidenced the absence of both modifications of the solid state of the drug and of significant interactions between the praziquantel and the carrier. These results suggested that the improvement of wettability of the drug and its solubilization by Gelucire®50/13 at the diffusion layer are the main mechanisms for the praziquantel enhanced dissolution rate.

In 2013, Freitas's group used SC to encapsulate CBZ into Gelucire-based microparticles [34]. Due to the solubilization of the drug in the molten carrier, the α-polymorph of CBZ was observed in final microparticles, although the drug was originally in the stable β-form. Thus, this study showed the possibility of SC process to cause the conversion of the drug into a metastable polymorph, determining an enhanced drug dissolution rate.

One of the more recent studies on the application of SC for bioavailability enhancement performed by our group utilized the Wide Pneumatic Nozzle (see Fig. 2C) to produce microparticles based on a combination of Gelucire®50/13 with surfactant and/or co-solvent (e.g., Cremophor EL, Poloxamer 188, PEG 4000) containing the BCS class II drug glibenclamide (GBD) [32]. The SEM images of the resulting microparticles exhibited non-aggregated spherical particles with mean dimensions around 150 μm. The rough surface was attributed to the rearrangement of the stearic acid chains that constitute Gelucire and the presence of drug crystal onto the particle surface. Interestingly, the spray congealed particles formed a colloidal system in aqueous medium (at 37 °C) within 60 min, with an average micelle size of ca. 350 nm, which was considered the main mechanisms at the basis of the increased (about five times) drug solubilization rate.

Another recent work from our group [17] confirmed the positive outcome of spray congealed Gelucire®-based microparticles for the bioavailability enhancement of the poorly water-soluble drug indomethacin (IND). The combination of Gelucire®50/13 and Gelucire®48/16 led to a significant solubility and dissolution enhancement in vitro, as shown in Fig. 3A, B. Moreover, in vivo studies on rats showed that the absolute bioavailability was enhanced by 2.5 times. Notably, the absolute bioavailability of the original crystalline form of the drug, equal to 19.2%, increased to only 21.0% by administering a physical mixture of drug and carrier, but reached the 47.5% in case of spray congealed formulation (Fig. 3C). This clearly indicates that the bioavailability enhancement was not dependent on the presence of the hydrophilic carrier itself, but rather on mechanisms related to the SC process. Specifically, X-ray diffraction analysis showed that IND was transformed in the amorphous state.

Drug/carrier interactions and solid state modifications of drug upon partial or complete dissolution in the carrier can occur during SC process. In one of the latest studies from our group [35], three different BCS class II drugs (carbamazepine, tolbutamide, and cinnarizine) were loaded into Gelucire-based microparticles by SC technology. Results showed that the properties of the incorporated drug strongly influence the structure of the solid dispersion obtained by SC: carbamazepine recrystallized in a different polymorphic form, tolbutamide crystallinity was significantly reduced owing to specific interactions with the carrier, while smaller crystals were observed in case of cinnarizine. These modifications, concurrently with the physicochemical characteristics of the drug (log P and pKa), deeply affected the drug dissolution performance (Table 1).

Overall, the mechanisms of bioavailability enhancement of spray congealed systems may be various, depending by the API characteristics, the carrier, and other additives selected and by the SC process parameters utilized. The most common mechanisms include crystal size reduction of the drug

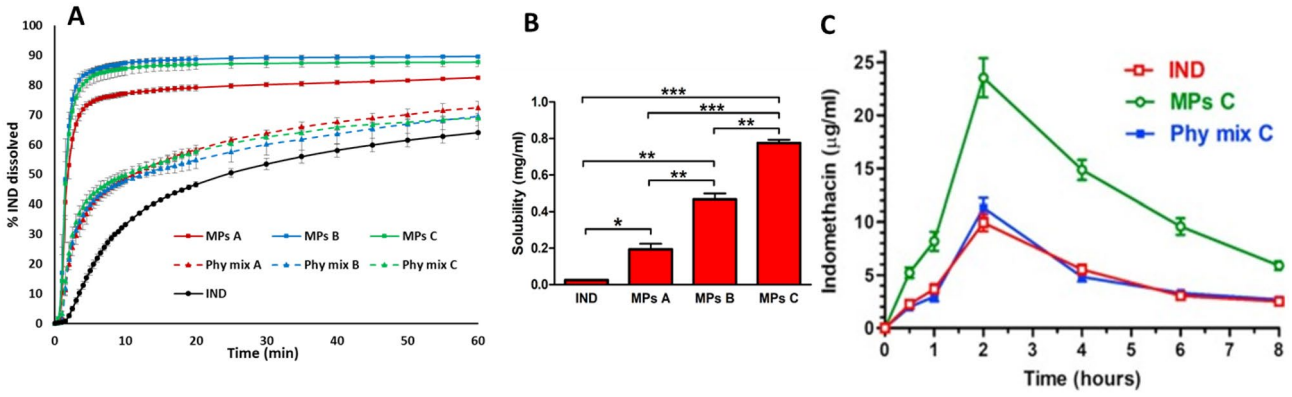

Fig. 3 **A** Dissolution profiles of IND, microparticles, and corresponding physical mixtures (Phy mix) in phosphate buffer pH 5.8; **B** 48-h equilibrium solubility of IND and microparticles in phosphate buffer pH 5.8; and **C** blood IND concentrations (μg/mL) obtained by oral administration of 2.0 mg dose to rats within 8 h. The formulations were constituted by the powders of free γ-indomethacin (IND), IND-loaded MPs (MPs C), and corresponding physical mixture (Phy mix C). Reproduced with permission from [17]

upon loading into the microparticles, improved wetting by the hydrophilic carriers, and enhanced solubilization due to formation of micelles in aqueous media when amphiphilic excipients, such as high HLB Gelucires, are used. Moreover, the rapid transition from the liquid to the solid phase in SC process can cause modifications of the original drug solid state, i.e., a transformation into the amorphous state or into a different polymorphic form. As these forms are metastable compared to the original crystalline stable state, the solubility and dissolution rate of the spray congealed microparticles would be improved, resulting in enhanced oral bioavailability. All these mechanisms have been discussed in details in a recent review article [19]. The researches carried out on SC technology evidenced the complexity of the solid state of drug-carrier system and its role in influencing the drug bioavailability.

Mechanochemical activation/ mechanochemistry

A formal definition of mechanochemistry is the chemical area that deals with "reactions involving reagents in any aggregate state that are induced by the input of mechanical energy" [36]. Frequently, however, such term is used in relation to solid-state processes and reactions initiated by any type of mechanical treatment, or involving reagents which are preliminarily activated mechanically [37]. The great potential of such technology has been recorded by several distinguished scientists including Faraday who in 1820 demonstrated for the first time the reduction of AgCl to pure Ag by grinding in a mortar and pestle a mixture of AgCl and Zn [37], or Carey Lea who performed some interesting experiments on the decomposition of silver halides [38]. Nowadays, the application of mechanochemistry is extended to a large number of inorganic [39] and organic reactions [40]. Specifically to pharmaceutical materials science, mechanochemistry is a relatively new technique and a significant growth of interest has been observed over the last 3 decades, where several independent studies have demonstrated the technique to be effective and often superior to other approaches, for example, during the screening for new solid forms. In fact, the recent review of Tan and co-authors [41] has highlighted the great efficiency of mechanochemistry as a screening method. In the pharmaceutical industry, it is a common practice to screen for new solid forms of drugs presenting several biopharmaceutical limitations such as poor solubility and/or limited absorbability in the gastrointestinal tract. The objective of such screening studies is to find the best solid form of the specific drug to achieve its intended role [42].

Table 1 Table summarizing the effects of formulation of three BCS class II drugs into Gelucire-based microparticles by spray congealing, including solid state modification observed and biopharmaceutical properties [35]

BCS class II drug	Drug solid state modification	Solubility enhancement of microparticles *vs* free drug	Dissolution enhancement of microparticles *vs* free drug
Carbamazepine	Formation of a different polymorph	4.5 fold	40% after 10 min
Tolbutamide	Reduced crystallinity	3.8 fold	80% after 10 min
Cinnarizine	Decrease in crystal size	400 fold	7% after 5 min

Possible modifications of the crystal form of drugs would include polymorphism, hydrate/solvate formation, or generating other multicomponent crystalline solids such as cocrystals [43]. Another option is to convert the drug into its amorphous state, described as when molecules within a solid are not packed in an ordered lattice, exhibiting different properties to that of a crystal form. In this context, research has suggested that poorly soluble (particularly non-ionizable) compounds formulated as an amorphous drug delivery system can exhibit vastly improved aqueous solubility characteristics, as well as increased absorption through the intestinal membrane [44]. Solid state mechanochemical amorphization therefore represents an important process to help alter the crystal structure of poorly soluble drugs. An initial effect of milling pharmaceutical solids would consist on the reduction of the particle size of the loaded powder, bringing to an increase of the total surface area of the drug. Often, only such initial enhancement of the surface area leads to an improvement of the dissolution rate of drugs. Evidence suggests, however, that further mechanochemical processing of crystalline materials induces amorphization and increases the Gibbs free energy of the solid, thus resulting in improved dissolution profiles [45]. The simplest example of mechanochemical processing would consist on a single solid inserted in the chamber (or jar) of a ball mill. Under such conditions, the mechanical energy will be transferred to the solid material (via shear and normal stresses acting on the solid material surfaces) in pulse form every time it is trapped between two or more grinding media or between the mill wall and one or more grinding media [39]. The energy is "absorbed" by the crystalline structure of the solid inducing a series of events at the microscopic level, the most important being (a) atoms shifting from the equilibrium positions of the ordered crystalline state and (b) changes of bond length or even excitement of the electronic subsystem. Consequently, existing intermolecular (but also covalent) bonds among and within molecules contain a higher energy level than the initial state. Such excess of energy transferred to the solid may therefore lead to plastic deformation phenomena inducing a partial or total disruption of the original crystal structure. It is specifically during the relaxation of such energy excess that the final solid structure can be physically altered. The specific mechanisms involved are still not completely clear; however, there are two main theories that specifically address the crystal disruption/amorphization phenomenon:

(a) Mechanical destabilization [46]. According to this theory, the crystal structure collapses due to high vibration anharmonicity that violates the Born stability criteria for a ordered structure.

(b) Thermodynamic destabilization [47]. According to this theory, the crystal structure collapses gradually, depending on the energy supplied. Hence, the crystal defects start in certain zones of the crystal (the rationale for crystal defects concentration in these areas is yet to be clarified) and then, with a further mechanical energy supplement, propagate to the entire solid bulk.

According to the thermodynamic destabilization theory, the collapse of the crystalline structure under the pulses of mechanical energy can therefore be described as a multistep process as a function of the stress absorbed; initially, at low stress levels, the crystal structure deforms only elastically. The first plastic deformations appear later with further energy administration. Subsequently, a series of other events occur, and when the stress equals the breaking point of a single crystal (unit cell), its fracture will start leading to a complete crystal lattice disruption. Importantly, the energy absorbed from the solid is not completely released: part of the mechanical energy is retained by the solid material in the form of the so-called excess Gibbs free energy that reaches its maximum when a complete crystal structure disruption (complete amorphization) occurs [48]. Consequently, the amorphous form shows a higher activity than the initial crystalline solid. For this reason, when the mechanochemical process is used in order to disrupt the crystalline structure, i.e., to transform a non-activated microcrystalline form into an active amorphous and/or nanocrystalline form, it is often called mechanical activation or more frequently mechanochemical activation. Smekal was the first scientist that used this term when he observed an increase of the reactivity of solids due to plastic deformation [49]. Colombo et al. [48] reported that the term "activation" expresses an intrinsic potentiality of the amorphous solid due to the fact that, in the conditions where the solid is subjected to mechanical stress, the energetic barriers hindering the evolution to a new equilibrium are lower than those of a non-activated system. It is however important to highlight that most activated solids will show a tendency to "collapse" in a more thermodynamically favorable energy status, making the real lifetime of such activated structures in the order of nanoseconds. Clearly, such period is not acceptable for the development of a pharmaceutical dosage form, which is expected to be stable for a much longer time (months, even years). For these reasons, drugs are often processed in the presence of a stabilizer agent forming a solid dispersion. The stabilizer by establishing week intermolecular bonds or reducing the mobility of the amorphous and nanocrystalline solid is able to slow the recrystallization kinetics of the activated structures.

In the context of mechanochemical activation of pharmaceutically relevant solids, the first study performed in our group dates back in 2008, and consisted on milling the *Silybum marianum* phytocomplex in the presence of

two crosslinked polymers [50], namely crosslinked polyvinylpyrrolidone and carboxymethylcellulose sodium that had the function of carrier and stabilizing agents for the activated extract. The 1:1 weight/weight (w/w) and 1:3 w/w extract:carrier mixtures were processed for 60 min using a planetary mill, and the resulting solid products were characterized using different solid-state techniques. Interestingly, the results indicated that as a consequence of mechanochemical activation and dispersion in the polymeric matrix, all the constituents of the *Silybum marianum* phytocomplex resulted X-ray amorphous and stable for (at least) 2 years. Additional in vitro tests revealed that the solid dispersion product obtained by processing the phytocomplex in the presence of corboxymethylcellulose sodium presents a better dissolution profile of the main flavonoids, obtaining a concentration increase of about 31- and 27-fold for silybin A and B, respectively, compared to the original phytocomplex. Importantly, in vivo studies in rats revealed a remarkable improvement of the bioavailability of all the tested flavolignans in solid dispersions with carboxymethylcellulose sodium (Fig. 4).

In another study [51], the same phytocomplex was processed using a planetary mill in the presence of β-cyclodextrin at a 1:2.5 w/w ratio. Co-milling led to the amorphization of the main extract component, silybin, with changes in size and surface area of the powders, showing an improved dissolution rate in water. Such activated status of the dry extract remained stable over a period of at least 12 months, due to the interactions established at the solid state with the carrier that were confirmed by DRIFT and Raman spectroscopy. Finally, the in vivo absorption studies in rats revealed a six-fold improvement of the oral bioavailability with respect to the reference product [51].

In subsequent studies, our research group focused also on the development of characterization techniques that would give more detailed information of how the mechanical energy would affect the physical status of a specific drug. In this context, we developed a facile ad hoc mathematical

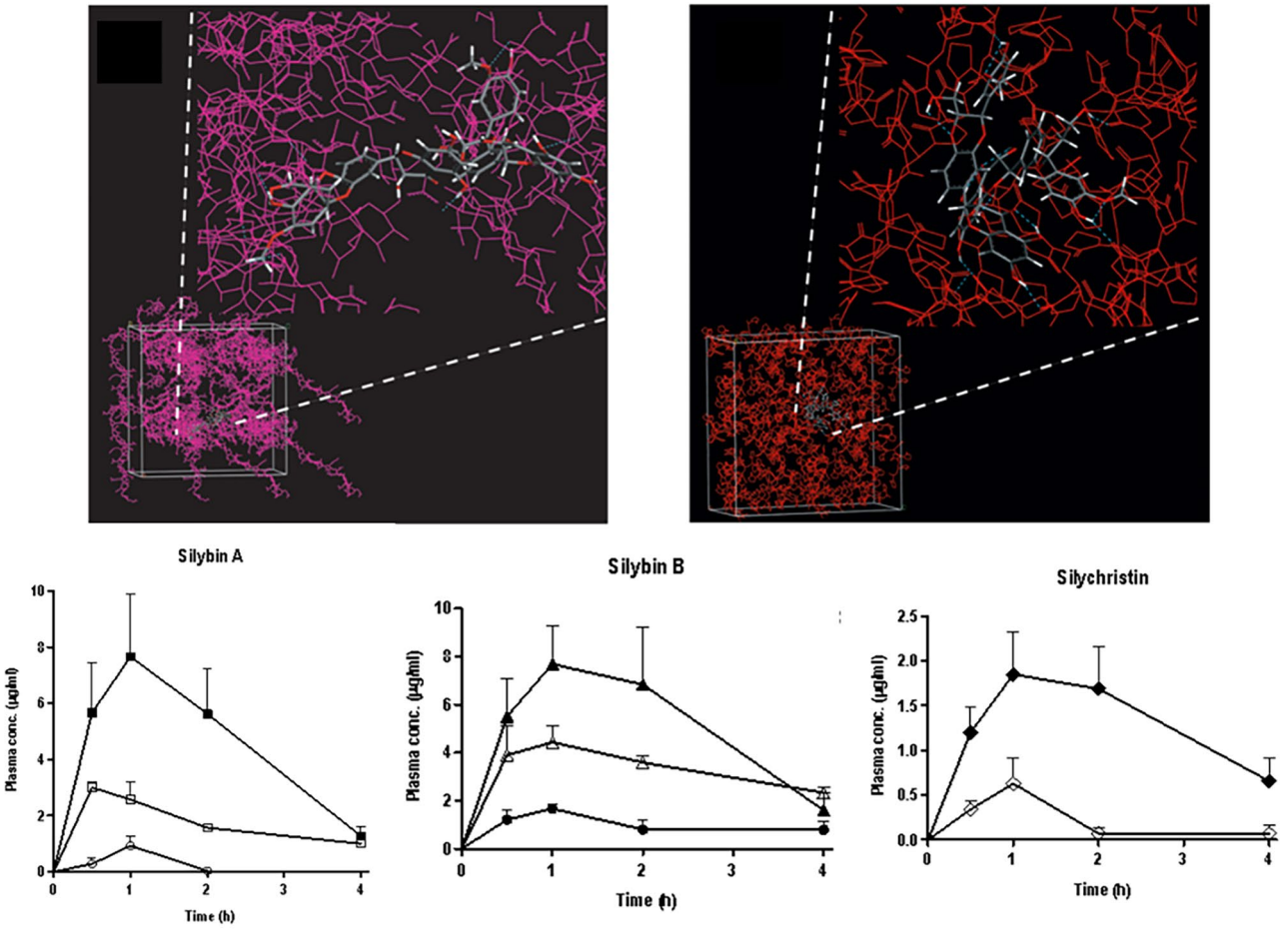

Fig. 4 Schematic representation of the composite structure and possible interactions between the flavonolignans and the polymeric carrier (top), and (bottom) mean plasma levels of the main flavolignans of Silybum Marianum, obtained after single oral dose (50 mg/kg) of different solid dispersions. Adapted from ref [50]

model that can calculate the nanocrystal fraction and size distribution of solid dispersions obtained through mechanochemical activation [52]. Going into more details, several solid dispersions containing vinpocetine (a poorly soluble drug that increases the cerebral flow in the ischemic areas thus showing a neuroprotective effect against brain ischemia in patients with cerebrovascular diseases) and crosslinked polyvinylpolypyrrolidone as carrier were prepared and analyzed using differential scanning calorimetry. The calorimetric data were subsequently elaborated through the model, allowing to quantify the amorphous content for each solid dispersion and the nanocrystal size distribution of the residual nanocrystalline fraction (Fig. 5).

According to such home-made software [52], the resulting percentages of amorphous drug in the co-milled systems increased proportionally with the polymer content while that of nanocrystalline drug simultaneously diminished, indicating a progressive destructuration of crystalline lattice of vinpocetine and of its progressive amorphous conversion with increased polymer content.

As for the differential distribution of the crystal radius in the composites having various compositions, it appeared that while peak frequency is almost constant (around 5 nm), nanocrystal size distribution is progressively narrowing as polymer content increased. This underlines the importance played by polymer content in getting a homogeneous system from the nanocrystal size distribution point of view. Probably, this behavior can be narrowly related to the stabilization action of the polymer that should be proportional to its content in the solid dispersion. Such detailed solid-state characterization eventually allowed selecting the best performing system, which was subsequently tested in vivo in rats demonstrating a fourfold oral bioavailability improvement compared to the original drug.

In the context of interactions between the drug and polymeric carriers, the research performed on vinpocetine was extended to vincamine, which was initially processed in the presence of two cross-linked polymers [53]. In that study, it was observed that the two cross-linked polymers had different roles on the mechanochemical activation of the active ingredient. Indeed, although both crosslinked polymers generated solid dispersions having a superior in vivo oral bioavailability compared to the original drug, very different plasma profiles were obtained for solid dispersions of vincamine with each of the two polymeric carriers. Since the drug was present as mostly amorphous (with traces of nanocrystal solid), the differences were prevalently attributed to the different chemical affinity among the drug and polymer and to the particle size distribution of the solid product that can affect the dissolution rate of the activated drug [53].

Crosslinked polymers or other porous carriers are preferred for application as stabilizers of the mechanochemically activated drugs [48]. However, their complex (physical)

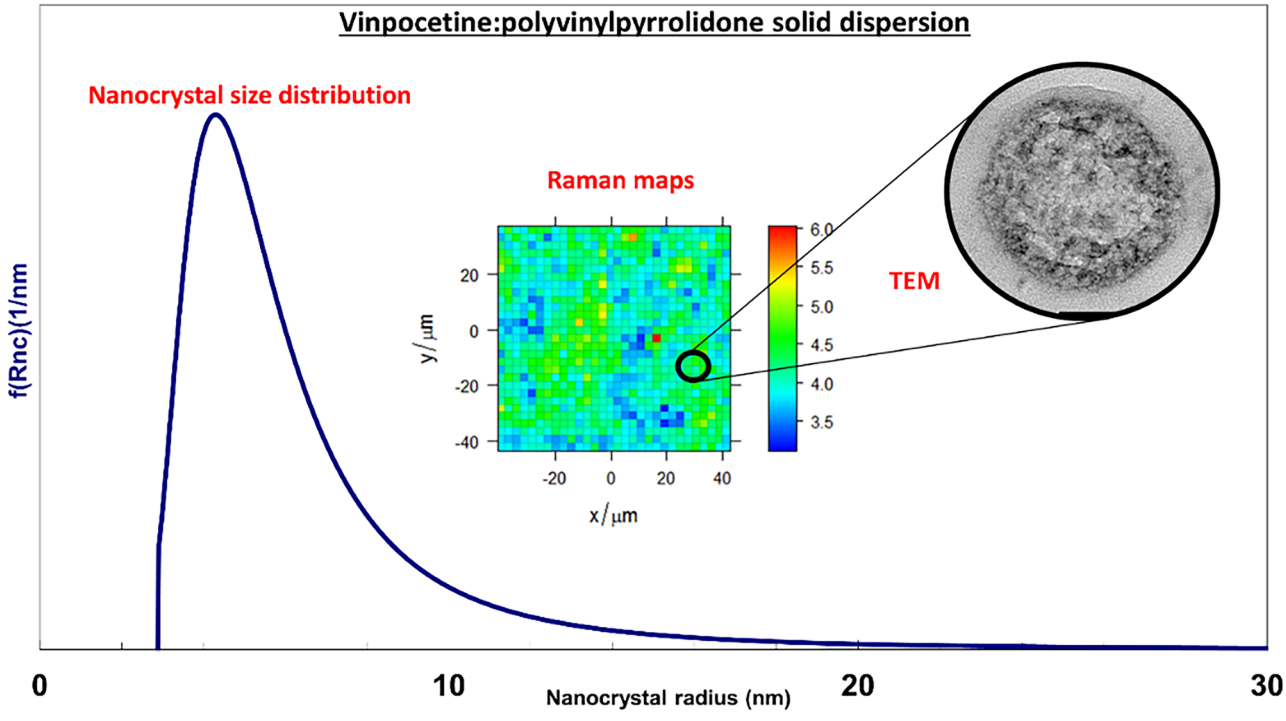

Fig. 5 Nanocrystal size distribution, Raman maps, and TEM image (indicating presence of the active ingredient both in the nanocrystalline amorphous forms) of the best performing solid dispersion formed by vinpocetine and polyvinylpyrrolidone. Adapted from ref [52]

structure can possibly block the release of the drug although it is present in the amorphous form thus prone to solubilization, as in the case of vincamine. Liner polymers can therefore be valid alternatives in such situations due to their simpler structure that would reduce the risks of "impeding" drug molecules from solubilization. Such polymers, on the other hand, are often less able of stabilizing highly energetic amorphous solids; therefore, an appropriate drug-to-polymer affinity should be performed. Indeed, in another study [54], vincamine was processed mechanochemically in the presence of linear polyvinylpyrrolidone and carboxymethylcellulose sodium. The three-dimensional contour surfaces of vincamine and the monomer units of the polymeric carriers (generated using a GRID mapping) indicated a higher similarity between vincamine and polyvinylpyrrolidone, thus suggesting a higher possibility of interaction/stabilization between these two materials. Additionally, the energies of the interaction between the drug and the monomer of each polymer were estimated by performing molecular docking simulation. During the docking procedure, all the molecule flexibilities were taken into account, so that, no conformational possibility restriction was applied. The best 10 poses for each docking experiment were selected and scored by means of a semi-empirical free energy force field based, and the best pose for each docking experiment is always shown in Fig. 6.

Although the best poses of each polymer were similar, the interaction energy calculated for the best pose of the binary system vincamine:polyvinylpyrrolidone was −1.83 kcal/mol while −0.58 kcal/mol for the vincamine:carboxymethylcell ulose sodium system. Polyvinylpyrrolidone was therefore selected as more suitable linear polymeric carrier. Highly soluble solid dispersions vincamine:linear polyvinylpyrrolidone were produced. Importantly, such solid dispersions remained stable for at least 12 months (Fig. 6).

If the poorly soluble drug is ionizable, salt formation represents another important strategy for improving the physicochemical properties of poorly soluble drugs [55]. Similar to other chemical reactions, however, salts are typically produced in solution and the consumption of great amounts of solvents is therefore implied. Mechanochemical technology can be a valid alternative where the amount of solvents used is drastically reduced or totally eliminated. The first proton transfer reaction through mechanochemistry was reported by Trask et al. in 2006 [56], while recently (2017), Lee and co-authors reported the continuous preparation of 1:1 Haloperidol–Maleic Acid salt by a novel solvent-free method using a twin screw melt extruder [57]. In 2011, we reported the first case of the mechanochemical formation of an amorphous salt between vinpocetine and citric acid [58]. In that study, different advanced characterization techniques including X-ray photoelectron spectroscopy and solid-state NMR were used to demonstrate the formation of an amorphous salt in total absence of solvents. The amorphous salt prepared mechanochemically was tested in vivo in rats resulting highly bioavailable compared to the original (unprotonated) vinpocetine and bioequivalent to a commercial product obtained through classical solution-based synthesis.

In another study, we proposed the use of polymer additives for improving the rate of the solid-state mechanochemical salt formation of vincamine, a weak base having important solubility and dissolution issues [59]. Specifically, the influence of three process and formulation variables on the percentage of salt formation was studied. Going into more details, the milling time (in a planetary mill), the molar ratio between the drug and the salt forming agent (citric acid), and the presence or absence of a polymer (carboxymethylcellulose sodium) were varied in order to evaluate their effect on the yield of the process. X-ray photoelectron spectroscopy was employed as a quantitative technique for measuring the

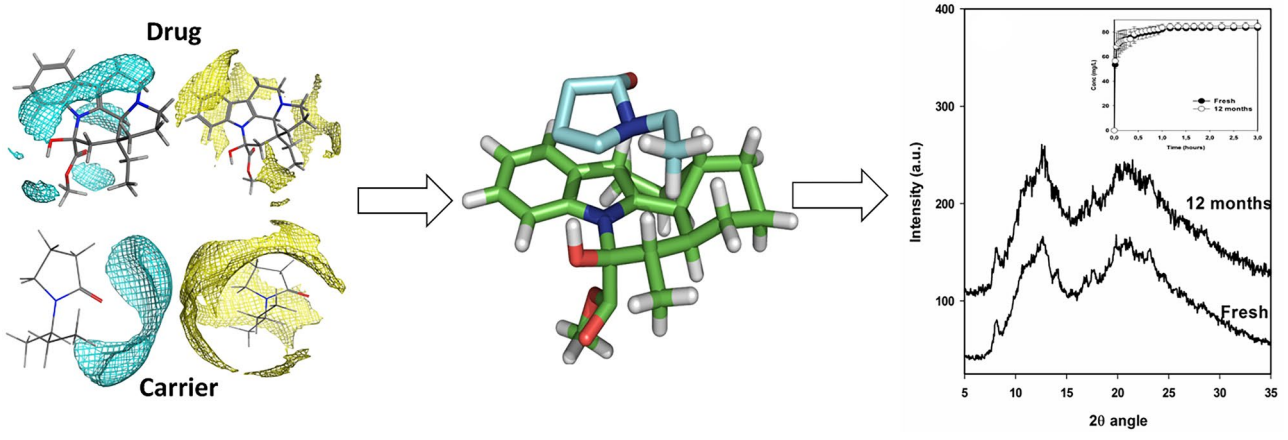

Fig. 6 Contour surfaces (left), the best pose of interaction (center) between vincamine and linear polyvinylpyrrolidone, and the powder X-ray diffraction patterns of the fresh solid dispersion and after twelve months (right). Adapted from ref [54]

amount of protonated drug as a function of each variable considered. The results suggested that among the three variables mentioned above, the solid-state mechanochemical salt formation completed only in the presence of the polymer and with a slight excess of salt forming agent. The process was therefore called "solid excipient-assisted mechanochemical salt formation (SEAMS)" [59].

Polymers are versatile materials, and can be used in mechanochemical process not only to accelerate reactions in the solid state and/or to stabilize amorphous phases but also for promoting the formation of new crystalline solid forms. Indeed, Hasa et al. [60] reported for the first time the possibility of using polymeric additives for promoting the formation of a multicomponent crystal (cocrystal) formed by caffeine and citric acid. In that study, the authors reported that milling caffeine and citric acid for 20 min in absence of any additive did not lead to a cocrystal but only a simple physical mixture of the starting materials. The addition of low amounts (1 weight percent) of a common pharmaceutical polymer such as polyethylene glycol led to the formation of caffeine-citric acid cocrystal. The process was called "polymer-assisted grinding (POLAG)" [60]. In a more recent study [61], it was observed that increasing the amount of the polymer above 5 weight percent in POLAG does not bring to a further significant acceleration of the solid-state cocrystallization reaction. The use POLAG has been also successful for the control of the polymorphic form [62] and for solid-state dehydration of hydrated drugs [63].

In the context of new crystalline solid forms of poorly soluble drugs, recently, our research group focused on praziquantel, a first-line drug used against schistosomiasis that is one of the most common parasitic diseases in the world [64]. The commercially available praziquantel has very low solubility in water and shows extensive first-pass metabolism [65]. We reported for the first time a new anhydrous polymorphic form of the racemic praziquantel, which was obtained from the original compound through neat grinding in a vibrational mill (Fig. 7). The new polymorph exhibited favorable biopharmaceutical properties: high in vitro and in vivo bioactivity against *Schistosoma mansoni* and prolonged physical stability [66].

In a subsequent study, we used a rotated Doehlert matrix to explore the experimental design space around the milling parameters that affect the formation of praziquantel polymorph B. In that study, an additional anhydrous polymorph (form C) was discovered, for which the crystal structure was solved using synchrotron XRPD data and the geometry was optimized by DFT calculations performed using CASTEP [67]. Subsequently, we probed the possibility of the formation of multicomponent forms of such drug through mechanochemistry that brought to the previously unreported racemic praziquantel hemihydrate [68], an isolate-site hydrate showing peculiar biopharmaceutical features including enhanced solubility and an intrinsic dissolution rate in water two times higher compared to the commercially available form. Noteworthy, the formation of the new hemihydrate strongly depended on the initial polymorphic form of praziquantel and on the experimental conditions used. Single-step grinding in the presence of water resulted in the hemihydrate when

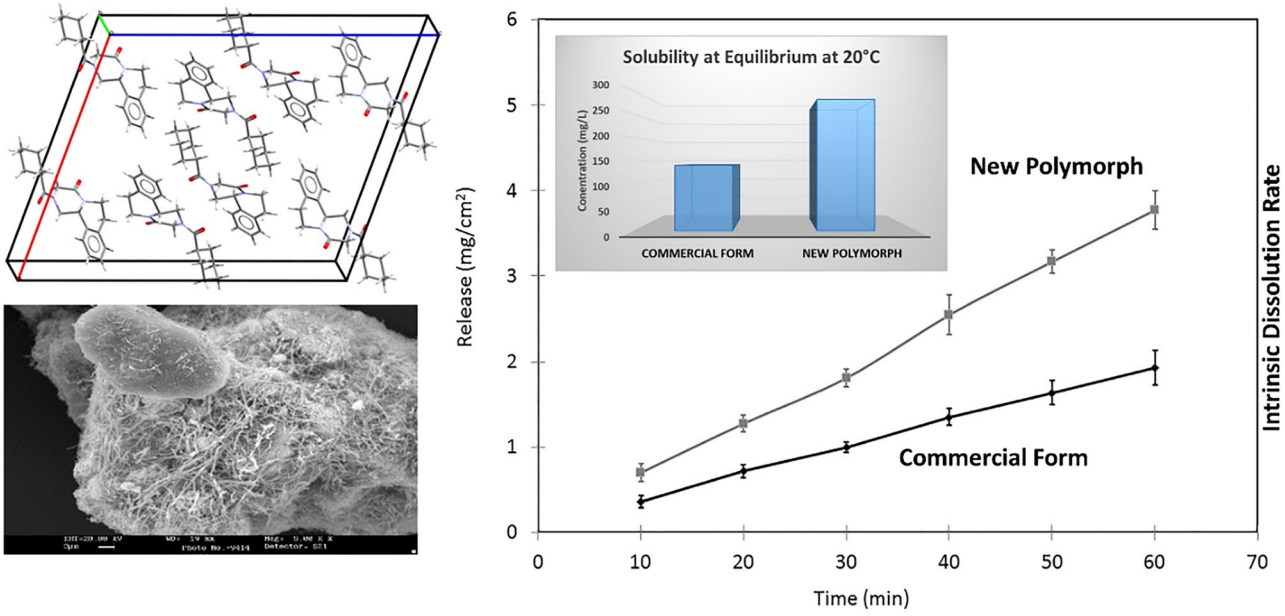

Fig. 7 Crystal structure, SEM image, and in vitro performance of the new polymorphic form of praziquantel. Adapted from ref [66]

the reactant was praziquantel form B, whereas a two-step grinding mixed process (neat and subsequently liquid-assisted grinding) was necessary when the anhydrous form A was used as the starting material.

Moreover, our group has also reported the possibility of obtaining PZQ in a highly amorphous state, physically stable for several months, by a mechanochemical treatment in the presence of different polymeric excipients [34] or mesoporous silica [35]. Such amorphous dispersions, however, presented a diminished drug recovery, which was found to be highly dependent, in terms of percentage and type of degradation products, on the used excipient [35–37]. Not even the switch to a cryogenic environment, that is, operating at temperatures lower than drug glass transition, allowed to reduce significantly this experimental response. Conversely, praziquantel did not degrade and residual crystallinity remained pronounced upon milling when the drug was milled alone [36]. The monitoring of the temperature during the mechanochemical process interestingly revealed that the temperature is statistically dependent on the process conditions (such as milling frequency and time) [67]. Contrariwise, detected temperatures were almost superimposable when material composition inside the jars was varied.

Association of mechanochemical activation and spray congealing

As several examples on the efficiency of mechanochemistry and SC on improving the solubility and/or the dissolution rate of drugs (with different mechanisms) have been shown; in this paragraph, we report examples where such two important technologies have been combined. The first example was proposed by our research groups and dates back in 2012 [69]. In that study, we investigated for the first time the potential of combining these two technologies to enhance the bioavailability of the poorly water-soluble dry extract *Silybum marianum*. An innovative delivery system containing the main flavolignans (silybins A and B) of *Silybum marianum* was produced. The dry extract was initially milled in a planetary mill in the presence of sodium croscarmellose obtaining a stable solid dispersion with reduced degree of crystallinity of both silybins A and B. Subsequently, the solid dispersion obtained mechanochemically was employed to obtain microparticles through the spray congealing technology, selecting the self-emulsifying agent Gelucire®50/13 as carrier. In vitro solubilization kinetic study and in vivo study in rats showed that the spray congealed microparticles containing the activated system (M3) displayed better performance in comparison to products that were processed only through one of the technologies mentioned above (Fig. 8).

To confirm the potential of combining mechanochemistry with SC, we have recently extended the study to praziquantel, with the aim of obtaining a suitable dosage form for pediatric use [70]. Two systems (drug solid dispersions with povidone and the new polymorph B) were first obtained through mechanochemistry and subsequently loaded into Gelucire®50/13 spray congealed microparticles. In vitro results demonstrated a significant improvement of the biopharmaceutical properties of microparticles to the milled powders.

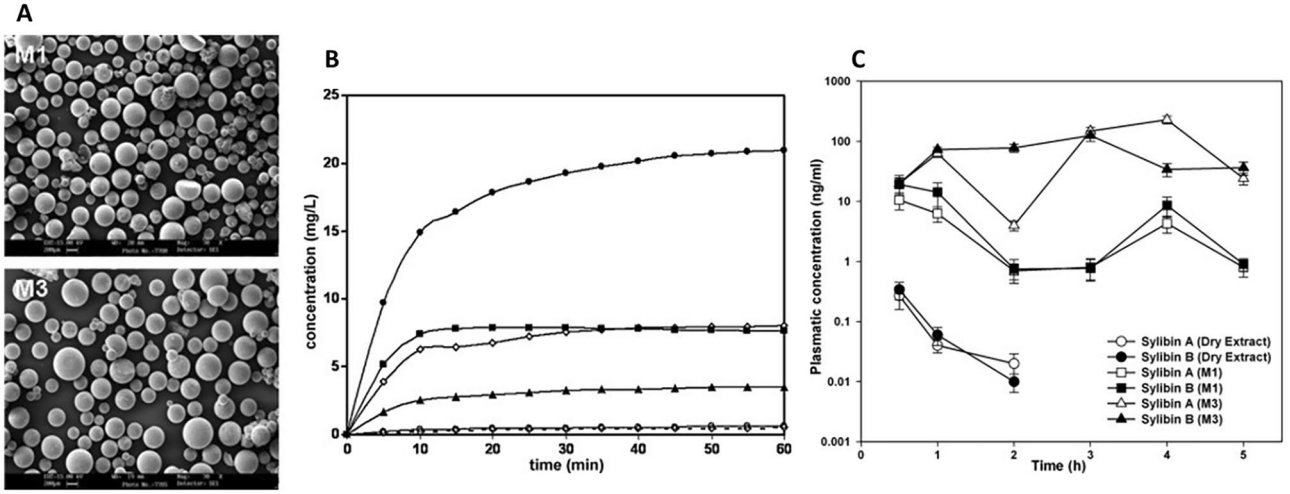

Fig. 8 **A** SEM micrographs of Microparticles M1 (with non-activated dry extract) and M3 (with activated coground dry extract) microparticles; **B** in vitro solubilization kinetics in water of various systems containing the *Silybum marianum* dry extract: native dry extract (- -), physical mixture PM1 (○), coground CG (▲), microparticles M1 (◇), microparticles M2 (■), microparticles M3 (●); **C** plasmatic profiles (where concentration is expressed as log scale) of silybins A and B after oral administration of dry extract and microparticles M1 and M3. Reproduced with permission from [69]

Finally, both case-studies reported above evidenced that the combination of SC with mechanochemistry brings to an important improvement of the technological characteristics of the activated powders. Indeed, while the original drugs showed poor flowability, all the microparticles obtained by the combined approach had a particle size in the range 75–500 μm and were spherical in shape, thus showing excellent flowability, which ensure better handling and processability to the final dosage form.

Conclusions

Spray congealing and mechanochemistry are two promising approaches for addressing several challenges associated with oral poorly bioavailable drugs. Both technologies can be used to prepare pharmaceutical solids in "active" states (e.g., nanocrystals, amorphous, solids with crystalline defects, and metastable polymorphs) stabilized by interactions with the polymeric-based or lipid-based carrier formed during the process. Compared to other pharmaceutical processing techniques, the two technologies described here present a series of relevant advantages. From the industrial perspective, both processes avoid the use of significant amounts of water and other solvents. Indeed, it is important to highlight the fact that the use of large amounts of organic solvents, besides involving various health and safety considerations and raising the risk of environmental hazards, would add to the manufacturing process some expensive extra waste disposal systems or other processes related to the removal of solvents from the final pharmaceutical product. In this context, moisture sensitive drugs can be employed with a significantly lower risk of degradation. Being based on solidification of molten sprayed droplets and on a relatively simple mechanical treatment, respectively, spray congealing and mechanochemical activation are simple one-step processes, where the loss of processed materials is minimal while maintaining a high product yield. These features make such processes time- and cost-effective manufacturing technologies.

Spray congealing and mechanochemistry represent, therefore, very attractive and promising platforms for addressing some of the challenges related to oral drug delivery of poorly bioavailable drugs and at the same time satisfying more than one of the principles of Green Chemistry [71].

Author contribution Conceptualization: Nadia Passerini. Literature search and data analysis: Serena Bertoni and Dritan Hasa. Original draft: Serena Bertoni and Dritan Hasa. Critical revision of the draft: Beatrice Albertini, Beatrice Perissutti, Mario Grassi, Dario Voinovich, and Nadia Passerini.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Göke K, Lorenz T, Repanas A, Schneider F, Steiner D, Baumann K, et al. Novel strategies for the formulation and processing of poorly water-soluble drugs. Eur J Pharm Biopharm. 2018;126:40–56.
2. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–20.
3. Desai N. Challenges in development of nanoparticle-based therapeutics. AAPS J. 2012;14:282–95.
4. Ghadi R, Dand N. BCS class IV drugs: Highly notorious candidates for formulation development. J Control Release. 2017;248:71–95.
5. James SL, Adams CJ, Bolm C, Braga D, Collier P, Friščić T, et al. Mechanochemistry: opportunities for new and cleaner synthesis. Chem Soc Rev. 2012;41:413–47.
6. Ardila-Fierro KJ, Hernández JG. Sustainability assessment of mechanochemistry by using the twelve principles of green chemistry. Chemsuschem. 2021;14:2145–62.
7. Scott MW, Robinson MJ, Pauls JF, Lantz RJ. Spray congealing: particle size relationships using a centrifugal wheel atomizer. J Pharm Sci. 1964;53:670–5.
8. Robinson MJ, Swintosky JV. Sulfaethylthiadiazole V*: Design and study of an oral sustained release dosage form. J Am Pharm Assoc (Scientific ed). 1959;48:473–8.
9. Javaid KA, Fincher JH, Hartman CW. Timed-release tablets employing lipase-lipid-sulfamethizole systems prepared by spray congealing. J Pharm Sci. 1971;60:1709–12.
10. Eldem T, Speiser P, Altorfer H. Polymorphic behavior of sprayed lipid micropellets and its evaluation by differential scanning calorimetry and scanning electron microscopy. Pharm Res. 1991;8:178–84.
11. Lerk CF. Sasburg RH [The preparation of uniform granules by vibration-spray congealing]. Pharm Weekbl. 1971;106:149–57.
12. Emås M, Nyqvist H. Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1. Microcalorimetric investigation. Int J Pharm. 2000;197:117–27.
13. Bertoni S, Dolci LS, Albertini B, Passerini N. Spray congealing: a versatile technology for advanced drug-delivery systems. Ther Deliv. 2018;9:833–45.
14. Oh CM, Guo Q, Heng PWS, Chan LW. Spray-congealed microparticles for drug delivery - an overview of factors influencing their production and characteristics. Expert Opin Drug Deliv. 2014;11:1047–60.
15. Favaro-Trindade C, Okuro P, de Matos Jr F. Encapsulation via Spray Chilling/Cooling/Congealing ISBN 9781482232325. 2015. p. 71–87.
16. Censi R, Gigliobianco M, Casadidio C, Di Martino P. Hot melt extrusion: highlighting physicochemical factors to be investigated while designing and optimizing a hot melt extrusion process. Pharmaceutics. 2018;10:89.
17. Bertoni S, Albertini B, Ferraro L, Beggiato S, Dalpiaz A, Passerini N. Exploring the use of spray congealing to produce solid dispersions with enhanced indomethacin bioavailability: In vitro characterization and in vivo study. Eur J Pharm Biopharm. 2019;139:132–41.
18. Rodriguez L, Passerini N, Cavallari C, Cini M, Sancin P, Fini A. Description and preliminary evaluation of a new ultrasonic atomizer for spray-congealing processes. Int J Pharm. 1999;183:133–43.
19. Bertoni S, Albertini B, Passerini N. Spray congealing: an emerging technology to prepare solid dispersions with enhanced oral bioavailability of poorly water soluble drugs. Molecules. 2019;24(19):3471.

20. Passerini N, Qi S, Albertini B, Grassi M, Rodriguez L, Craig DQM. Solid lipid microparticles produced by spray congealing: influence of the atomizer on microparticle characteristics and mathematical modeling of the drug release. J Pharm Sci. 2009.
21. Passerini N, Albertini B, Perissutti B, Rodriguez L. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int J Pharm. 2006;318:92–102.
22. Albertini B, Passerini N, Pattarino F, Rodriguez L. New spray congealing atomizer for the microencapsulation of highly concentrated solid and liquid substances. Eur J Pharm Biopharm. 2008;69:348–57.
23. Ouyang H, Poh ASY, Heng P, Chan L. Effect of surfactants on the melt viscosity and extent of drug embedment of paraffin wax blends in spray congealing. J Pharm Innov. 2020;1–15.
24. Wong PCH, Heng PWS, Chan LW. Viscosity–temperature relationship of lipid-based excipients amenable for spray congealing: derivation of a rheological parameter with good correlation to particle size. Eur J Lipid Sci Technol. 2016;118:1062–73.
25. Albertini B, Bertoni S, Perissutti B, Passerini N. An investigation into the release behavior of solid lipid microparticles in different simulated gastrointestinal fluids. Colloids Surf B Biointerfaces. 2019;173:276–85.
26. Bertoni S, Albertini B, Dolci LS, Passerini N. Spray congealed lipid microparticles for the local delivery of β-galactosidase. Eur J Pharm Biopharm. 2018;132:1–10.
27. Gonçalves LMD, Maestrelli F, Di Cesare ML, Ghelardini C, Almeida AJ, Mura P. Development of solid lipid nanoparticles as carriers for improving oral bioavailability of glibenclamide. Eur J Pharm Biopharm. 2016;102:41–50.
28. Panigrahi KC, Patra ChN, Jena GK, Ghose D, Jena J, Panda SK, et al. Gelucire: a versatile polymer for modified release drug delivery system. Future J Pharm Sci. 2018;4:102–8.
29. Albertini B, Passerini N, Di SM, Monti D, Burgalassi S, Chetoni P, et al. Poloxamer 407 microspheres for orotransmucosal drug delivery. Part I : Formulation, manufacturing and characterization. Int J Pharm. 2010;399:71–9.
30. Monti D, Burgalassi S, Rossato MS, Albertini B, Passerini N, Rodriguez L, et al. Poloxamer 407 microspheres for orotransmucosal drug delivery. Part II : In vitro/in vivo evaluation. Int J Pharm. 2010;400:32–6.
31. Cavallari C, Gonzalez-rodriguez M, Tarterini F, Fini A. Image analysis of lutrol/gelucire/olanzapine microspheres prepared by ultrasound-assisted spray congealing. Eur J Pharm Biopharm. 2014;88:909–18.
32. Albertini B, Di Sabatino M, Melegari C, Passerini N. Formulation of spray congealed microparticles with self-emulsifying ability for enhanced glibenclamide dissolution performance. J Microencapsul. 2015;32:181–92.
33. Passerini N, Perissutti B, Moneghini M, Voinovich D, Albertini B, Cavallari C, et al. Characterization of carbamazepine - Gelucire 50/13 microparticles prepared by a spray-congealing process using ultrasounds. J Pharm Sci. 2002;91:699–707.
34. Fini A, Rodriguez L, Ca C, Albertini B, Passerini N. Ultrasound-compacted and spray-congealed indomethacin / polyethyleneglycol systems. Int J Pharm. 2002;247:11–22.
35. Bertoni S, Albertini B, Passerini N. Different BCS Class II Drug-Gelucire Solid Dispersions Prepared by Spray Congealing: Evaluation of Solid State Properties and In Vitro Performances. Pharmaceutics. 2020;12:548.
36. Padrela L, Rodrigues MA, Velaga SP, Fernandes AC, Matos HA, de Azevedo EG. Screening for pharmaceutical cocrystals using the supercritical fluid enhanced atomization process. J Supercrit Fluids. 2010;53:156–64.
37. Aher S, Dhumal R, Mahadik K, Paradkar A, York P. Ultrasound assisted cocrystallization from solution (USSC) containing a non-congruently soluble cocrystal component pair: caffeine/maleic acid. Eur J Pharm Sci. 2010;41:597–602.
38. Boldyreva EV. High pressure and supramolecular systems. Russ Chem Bull. 2004;53:1369–78.
39. Boldyreva E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? Chem Soc Rev. 2013;42:7719.
40. Friščić T, Mottillo C, Titi HM. Mechanochemistry for Synthesis. Angew Chem Int Ed. 2020;59:1018–29.
41. Tan D, Loots L, Friščić T. Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). Chem Commun. 2016;52:7760–81.
42. Malamatari M, Ross SA, Douroumis D, Velaga SP. Experimental cocrystal screening and solution based scale-up cocrystallization methods. Adv Drug Deliv Rev. 2017;117:162–77.
43. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: along the path to improved medicines. Chem Commun. 2016;52:640–55.
44. Dahan A, Beig A, Ioffe-Dahan V, Agbaria R, Miller JM. The twofold advantage of the amorphous form as an oral drug delivery practice for lipophilic compounds: increased apparent solubility and drug flux through the intestinal membrane. AAPS J. 2013;15:347–53.
45. Einfalt T, Planinšek O, Hrovat K. Methods of amorphization and investigation of the amorphous state. Acta Pharm. 2013;63:305–34.
46. Tse JS. Mechanical instability in ice I h. A mechanism for pressure-induced amorphization. J Chem Phys. 1992;96:5482–7.
47. Johnson WL, Li M, Krill CE. The crystal to glass transformation in relation to melting. J Non-Cryst Solids. 1993;156–158:481–92.
48. Colombo I, Grassi G, Grassi M. Drug mechanochemical activation. J Pharm Sci. 2009.
49. Takacs L. The historical development of mechanochemistry. Chem Soc Rev. 2013;42:7459–649.
50. Voinovich D, Perissutti B, Magarotto L, Ceschia D, Guiotto P, Bilia AR. Solid state mechanochemical simultaneous activation of the constituents of the Silybum marianum phytocomplex with crosslinked polymers. J Pharm Sci. 2009;98:215–28.
51. Voinovich D, Perissutti B, Grassi M, Passerini N, Bigotto A. Solid state mechanochemical activation of Silybum marianum dry extract with betacyclodextrins: characterization and bioavailability of the coground systems. J Pharm Sci. 2009;98:4119–29.
52. Hasa D, Voinovich D, Perissutti B, Bonifacio A, Grassi M, Franceschinis E, et al. Multidisciplinary approach on characterizing a mechanochemically activated composite of vinpocetine and crospovidone. J Pharm Sci. 2011;100:915–32.
53. Hasa D, Perissutti B, Chierotti MRMR, Gobetto R, Grabnar I, Bonifacio A, et al. Mechanochemically induced disordered structures of vincamine: the different mediation of two cross-linked polymers. Int J Pharm. 2012;436:41–57.
54. Hasa D, Perissutti B, Grassi M, Chierotti MR, Gobetto R, Ferrario V, et al. Mechanochemical activation of vincamine mediated by linear polymers: assessment of some “critical” steps. Eur J Pharm Sci. 2013;50:56–68.
55. Kumar L, Baheti A, Bansal AK. Effect of a Counterion on the Glass Transition Temperature (T g ′) during Lyophilization of Ganciclovir Salt Forms. Mol Pharm. 2011;8:309–14.
56. Trask AV, Haynes DA, Motherwell WDS, Jones W. Screening for crystalline salts via mechanochemistry. Chemical Commun. 2006;51–3.
57. Lee HL, Vasoya JM, Cirqueira MDL, Yeh KL, Lee T, Serajuddin ATM. Continuous preparation of 1:1 haloperidol–maleic acid salt by a novel solvent-free method using a twin screw melt extruder. Mol Pharm. 2017;14:1278–91.

58. Hasa D, Voinovich D, Perissutti B, Grassi M, Bonifacio A, Sergo V, et al. Enhanced oral bioavailability of vinpocetine through mechanochemical salt formation: physico-chemical characterization and in vivo studies. Pharm Res. 2011;28:1870–83.
59. Hasa D, Perissutti B, Cepek C, Bhardwaj S, Carlino E, Grassi M, et al. Drug salt formation via mechanochemistry: the case study of vincamine. Mol Pharm. 2013;10:211–24.
60. Hasa D, Schneider Rauber G, Voinovich D, Jones W, Schneider G, Voinovich D, et al. Cocrystal Formation through Mechanochemistry: from Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding. Angew Chem Int Ed. 2015;54:7371–5.
61. Germann LS, Emmerling ST, Wilke M, Dinnebier RE, Moneghini M, Hasa D. Monitoring polymer-assisted mechanochemical cocrystallisation through in situ X-ray powder diffraction. Chem Commun. 2020;56:8743–6.
62. Hasa D, Carlino E, Jones W. Polymer-assisted grinding, a versatile method for polymorph control of cocrystallization. Cryst Growth Des. 2016;16:1772–9.
63. Scaramuzza D, Schneider Rauber G, Voinovich D, Hasa D. Dehydration without heating: use of polymer-assisted grinding for understanding the stability of hydrates in the presence of polymeric excipients. Cryst Growth Des. 2018;18:5245–53.
64. Nogi T, Zhang D, Chan JD, Marchant JS. A novel biological activity of praziquantel requiring voltage-operated Ca2+ channel β subunits: subversion of flatworm regenerative polarity. PLoS Negl Trop Dis. 2009;3:e464.
65. Huang J, Bathena SPR, Alnouti Y. Metabolite profiling of praziquantel and its analogs during the analysis of in vitro metabolic stability using information-dependent acquisition on a hybrid triple quadrupole linear ion trap mass spectrometer. Drug Metab Pharmacokinet. 2010;25:487–99.
66. Zanolla D, Perissutti B, Passerini N, Chierotti MR, Hasa D, Voinovich D, et al. A new soluble and bioactive polymorph of praziquantel. Eur J Pharm Biopharm. 2018;127:19–28.
67. Zanolla D, Perissutti B, Vioglio PC, Chierotti MR, Gigli L, Demitri N, et al. Exploring mechanochemical parameters using a DoE approach: crystal structure solution from synchrotron XRPD and characterization of a new praziquantel polymorph. Eur J Pharm Sci. 2019;140:105084.
68. Zanolla D, Hasa D, Arhangelskis M, Schneider-Rauber G, Chierotti MR, Keiser J, et al. Mechanochemical Formation of Racemic Praziquantel Hemihydrate with Improved Biopharmaceutical Properties. Pharmaceutics. 2020;12:289.
69. Passerini N, Perissutti B, Albertini B, Franceschinis E, Lenaz D, Hasa D, et al. A new approach to enhance oral bioavailability of Silybum Marianum dry extract: association of mechanochemical activation and spray congealing. Phytomedicine. 2012;19:160–8.
70. Albertini B, Perissutti B, Bertoni S, Zanolla D, Franceschinis E, Voinovich D, et al. Combining mechanochemistry and spray congealing for new praziquantel pediatric formulations in schistosomiasis treatment. Int J Mol Sci. 2019.
71. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. New York: Oxford University Press; 1998.