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Mechanochemical Synthesis of Praziquantel Hemihydrate in the Presence of Five Solvents with Different Water Miscibility †

Ilenia D'Abbrunzo, Dario Voinovich and Beatrice Perissutti *

Department of Chemical and Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy; ilenia.d'abbrunzo@phd.units.it (I.D.); vojnovic@units.it (D.V.)

* Correspondence: bperissutti@units.it

† In the loving memory of Guglielmo Zingone.

Abstract: In this study, we report the mechanochemical synthesis of praziquantel hemihydrate in the presence of five solvents with different water miscibility. The commercially available praziquantel Form A (a racemic anhydrate structure) was ground in the presence of several water–solvent mixtures using two grinding procedures (i.e., direct liquid-assisted grinding and neat grinding plus liquid-assisted grinding). Five organic solvents (i.e., acetic acid, 2-pyrrolidone, ethanol, ethyl acetate and hexane) were chosen considering their different miscibility with water and their capability to form solvates with praziquantel (documented for acetic acid and 2-pyrrolidone). The results suggested that the use of a second solvent has a detrimental effect on the formation of the hemihydrate. The inclusion of water in the solid is even worse in the case of water-miscible solvents, probably due to the favored interactions between the liquids. In fact, hexane is the only solvent permitting the mechanochemical crystallization of praziquantel hemihydrate to a limited extent. Importantly, interconversion studies between the hydrate/monosolvate/anhydrous forms revealed a preferential inclusion of solvents over water in the crystal lattice when using acetic acid or 2-pyrrolidone and complete dehydration of the hemihydrate and conversion in the most thermodynamically stable polymorph A of praziquantel with ethanol, ethyl acetate and hexane.

Keywords: mechanochemistry; solid form screening; praziquantel hemihydrate; praziquantel solvates; solvents miscibility

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1. Introduction

In many steps of chemical and pharmaceutical industrial processing, substances could be exposed to water or other solvents during solvent-based preparation techniques (e.g., classical solution crystallization, coacervation, lyophilization, spray-drying, wet granulation) or by contact with environmental humidity during storage. Sometimes, these solvents remain "entrapped" in the crystal structure, causing the formation of hydrated/solvated forms of the solid substance. Drug solvents generally have different crystal structures than the anhydrous form and, therefore, different physicochemical properties such as solubility, dissolution rate and physical and chemical stability. These aspects may affect not only technological properties such as industrial processability but also—and more importantly—the bioavailability of the drug, determining marked differences in the absorbed amount of the active pharmaceutical ingredient (API) [1]. Differently from hydrates, the inclusion of solvated API in a drug product must be pondered in light of the ICH guideline Q3C on residual solvents in pharmaceuticals, in consideration of possible toxicity issues [2]. In addition, since in the pharmaceutical industry, both water and solvents are used in different steps of the production processes [3], hydrate–solvate interconversions are likely to happen.

In this context, in a previous study, the API theophylline was successfully used as a model drug to investigate the mechanochemical competitive solvate formation in the presence of two solvate/hydrate-forming miscible liquids (i.e., water (H_2O) and 2-pyrrolidone

(2-pyr)) [4]. The drug is known to convert into a monohydrate in the presence of H_2O, whereas it gives a monosolvate or a sesquisolvate in the presence of 2-pyr. Different solid/liquid ratios and several H_2O/2-pyr mixtures have been used to understand the hydrate/solvate competitive formation. The results suggested that H_2O and 2-pyr, when used simultaneously, reduced their efficiency in being incorporated into the crystal structure: due to their mutual miscibility, more liquid than the solid-to-solvent stoichiometric ratio was required to obtain a pure specific solvated phase. Interconversion experiments between hydrate/monosolvate/sesquisolvate suggested a preferential inclusion of 2-pyr over H_2O in the crystal structure.

Based on the above-mentioned study, in this work, the experimental research was extended to another API, that is praziquantel (PZQ), the recommended drug against all species of schistosomiasis [5–11], included in the WHO (World Health Organization) Model List of Essential Drugs for the treatment of both adults and children [12,13]. This API, commercially available in racemic anhydrous solid dosage forms (trade name Biltricide® (Bayer Vital, 51368 Leverkusen, Germany)) [14], has been demonstrated to be prone to solid-state transformations (especially through mechanochemistry).

To date, the literature provides seven PZQ anhydrous polymorphic forms (including the commercial Form A) [15–18], six hydrates [7,19–23], three solvates [18,24] and forty-eight cocrystals, including one cocrystal monohydrate and six cocrystal solvates [25–36], demonstrating a very high propensity to solid-state transformation and interaction with water/solvents [37]. Moreover, the industrial production of PZQ tablets often involves the use of solvents during its crystallization and wet granulation before tablet production [38,39], and consequently, hydrates or solvates of PZQ could unexpectedly arise. In this context, one hemihydrate (i.e., PZQ-HH) and two monosolvates of PZQ (i.e., PZQ-2-pyr and PZQ-AA) are reported in the Cambridge Structural Database (CSD) [40] and indexed as WUHQAU, DAJCAW and DAJCEA, respectively. Figure 1 indicates the chemical structure of commercial PZQ Form A and the crystal structures of the above-mentioned hemihydrate PZQ-HH and two solvates (PZQ-AA and PZQ-2-pyr).

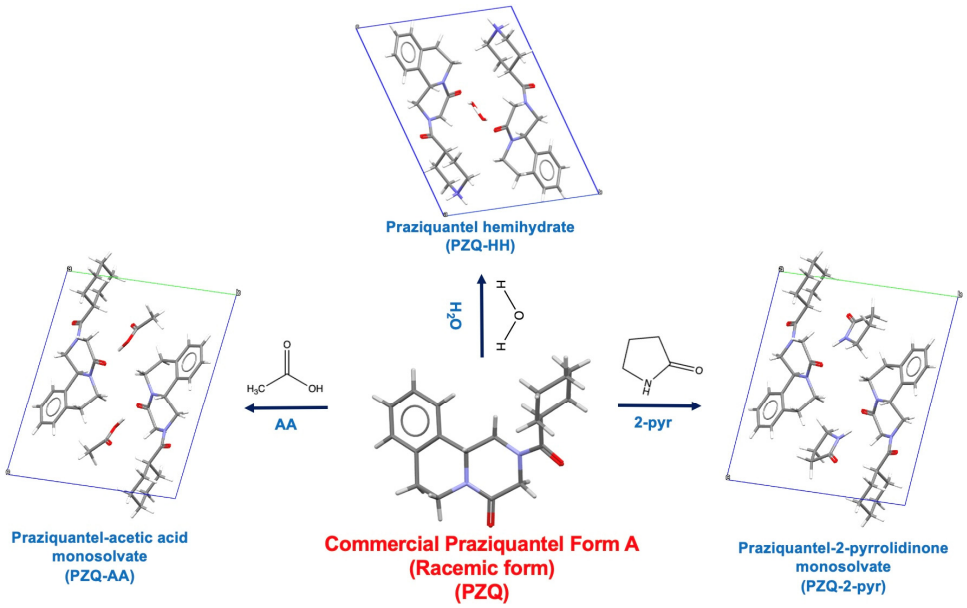

Figure 1. Crystal structures of commercial PZQ Form A (racemic form, bottom centre) compared to PZQ hemihydrate (PZQ-HH, top) and racemic PZQ acetic acid monosolvate (PZQ-AA, bottom left) and racemic PZQ 2-pyrrolidone monosolvate (PZQ-2-pyr, bottom right).

Considering these multicomponent solvates, PZQ-2-pyr and PZQ-AA are obtained through direct grinding of anhydrous PZQ Form A with an equimolar ratio of each solvent [24]. On the other hand, PZQ-HH can only be obtained starting from Form A via

a two-step process, using initially neat grinding (NG) (for the formation of a mainly amorphous intermediate) and, subsequently, liquid-assisted grinding (LAG) in H_2O. Alternatively, single-step LAG of PZQ Form B in H_2O results in the hemihydrate, possibly related to the structural similarity between PZQ-HH and anhydrous Form B [21,37]. As for the physical stability, mechanical treatment at 25 Hz for 200 min without interruptions was almost ineffective on both solvates, while PZQ-HH gave PZQ Form B after 1 h, probably due to the similarity of their crystal structures [21].

The racemic PZQ-HH is a very promising PZQ multicomponent crystal, as both its aqueous solubility and intrinsic dissolution rate (IDR) are largely superior to those of the commercially available PZQ Form A, counteracting the general rule that an anhydrous form is usually more soluble in H_2O than the hydrated form [41]. Further, PZQ-HH maintains an unaltered antischistosomal activity level and physical state for three months at room temperature. As all these promising features could suggest a possible future industrial production of this solid, it is highly recommended to study, in detail, PZQ-HH and obtain provisional information on its possible transition in other solid forms because of the presence of common solvents.

Additionally, compared to the significant number of publications exploring mechanochemistry as a suitable technique for cocrystal formation, studies about the mechanochemical synthesis of solvates are still limited [24,42–46]; the solvate outcome is often regarded as an undesired by-product rather than its main goal, and in most cases, the investigation is carried out by using only one solvent [47–49].

Therefore, focusing this experimental research on PZQ-HH and using mechanochemistry as a fast-screening technique, PZQ was ground in the presence of several H_2O–solvent mixtures with two different grinding procedures: (i) direct LAG of PZQ for 60 min (hereinafter referred as to Di-LAG); (ii) previous NG of anhydrous PZQ for 30 min followed by 1 h LAG (hereinafter referred as to NG+LAG).

Five different solvents (i.e., acetic acid (AA), 2-pyrrolidone (2-pyr), ethanol (EtOH), ethyl acetate (EA) and hexane (HXN)) were tested considering their capability to form solvates with PZQ and their miscibility in H_2O. Four of these (AA, 2-pyr, EtOH, EA) were selected from previous works on the mechanochemical formation of PZQ solvates and the formation of PZQ solid dispersions with PVP [24,50], while HXN was chosen for its well-known immiscibility with H_2O [51]. The miscibility of the five solvents in H_2O is reported in Section 2.2.2.

Going into details, solvents were chosen based on this rationale:

- Two solvents able to form solvates with PZQ, one miscible and one less miscible, such as AA and 2-pyr, respectively;
- Two solvents not forming PZQ solvate, one miscible and one slightly miscible, i.e., EtOH and EA, respectively;
- One solvent that does not form PZQ solvate and is immiscible, such as HXN.

As for 2-pyr and AA, since both are miscible in H_2O, the main objective was to understand if they compete with H_2O for inclusion in the PZQ crystal lattice. Further, it was also intended to check if in the PZQ case, as seen in the theophylline example, when using H_2O–solvent mixed liquids, a largely superior amount than the stoichiometric quantity was needed to form a pure multicomponent phase. EtOH, EA and HXN, with H_2O miscibility in descending order, were also tested to further investigate the competitive effect between H_2O and the second solvent on PZQ-HH formation in relation to their miscibility. Furthermore, we wanted to establish if the copresence of a second liquid during the grinding of PZQ with H_2O could accelerate PZQ-HH formation, bypassing the NG limiting step.

Moreover, following our previous experimental work on theophylline [4], interconversion experiments were also conducted by grinding preformed PZQ-HH in the presence of the above-mentioned five solvents for 60 min at 25 Hz.

2. Materials and Methods

2.1. Materials

Commercially available PZQ Form A (racemic anhydrate form), (RS)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4-H-pyrazino[2,1-a]-isoquinolin-4-one], of Ph. Eur. grade was kindly donated by Fatro S.p.a. (Bologna, Italy). Acetic acid (AA) and 2-pyrrolidone (2-pyr) were provided from Carlo Erba (Rodano-Milan, Italy), while ethanol (EtOH) and ethyl acetate (EA) were purchased from Honeywell Riedel-de Haën (St. Louis, MO, USA). HPLC-grade hexane (HXN) was provided by Sigma-Aldrich Ltd. (Milan, Italy).

All the actives and chemicals were used without further purification. Water (H_2O) was freshly distilled.

2.2. Sample Preparation

2.2.1. Milling Experiments

Milling experiments were performed in Retsch MM400 vibrational mills (Retsch, Haan, Germany) equipped with two 25 mL stainless steel jars and one 10 mm Ø bead, respectively. The milling frequency was kept fixed at 25 Hz. For each mechanochemical experiment, the amount of commercially available PZQ Form A was kept fixed at 400 mg. AA, 2-pyr, EtOH, EA and HXN were the five selected solvents used with H_2O for the research purpose.

Each experiment was developed by adding to the drug an equimolar amount of liquid, either as pure H_2O, one of the five selected solvents, or in the form of seven H_2O–solvent mixtures. Specifically, eight different molar fractions of each of the two solvents were added directly to the milling jars using Eppendorf Research plus micropipettes (Eppendorf, Hamburg, Germany) (Table 1).

Table 1. Composition of the liquid added during grinding experiments to 400 mg of PZQ Form A (solid).

	Solvent Molar Fractions							
H_2O	0	0.25	0.33	0.50	0.67	0.75	0.90 *	1
Second Solvent **	1	0.75	0.67	0.50	0.33	0.25	0.10 *	0

* Only in the NG+LAG procedure. ** e.g., AA, 2-pyr, EtOH, EA, HXN; in the case of using AA as a second solvent, a 1:2 PZQ/liquid molar ratio was considered to compensate for AA evaporation.

For each of the five sets of experiments, two different grinding procedures were carried out: (i) direct LAG for 60 min of PZQ in the presence of H_2O–solvent mixture (Di-LAG); (ii) NG for 30 min of anhydrous PZQ followed by 1 h LAG with H_2O–solvent mixture (NG+LAG).

The mechanochemical products were stored in a desiccator at room temperature and characterized the day after preparation by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) (see Sections 2.3.1 and 2.3.2).

2.2.2. Solvent Properties

As previously mentioned, five different solvents were chosen considering both their ability to form PZQ solvates and their miscibility with H_2O, to evaluate the effect of each solvent on PZQ-HH formation (possible H_2O–solvent competitivity). These two characteristics are summarized in Table 2.

In this research, other solvent properties (such as interfacial tension, boiling temperature, API dissolution rate in solvents, density, viscosity, etc.) were not considered because, in our previous work, we noticed that there was no direct correlation between the experimental results and the characteristics of the solvent considered [4]. The same was applied for H_2O activity [4], which cannot be calculated in this survey because the H_2O activity equation cannot be applied in the case of using H_2O-immiscible solvents.

Table 2. Ability to form PZQ solvates and miscibility values in H_2O of the five screened solvents.

Solvents	AA	2-pyr	EtOH	EA	HXN
Known PZQ solvates [18,21–24,31]	Yes	Yes	No	No	No
Miscibility with H_2O [51–56]	Miscible 1050 g/L	Miscible >65 g/L	Miscible 100 g/L	Slightly miscible 0.8 g/L	Immiscible <0.1 g/L

2.2.3. Mechanochemical Interconversion Experiments

Preformed PZQ-HH was also used as a starting material in a series of mechanochemical interconversion experiments based on the experimental work on theophylline [4]. PZQ-HH was prepared mechanochemically, following the procedure reported by Zanolla and coauthors [21].

The interconversion milling experiments were performed by adding the amount of liquid needed to give a PZQ/solvent 1:1 molar ratio, considering the amount of H_2O in the crystalline lattice of preformed PZQ-HH. The transformation of the selected molar ratios into practical volumes was performed by considering the density of the liquids at 25° C [51]. Table 3 summarizes the micromolar amount of each solvent used for the five sets of experiments.

Table 3. Overview of the mechanochemical interconversion experiments.

Starting Solid (PZQ-HH)	AA	2-pyr	EtOH	EA	HXN
411.5 mg	73 µL	98 µL	75 µL	125 µL	167 µL

The process conditions (e.g., milling time and frequency, number and size of milling media) were kept fixed.

2.3. Sample Characterization

As mentioned in the introduction, all ground products were characterized through PXRD and DSC by comparison with anhydrous PZQ Form A, B, PZQ-AA and PZQ-2-pyr monosolvates (in the case of using AA and 2-pyr as second solvents) and PZQ-HH.

2.3.1. Powder X-ray Diffraction (PXRD)

PXRD analyses were carried out by a Bruker D2 Phaser benchtop diffractometer (Bruker, Manheim, Germany) using the Bragg–Brentano geometry and Cu-Kα radiation (λ = 1.5418 Å) with a 300 W low-power X-ray generator (30 kV at 10 mA). All the measurements were conducted in a 2θ range of 3–40° with a step size of 0.02° and a scan speed of 0.6°/s.

Each sample was prepared by gently pressing approximately 200 mg of ground product into the cavity of a steel sample holder equipped with a cylindrical polyvinylidene fluoride (PVDF) reducer.

2.3.2. Differential Scanning Calorimetry (DSC)

For DSC analysis, each sample weighing 2–4 mg was introduced into an aluminum sealed and pierced 40 µL crucible and analyzed by a Mettler Toledo DSC 3 Star System (Milan, Italy) with a heating program of 30–160 °C (10 °C/min) under a nitrogen atmosphere (50 mL/min flow rate).

3. Results

The results of the experimental work are presented below and organized in different sections as a function of the type of H_2O–second solvent mixture.

For the sake of simplicity, the PXRD and DSC results are only presented for the first set of experiments considered (H_2O-AA mixture); in the case of the other four sets, the results are reported as qualitative tables, to make more immediate and intuitive the comparison with Form A, B, PZQ-2-pyr and PZQ-HH. PXRD and DSC analyses of these sets are reported in the Supporting Information (SI) File.

Also, the Di-LAG results for all five H_2O–second solvent mixtures are reported in the SI file (Figures S1–S10), as the copresence of a second liquid during grinding, rather than promoting PZQ-HH formation, always gave origin to PZQ Form A, confirming NG as a mandatory preliminary step for the synthesis of the hemihydrate. Thus, only NG+LAG results will be presented below.

3.1. Grinding Tests in the Presence of H_2O-AA Mixture

Figures 2 and 3 show the PXRD and DSC results of the tests of the H_2O-AA mixture in the NG+LAG procedure.

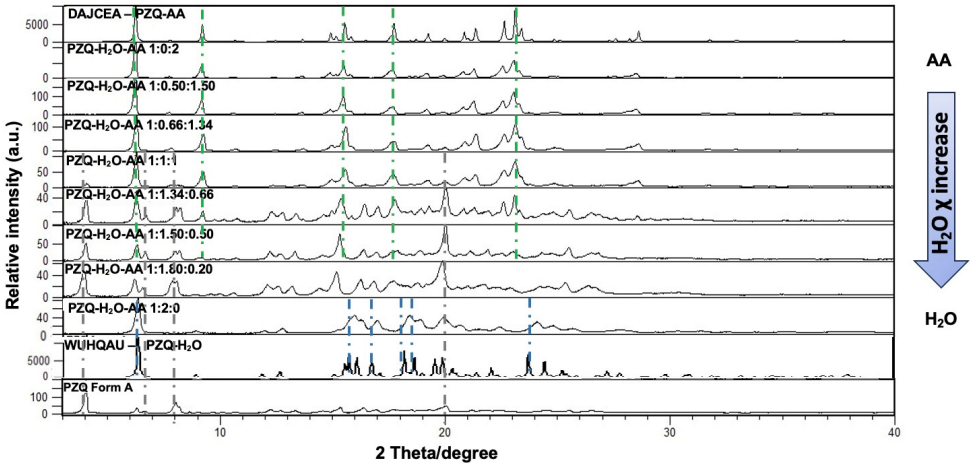

Figure 2. PXRD results of the tests in the presence of H_2O-AA mixture. Green, blue and grey dotted lines highlight PZQ-AA, PZQ-HH and PZQ reflections, respectively.

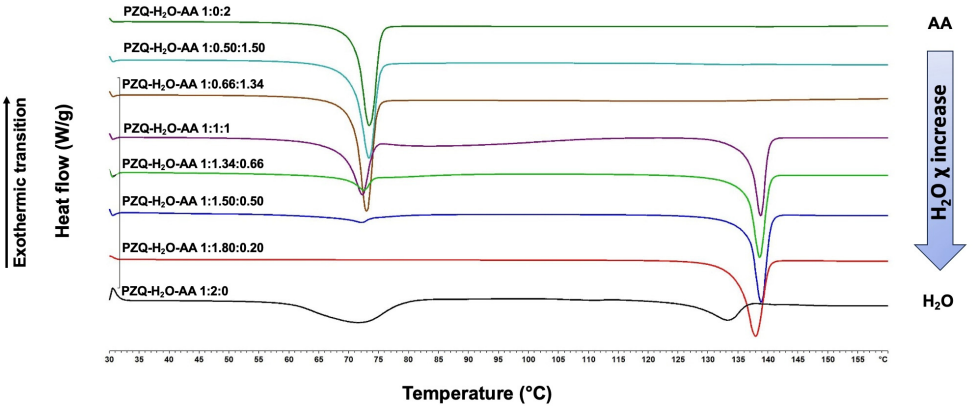

Figure 3. DSC results of the tests conducted in the presence of H_2O-AA mixture.

In this set of experiments, PZQ-HH appeared in only one case, e.g., when PZQ was ground in the presence of pure H_2O, whereas the presence of even small amounts of AA (i.e., H_2O/AA molar fractions of 1.80:0.20) avoided the formation of the hemihydrate, suggesting a strong competitive effect between the two miscible liquids.

The formation of PZQ-HH was attested by PXRD from the characteristic peaks at 6°, 16° and 18–19° 2θ (see the bottom pattern in Figure 2) and from the typical dehydration at about 70–75 °C in DSC (bottom curve in Figure 3).

Considering the formation of PZQ-AA monosolvate, we observed the complete conversion of anhydrous PZQ in PZQ-AA up to a H_2O/AA molar fraction of 0.66:1.34, even though at lower AA molar fractions (i.e., H_2O/AA 1:1), the amount of AA was sufficient to form the monosolvate as a pure phase. On the one hand, from the PXRD results (Figure 2), it is possible to note that the intensity of the characteristic peaks of the monosolvate at 6.3°, 9.3°, 15.6°, 17.8°, 22.7° and 23.16° 2 progressively decreases as the molar fraction of AA in the H_2O-AA mixture decreases. On the other hand, starting from a 1:1 H_2O/AA molar fraction, characteristic peaks of anhydrous Form A (at 4°, 6–7°, 8° e 12–13° 2θ) appear and become more intense as the quantity of H_2O increases, up to the appearance of PZQ-HH at 2:0 of H_2O/AA.

Noteworthy is the fact that the formation of PZQ-AA was observed up to a H_2O/AA molar fraction of 1.50:0.50, while proportions of 1.80:0.20 gave anhydrous Form A, even though a small amount of AA is still present and theoretically able to form the monosolvate.

The DSC results (Figure 3) were consistent with the PXRD analyses: the typical desolvation band of PZQ-AA at 70–75 °C, visible in the case of grinding PZQ with pure AA, gradually becomes less intense and defined—moving at lower temperatures—with a decreased AA molar fraction. From H_2O/AA proportions of 1:1, it is possible to note the copresence of the melting peak of Form A, as also attested from PXRD results. The PZQ-AA desolvation band disappears in the presence of a H_2O/AA molar ratio of 1.80:0.20, which, instead, shows the melting peak of Form A. The DSC curve shown at the bottom of Figure 3 corresponds to the PZQ-HH thermogram (H_2O/AA molar fraction of 2:0). In this thermogram, its typical dehydration range at about 75 °C is visible, followed by the melting of Form A, shifted at lower temperatures due to the particle size reduction during grinding [57].

Despite the similarity between PZQ-HH and polymorph B of PZQ, in such a set of grindings, rather than observing the formation of Form B, the only outcome was Form A, as evident from the PXRD and DSC analyses.

3.2. Grinding Tests in the Presence of H_2O-2-pyr Mixture

Figure 4 qualitatively summarizes the results obtained from grinding tests in the presence of H_2O-2-pyr mixtures. The PXRD and DSC results are reported in the SI File (Figures S11 and S12). Grinding PZQ with 2-pyr as an individual solvent caused the formation of PZQ-2-pyr monosolvate with a decreasing yield as the 2-pyr molar fraction in the aqueous mixture decreased. In parallel, a progressive increase in the signals both in PXRD and DSC (Figures S12 and S13) corresponding to anhydrous Form A was noticed.

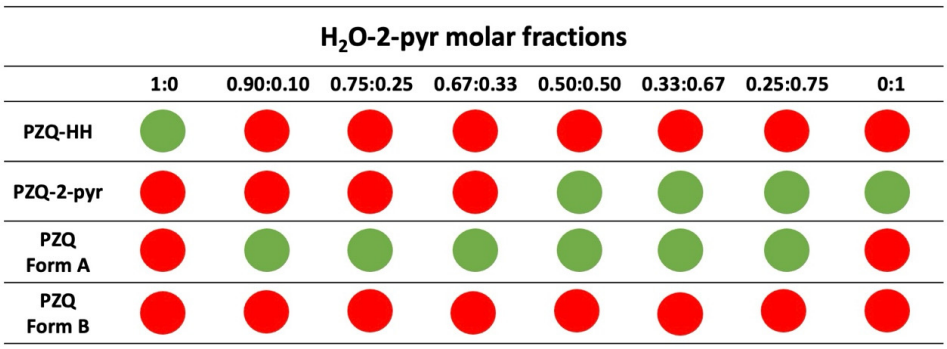

Figure 4. Solid phases recovered from each molar fraction of H_2O-2-pyr mixtures. Green circles stand for solid phase present and red circles for solid phase absent.

As noticed in the previous H_2O-AA case, the formation of PZQ-2-pyr monosolvate was detected up to a 0.50:0.50 H_2O/2-pyr molar ratio; after that extent, only PZQ Form A was observed or PZQ-HH, when H_2O was used as an individual solvent.

Again, in no case was the formation of anhydrous polymorph B observed.

3.3. Grinding Tests in the Presence of H_2O-EtOH Mixture

According to the previous experimental work of Zanolla and coauthors [24], EtOH does not produce any PZQ solvate when used through LAG, but it has a well-known high miscibility with H_2O (see Table 2 in Section 2.2.2).

As in the previous H_2O-AA and H_2O-2-pyr cases, the formation of PZQ-HH was observed in the case of using pure H_2O (e.g., molar fractions of H_2O/EtOH of 1:0), and even H_2O/EtOH molar fractions of 0.90:0.10 did not give rise to PZQ-HH, confirming a strong competitive effect between the miscible liquids.

The outcomes after grinding with all H_2O/EtOH molar fractions were the same: the only product recovered was the starting solid, PZQ Form A, and no traces of Form B emerged.

The results are reported in Figure 5 as a qualitative table, whereas PXRD patterns and DSC curves are reported in the SI File (Figures S13 and S14).

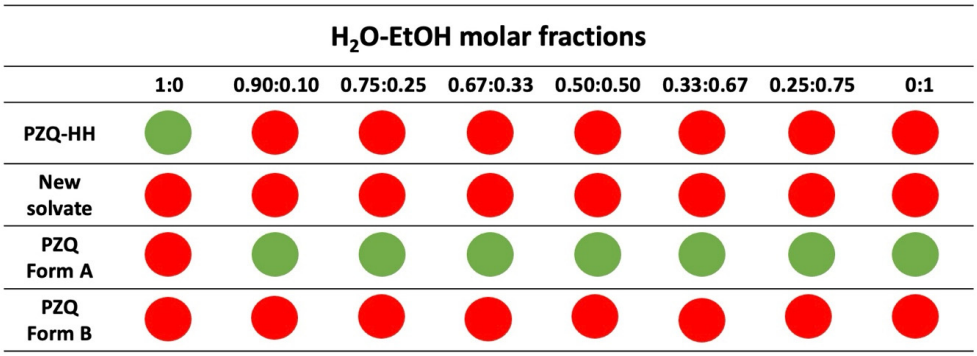

Figure 5. Solid phases recovered from each molar fraction of H_2O-EtOH mixtures. Green circles stand for solid phase present and red circles for solid phase absent.

3.4. Grinding Tests in the Presence of H_2O-EA Mixtures

According to solubility properties (see Section 2.2.2), the polar aprotic EA is slightly miscible in H_2O, so one would expect an increased formation of PZQ-HH, even at H_2O/EA molar fractions different from 1:0 (e.g., 0.90:0.10, 0.75:0.25, 0.67:0.33). However, as shown in Figure 6 (see Figures S15 and S16 in the SI file for PXRD and DSC results), the results obtained were identical to those previously described for EtOH: the formation of PZQ-HH was observed only when PZQ was ground in the presence of pure H_2O, whereas all the liquid mixtures gave anhydrous Form A.

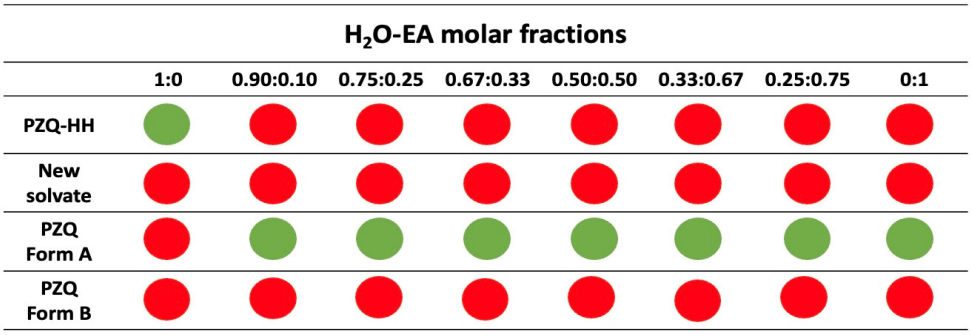

Figure 6. Solid phases recovered from each molar fraction of H_2O-EA mixtures. Green circles stand for solid phase present and red circles for solid phase absent.

3.5. Grinding Tests in the Presence of H_2O-HXN Mixtures

Non-polar HXN, which is completely H_2O-immiscible, was demonstrated to be the only solvent able to produce PZQ-HH with two liquid mixtures: 0.90:0.10 H_2O/HXN and, as usual, pure H_2O.

For all other H_2O/HXN molar fractions, starting PZQ Form A was the unique recovered solid phase, and no traces of other PZQ polymorphs were detected.

PXRD and DSC results are reported in Figures S17 and S18 in the SI file, while a qualitative representation is shown in Figure 7.

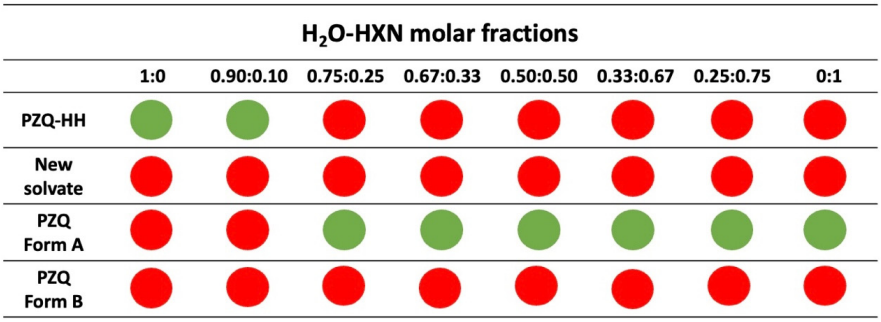

Figure 7. Solid phases recovered from each molar fraction of H_2O-HXN mixtures. Green circles stand for solid phase present and red circles for solid phase absent.

3.6. Mechanochemical Interconversion Experiments

This set of experiments was conducted by grinding preformed PZQ-HH in the presence of the above-mentioned five solvents as individual liquids (see Figure 8 for qualitative results and Figures S19 and S20 for PXRD and DSC results).

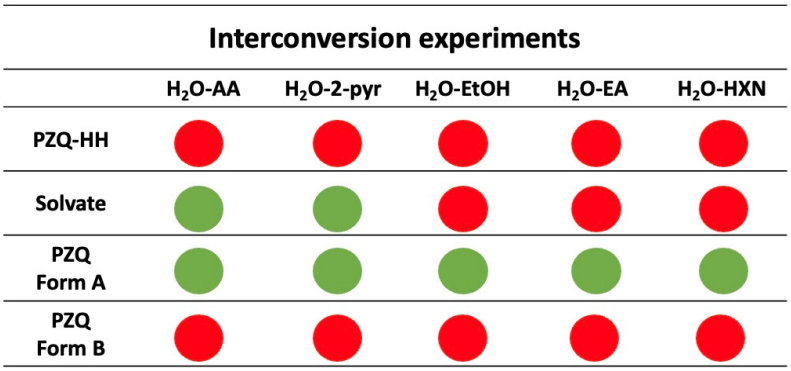

Figure 8. Solid phases recovered from the interconversion milling experiments. Green circles stand for solid phase present and red circles for solid phase absent.

The objectives of this set of experiments could be divided into two categories depending on the type of second solvent used. Specifically, in the case of using AA and 2-pyr, which form PZQ solvates, we wanted to understand if PZQ-HH is stable after grinding or if it preferentially switches into the two solvates, while for the remaining three (not able to form PZQ solvates), the aim was to understand the outcome of an LAG process in the presence of EtOH, EA or HXN.

Turning to the results, it is noteworthy that PZQ-HH never persists. On the one hand, with AA and 2-pyr, PZQ-HH converts into the respective monosolvate (with traces of PZQ Form A); on the other hand, EtOH, EA and HXN cause the complete dehydration of PZQ-HH, which converts into the most thermodynamically stable polymorph A of PZQ. Even in this set of experiments, no traces of polymorph B emerged.

4. Discussion

PZQ-HH, a white crystalline powder, has peculiar beneficial properties in comparison to commercially available PZQ Form A (e.g., double solubility and IDR, unaltered in vitro anthelmintic activity, absence of harmful organic solvents) [21]. This study, conducted by mechanochemistry, investigated the influence of five commonly used solvents in addition

to H_2O (as H_2O is often mixed with other solvents in many industrial processes) on the formation of the hydrated crystal.

For this aim, the anthelmintic drug PZQ, in its commercially available Form A, was ground in the presence of several H_2O–solvent mixtures, through Di-LAG and NG+LAG procedures. Five organic solvents (AA, 2-pyr, EtOH, EA, HXN) were chosen considering their different miscibility with H_2O and their capability to form solvates with PZQ. In our previous work, carried out on a different API, we noticed a detrimental effect of the addition of H_2O–miscible liquid on the inclusion of H_2O in the crystal lattice [4].

Interconversion studies between the hydrate/monosolvate/anhydrous forms were also conducted, as PZQ-HH and PZQ solvates have different documented stability upon grinding [21,24].

The adopted mechanochemical approach has proven to be an efficient and sustainable technique for solid form screening, as it allows rapid and reproducible information with a very limited number of samples and almost no solvents [46,58], thus demonstrating its superiority over classical solution crystallization or slurry. The PZQ-HH case is one of those examples in which mechanochemistry allows access to a compound that cannot be obtained from solution-based routes. In fact, PZQ-HH, rather than being crystallizable from solution/suspension in H_2O from Form A, as usually happens for crystal hydrates, is crystallizable only via a mechanochemically activated form or starting from Form B.

The experimental findings here reported confirm and even exalt the conclusions of previous work. PZQ-HH formation is not only reduced but completely prevented in the presence of a second solvent. In some way, the exaltation of this phenomenon is expected, since PZQ-HH has a lower stoichiometry compared to that of theophylline (i.e., hemihydrate for PZQ instead of monohydrate for theophylline). The use of a second solvent has a detrimental effect on the formation of PZQ-HH, and if the solvent is miscible, as in the case of theophylline, this effect is enhanced due to existing interactions between the two miscible liquids, which can be favored with respect to those of singular liquids with the solid. In fact, HXN is the only solvent permitting the mechanochemical crystallization of PZQ-HH to a limited extent. This means that, to obtain a specific pure hydrated phase, more liquid than the pure solid-to-solvent stoichiometric ratio is required. Also, pointing the attention to the opposite site, i.e., the formation of PZQ solvates, in the case of H_2O-miscible AA or 2-pyr as second solvents, once again the formation of the two PZQ monosolvates is observed only at solvent molar ratios equal to or greater than 0.5, as for theophylline [4]. Therefore, the use of these two solvents in the presence of H_2O reduces their incorporation efficiency in the crystal lattice, and a higher amount than the stoichiometric ratio is necessary to form the two specific solvates as pure phases.

It is known from the literature that 2-pyr molecules form energetically favorable heterocomplexes with H_2O. The interaction between these two molecules is clearly favored through the formation of hydrogen bonds, which can lead to complex fluid structures. In aqueous-dominated H_2O-2-pyr mixtures, the presence of H_2O molecules exerts a strong effect on fluid structures, reducing the 2-pyr dimer population to an efficient development of liquid heterostructures [59]. This strong interaction between the two liquids can give a reason for the significant change in the amount of solvent needed to produce pure PZQ-2-pyr solvate. As for AA, it is also well known that AA and H_2O have strong interactions, so the separation of the H_2O-AA binary solution to obtain pure AA is very difficult. Indeed, AA forms different kinds of association molecules with H_2O depending on the composition of the H_2O-AA binary mixtures. AA and H_2O molecules mainly form a ring-opening association molecule in an aqueous solution, and cyclic AA dimers cannot exist in this environment. Increasing the AA molar fraction, H_2O molecules are bound to AA molecules, sacrificing H_2O-H_2O (or AA–AA at higher molar fractions) interactions and consequently PZQ-H_2O (or PZQ-AA) interaction and incorporation [60,61].

However, the miscibility of the second solvent cannot be stated as the only factor lowering the efficiency of PZQ-HH formation, as the presence of a second solvent is per se

deleterious, probably due to different mechanochemical dynamics inside the jars, resulting in a reduced probability of contact between H_2O and solid PZQ upon grinding.

As a logical consequence, in none of the samples analyzed in this survey with two contemporaneous solvents is PZQ-HH obtained by Di-LAG. Starting from PZQ Form A, PZQ-HH is formed in the presence of H_2O as an individual solvent exclusively via a two-step process, passing through the NG limiting step (which generates an almost amorphous intermediate phase). Therefore, rather than promoting the formation of the PZQ-HH in a one-step procedure, the presence of a second solvent is detrimental even for its formation in the two-step process.

Unlike the case of theophylline, where for some liquid compositions, mixed phases have been recovered (i.e., the monosolvate or the sesquisolvate together with the monohydrate), in this research, neither AA nor 2-pyr monosolvate was ever recovered together with the hemihydrate. When a second phase in addition to PZQ monosolvate was retrieved, this was traces of PZQ Form A. These results are in line with the physical stability of the hemihydrate compared to that of solvates and to the superior stability of the solvates upon grinding [21,24].

Interconversion grinding experiments confirmed that the solvated forms prevail over the hemihydrate, as the preformed hydrate converts in the presence of AA or 2-pyr into their respective monosolvates. When preformed PZQ-HH was ground in the presence of EtOH, EA and HXN, a complete dehydration of PZQ-HH and a conversion in the most thermodynamically stable polymorph A of PZQ were observed. This means that grinding PZQ-HH, rather than giving rise to PZQ Form B as reported in the literature [21], promotes the formation of Form A in the presence of solvent mixtures. This is a key point, as in the presence of solvent mixes, the system goes to the most stable phase (Form A), counteracting the structural similarity of PZQ-HH and PZQ Form B crystals.

Despite the large number of samples processed, in no case did we collect an anhydrous polymorph of PZQ different from commercial Form A, and neither new PZQ solid forms nor mixed solvates (i.e., solids incorporating two solvents in the same crystal lattice) have been obtained. Moreover, no evidence of PZQ monohydrate [23] has ever been found in this experimental research.

These relevant data confirm that PZQ exclusively converts into anhydrous polymorphs in the absence of solvents. Indeed, the presence of binary solvent mixtures always produces the starting Form A or (if feasible, i.e., for AA and 2-pyr) PZQ crystal solvates. The overview of the outcome at the end of each mechanochemical process is summarized in Table 4.

Table 4. Nature of praziquantel polymorphs obtained in the presence of different solvent mixtures.

Initial Polymorph	Method/Technique	Condition/Duration	Outcome
PZQ Form A	LAG with H_2O	NG+LAG	PZQ-HH
PZQ Form A	LAG with H_2O	Di-LAG	PZQ Form A
PZQ Form A	Slurry [21]	7 days	PZQ Form A
PZQ Form B	Slurry [21]	3 days	PZQ-HH
PZQ-HH	NG [21]	60 min	PZQ Form B
PZQ Form A	LAG with H_2O-EtOH	NG+LAG or Di-LAG	PZQ Form A
PZQ Form A	LAG with H_2O-EA	NG+LAG or Di-LAG	PZQ Form A
PZQ Form A	LAG with 0.9 H_2O–0.1 HXN	NG+LAG	PZQ-HH
PZQ Form A	LAG with H_2O-HXN	NG+LAG or Di-LAG	PZQ Form A

Table 4. *Cont.*

Initial Polymorph	Method/Technique	Condition/Duration	Outcome
PZQ Form A	LAG with H_2O-AA (≥0.5AA)	NG+LAG or Di-LAG	PZQ-AA
PZQ Form A	LAG with H_2O-2-pyr (≥0.5AA)	NG+LAG or Di-LAG	PZQ-2-pyr
PZQ Form A	LAG with H_2O-AA (<0.5AA)	NG+LAG or Di-LAG	PZQ Form A
PZQ Form A	LAG with H_2O-2-pyr (<0.5AA)	NG+LAG or Di-LAG	PZQ Form A
PZQ-HH	LAG with AA	Di-LAG	PZQ-AA
PZQ Form A	LAG with 2-pyr	Di-LAG	PZQ-2-pyr
PZQ Form A	LAG with EtOH or EA or HXN	Di-LAG	PZQ Form A

5. Conclusions

Racemic praziquantel hemihydrate is a very promising multicomponent crystal, as it presents beneficial properties in comparison to the commercially available racemic anhydrous Form A (e.g., double solubility and intrinsic dissolution rate, unaltered in vitro anthelmintic activity, absence of harmful organic solvents). In this study, conducted by mechanochemistry, we investigated the influence of adding five commonly used solvents to water on the formation of the hydrated crystal. Specifically, anhydrous praziquantel Form A was ground in the presence of several water–solvent mixtures using two grinding procedures (i.e., direct liquid-assisted grinding and neat grinding plus liquid-assisted grinding). Five organic solvents (i.e., acetic acid, 2-pyrrolidone, ethanol, ethyl acetate and hexane) were chosen considering their different miscibility with water and their capability to form solvates with praziquantel (documented for acetic acid and 2-pyrrolidone).

The results suggested that the use of a second solvent has a detrimental effect on the formation of the hemihydrate and, if the solvent is miscible, this effect is enhanced due to the existing interactions between the two miscible solvents. In fact, hexane is the only solvent allowing the crystallization of the hydrated form in a limited content. Also, pointing the attention to the formation of praziquantel solvates, their formation was observed only at solvent molar ratios equal to or greater than 0.5, thus demonstrating that the use of these two solvents in the presence of water reduces their incorporation efficiency in the crystal lattice. This means that, to obtain a specific pure hemihydrated or solvated phase, more liquid than the pure solid-to-solvent stoichiometric ratio is required.

Moreover, interconversion experiments, conducted between the hydrate/monosolvate/anhydrous forms, revealed a preferential inclusion of solvents over water in the crystal lattice when using acetic acid or 2-pyrrolidone. Conversely, with ethanol, ethyl acetate and hexane, a complete dehydration of the hemihydrate occurred together with a conversion in the most thermodynamically stable polymorph A of praziquantel.

Surprisingly, we never assisted in the formation of anhydrous praziquantel polymorph B in the presence of solvent mixes. The grinding outcome in most cases was the most thermodynamically stable Form A, counteracting the structural similarity of PZQ-HH and PZQ Form B crystals.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cryst14040374/s1, Figure S1. PXRD results of the tests in the presence of H_2O-AA, Di-LAG. Green and grey dotted lines highlight PZQ-AA and PZQ reflections, respectively; Figure S2. DSC results of the tests in the presence of H_2O-AA, Di-LAG; Figure S3. PXRD results of the tests in the presence of H_2O-2-pyr, Di-LAG. Green and grey dotted lines highlight PZQ-2-pyr and PZQ reflections, respectively; Figure S4. DSC results of the tests in the presence of H_2O-2-pyr, Di-LAG; Figure S5. PXRD results of the tests in the presence of H_2O-EtOH, Di-LAG; Figure S6. DSC

results of the tests in the presence of H_2O-EtOH, Di-LAG; Figure S7. PXRD results of the tests in the presence of H_2O-EA, Di-LAG; Figure S8. DSC results of the tests in the presence of H_2O-EA, Di-LAG; Figure S9. PXRD results of the tests in the presence of H_2O-HXN, Di-LAG; Figure S10. DSC results of the tests in the presence of H_2O-HXN, Di-LAG; Figure S11. PXRD results of the tests in the presence of H_2O-2-pyr, NG+LAG procedure. Green, blue and grey dotted lines highlight PZQ-2-pyr, PZQ-HH and PZQ reflections, respectively; Figure S12. DSC results of the tests in the presence of H_2O-2-pyr, NG+LAG procedure; Figure S13. PXRD results of the tests in the presence of H_2O-EtOH, NG+LAG procedure. Blue and grey dotted lines highlight PZQ-HH and PZQ reflections, respectively; Figure S14. DSC results of the tests in the presence of H_2O-EtOH, NG+LAG procedure; Figure S15. PXRD results of the tests in the presence of H_2O-EA, NG+LAG procedure. Blue and grey dotted lines highlight PZQ-HH and PZQ reflections, respectively; Figure S16. DSC results of the tests in the presence of H_2O-EA, NG+LAG procedure; Figure S17. PXRD results of the tests in the presence of H_2O-HXN, NG+LAG procedure. Blue and grey dotted lines highlight PZQ-HH and PZQ reflections, respectively; Figure S18. DSC results of the tests in the presence of H_2O-HXN, NG+LAG procedure; Figure S19. PXRD results of the five interconversion experiments starting from preformed PZQ-HH; Figure S20. DSC results of the five interconversion experiments starting from preformed PZQ-HH.

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