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Article

Amorphous Solid Dispersion Formation for Enhanced Release Performance of Racemic and Enantiopure Praziquantel

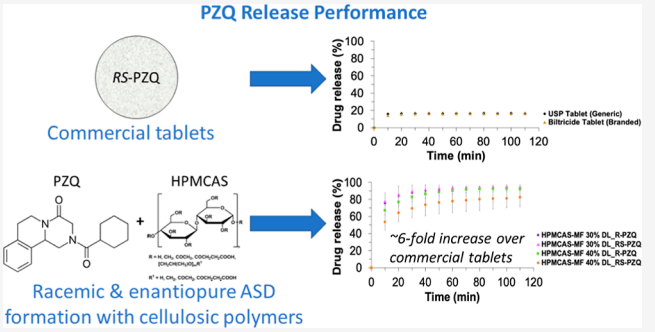
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ABSTRACT: Praziquantel (PZQ) is the treatment of choice for schistosomiasis, which affects more than 250 million people globally. Commercial tablets contain the crystalline racemic compound (*RS*-PZQ) which limits drug dissolution and oral bioavailability and can lead to unwanted side effects and poor patient compliance due to the presence of the *S*-enantiomer. While many approaches have been explored for improving PZQ's dissolution and oral bioavailability, studies focusing on investigating its release from amorphous solid dispersions (ASDs) have been limited. In this work, nucleation induction time experiments were performed to identify suitable polymers for preparing ASDs using *RS*-PZQ and *R*-PZQ, the therapeutically active enantiomer. Cellulose-based polymers, hydroxypropyl methylcellulose acetate succinate (HPMCAS, MF grade) and hydroxypropyl methylcellulose (HPMC, E5 LV grade), were the best crystallization inhibitors for *RS*-PZQ in aqueous media and were selected for ASD preparation using solvent evaporation (SE) and hot-melt extrusion (HME). ASDs prepared experimentally were subjected to X-ray powder diffraction to verify their amorphous nature and a selected number of ASDs were monitored and found to remain physically stable following several months of storage under accelerated-stability testing conditions. SE HPMCAS-MF ASDs of *RS*-PZQ and *R*-PZQ showed faster release than HPMC E5 LV ASDs and maintained good performance with an increase in drug loading (DL). HME ASDs of *RS*-PZQ formulated using HPMCAS-MF exhibited slightly enhanced release compared to that of SE ASDs. SE HPMCAS-MF ASDs showed a maximum release increase of the order of 6 times compared to generic and branded (Biltricide) PZQ tablets. More importantly, SE *R*-PZQ ASDs with HPMCAS-MF released the drug as effectively as *RS*-PZQ or better, depending on the DL used. These findings have significant implications for the development of commercial PZQ formulations comprised solely of the *R*-enantiomer, which can result in mitigation of the biopharmaceutical and compliance issues associated with current commercial tablets.



KEYWORDS: *praziquantel, amorphous solid dispersions, pharmaceutical polymers, drug release, chirality*

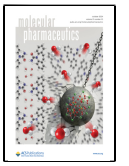
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1. INTRODUCTION

Praziquantel (PZQ) [2-(cyclohexylcarbonyl)1,2,3,6,7,11b hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one] is an essential anthelmintic drug recognized by the World Health Organization as the primary choice for treatment of schistosomiasis, a neglected parasitic disease caused by flatworms of the *Schistosoma* genus that has affected more than 250 million people globally in recent years.[1−4] As a class II drug in the Biopharmaceutics Classification System (BCS), PZQ exhibits good permeability across biological membranes, poor solubility in water (0.4 mg/mL at 25 °C), and oral bioavailability that is limited by the drug's slow dissolution rate in the gastrointestinal tract.[5−9] PZQ is commercially available in the form of tablets that contain a crystalline racemic compound (*RS*-PZQ) corresponding to an equal proportion (1:1) of the *R*-enantiomer of the drug, which is primarily responsible for its therapeutic efficacy, and the less-active *S*-enantiomer which brings about an unpleasant bitter taste and doubles the size of the commercial formulations, thus contributing toward patient noncompliance.[3,10,11] Because of PZQ's poor aqueous solubility and extensive first-pass metabolism following oral administration, a high dose (usually 20−40 mg/kg) is required for treatment.[1,3,7,10]

Over the course of the past two decades, many experimental approaches have been explored for the purpose of developing novel formulations of PZQ that can help overcome the solubility-, dissolution-, and bioavailability-related challenges

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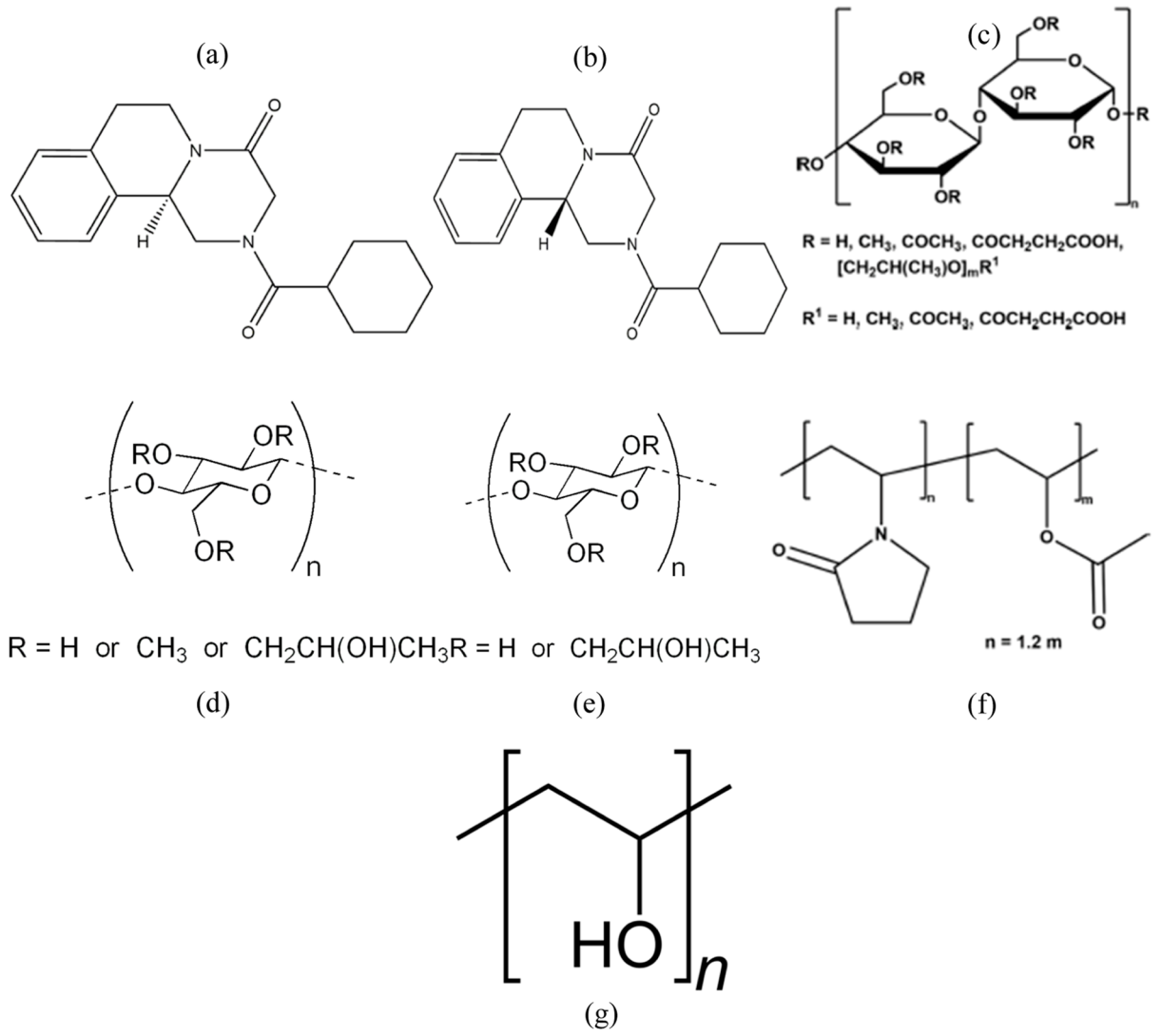


Figure 1. Chemical structures of *R*-PZQ (a), *S*-PZQ (b), HPMCAS (c), HPMC (d), HPC (e), PVPVA (f), and PVA (g).

presented by the commercial tablets that are available on the market. Such approaches include, but are not limited to, cocrystallization of PZQ with various carboxylic acids[12,13] or fellow anthelmintic niclosamide,[14] preparation of hydrated/solvated forms[15−19] and new anhydrous polymorphs,[19−22] cyclodextrin complexation,[13,23] development of micro/nanocrystals,[24] nanosuspensions,[25] solid lipid nanoparticles[26] and polymeric nanoparticles,[27] formation of drug delivery systems with clay minerals[28] and calcium carbonate,[29] and incorporation into liposomes[30] and polymeric implants.[31]

Amorphous solid dispersions (ASDs) are an increasingly popular formulation approach for improving the aqueous solubility, dissolution, and oral bioavailability profiles of poorly soluble drugs and have attracted significant attention from both academic and industrial research communities, with industry experiencing an uptick in the number of drugs that have gone through development and/or reached the market in the form of ASDs over the past decade.[32−40] In polymer-based ASD formulations, drugs are molecularly dispersed into a polymeric matrix in the amorphous rather than the crystalline state, allowing for improved particle wettability, enhanced solubility, quicker dissolution, and greater extent of supersaturation which contributes to improved membrane permeability and, ultimately, enhanced bioavailability.[32,41−44] While solid dispersions of PZQ with polymers such as sodium starch glycolate,[9] sodium alginate,[45] carboxymethylcellulose,[45] polyvinylpyrrolidone,[46] polyvinylpyrrolidone/vinyl acetate,[47] polyethylene glycol,[48] and poloxamer[48] have been developed and found to enhance the biopharmaceutical properties of the drug, research efforts focusing on understanding the drug release mechanism from ASDs have been limited to the best of our knowledge. Moreover, studies investigating drug release from enantiopure ASDs comprising solely the therapeutic *R*-enantiomer of PZQ have not been reported.

The work described herein was undertaken with the aim of formulating stable ASDs of PZQ capable of releasing the drug better than commercial tablets. Additional aims were to (1) gain insight into the release mechanism during dissolution testing by investigating the impact of parameters such as polymer type, sample preparation method, ASD drug loading (DL), drug concentration, dissolution medium pH, and PZQ chirality on drug release from polymer and (2) determine whether enantiopure ASDs comprising *R*-PZQ can release the drug with equal or greater efficiency than racemic ASDs comprising *RS*-PZQ.

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Mol. Pharmaceutics 2024, 21, 5285−5296

2. EXPERIMENTAL SECTION

2.1. Materials. *R*-PZQ (purity of 99.9%) was sourced from Tongli Biomedical Co. (Zhangjiagang, China). *RS*-PZQ (purity 95%+) was sourced from ChemShuttle (Burlingame, CA). PZQ tablets, USP (generic, 600 mg) were procured from Par Pharmaceutical (Chestnut Ridge, NY). Biltricide tablets (branded, 600 mg) were received from Bayer HealthCare Pharmaceuticals (Whippany, NJ). Hydroxypropyl methylcellulose acetate succinate LF grade (HPMCAS-LF; AQOAT AS-LF, Shin-Etsu, Tokyo, Japan), hydroxypropyl methylcellulose acetate succinate MF grade (HPMCAS-MF; AQOAT AS-MF, Shin-Etsu, Tokyo, Japan), hydroxypropyl methylcellulose PHARMACOAT 603 grade (HPMC; PHARMACOAT 603, Shin-Etsu, Tokyo, Japan), hydroxypropyl methylcellulose E5 LV grade (HPMC; Methocel E5 Premium LV, The Dow Chemical Company, Midland, MI), hydroxypropyl cellulose (HPC; KLUCEL EXF, Ashland, Wilmington, DE), polyvinylpyrrolidone/vinyl acetate (PVPVA; Kollidon VA 64, BASF Corporation, Ludwigshafen, Germany), and poly(vinyl alcohol) (PVA; Parteck MXP, Merck KGaA, Darmstadt, Germany) were the polymers used in this work. Dimethyl sulfoxide (DMSO), dichloromethane (DCM), methanol (MeOH), sodium chloride (NaCl), sodium phosphate monobasic monohydrate, sodium hydroxide (NaOH), and hydrochloric acid (HCl) were purchased from Fisher Chemical (Fair Lawn, NJ). HCl solution (pH 1.6) was prepared by mixing 8 g of NaCl and 5.6 mL of concentrated HCl in ultrapure water to make up a final volume of 4 L. The pH was adjusted by using 1 M HCl solution. pH 6.5 phosphate-buffered saline (PBS) was prepared by dissolving 4 ± 0.1 g of NaOH pellets, 31.6 g of sodium phosphate monobasic monohydrate, and 49.42 g of NaCl in ultrapure water to make up a final volume of 4 L and adjusting the pH using either a 1 M NaOH solution or 1 M HCl solution. The chemical structures of PZQ enantiomers and the polymers used in this work are shown in Figure 1.

2.2. Crystalline Solubility Determination. The equilibrium solubility of crystalline *RS*-PZQ and *R*-PZQ in hemihydrate form was determined at 37 °C with a stirring speed of 300 rpm. After 48 h, excess powder was removed by ultracentrifugation at 35,000 rpm (37 °C, 30 min) by an Optima L-100 XP ultracentrifuge (SW 41Ti rotor) (Beckman Coulter, Inc., Brea, CA). Supernatant (20 μL) was then injected into an Agilent high-performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, CA) with a C18 column (4.6 × 250 mm, 5 μm) and an ultraviolet (UV) detector set at 220 nm. The mobile phase comprised acetonitrile and water (50:50 v/v) at a flow rate of 1 mL/min. Solubility of PZQ was calculated as PZQ amount using a standard curve in the range of 1−100 μg/mL.

2.3. Amorphous Solubility Determination. The amorphous solubility of *R*-PZQ and *RS*-PZQ in PBS buffer (pH 6.5) and HCl solution (pH 1.6) was determined under constant stirring (400 rpm) at 37 °C using the UV-extinction method.[49] Fifty milliliters of each aqueous medium were added to water-jacketed beakers and allowed to equilibrate at the target temperature. Stock solutions of *R*-PZQ and *RS*-PZQ in DMSO with a concentration of 125 mg/mL were added to the aqueous media at a speed of 50−200 μL/min using a syringe pump (Harvard Apparatus, Holliston, MA). Light scattering in solution was monitored at a nonabsorbing wavelength (400 nm) with a SI Photonics UV/vis spectrometer (Tucson, Arizona). A 2 mm probe was used to collect data in intervals of 5 s. The amorphous solubility of *R*-PZQ and *RS*-PZQ was taken as the concentration at which a rapid increase in the amount of scattered light was observed.

2.4. Induction Time Experiments for ASD Polymer Carrier Selection. Suitable polymers for formulating ASDs with *R*-PZQ and *RS*-PZQ were selected by conducting induction time experiments to identify which polymers are the most potent inhibitors of drug crystallization in solution. Stock solutions of *R*-PZQ and *RS*-PZQ in DMSO with a concentration of 125 mg/mL were added to PBS buffer (pH 6.5) at a speed of 50−200 μL/min using a syringe pump (Harvard Apparatus, Holliston, MA) at a concentration corresponding to the amorphous solubility of *R*-PZQ and *RS*-PZQ in PBS. A SI Photonics UV/vis spectrometer (Tuscon, Arizona) coupled with a 2 mm probe was used for induction time determination. The increase in light scattering brought about by crystal nucleation and subsequent growth was monitored at intervals of 5−30 s by measuring the UV extinction at a nonabsorbing wavelength (400 nm). The induction time was determined under constant stirring (400 rpm) at 37 °C. The polymers of interest (HPMCAS-LF, HPMCAS-MF, HPMC PHARMACOAT 603, HPMC E5 LV, HPC, PVPVA, and PVA) were dissolved in PBS at a concentration of 300 μg/mL prior to measurements commencing.

2.5. ASD Preparation via Rotary Evaporation. Solvent-evaporated (SE) ASDs of *R*-PZQ and *RS*-PZQ with HPMCAS-MF and HPMC E5 LV were prepared using a Hei-VAP Core rotary evaporator (Heidolph Instruments, Schwabach, Germany) equipped with an EcoChyll S Cooler (Ecodyst, Apex, NC) and water bath set to 50 °C. Drug and polymer were dissolved in 1:1 DCM/MeOH v/v to prepare ASDs with DLs of 30 and 40% for *R*-PZQ and 20, 30, 40, and 50% for *RS*-PZQ. Following solvent removal, the ASDs were subjected to further drying overnight in a vacuum oven operating under ambient temperature. The ASDs were then transferred to grinding vials and pulverized with a 6750 Freezer/Mill cryogenic impact mill (SPEX SamplePrep, Metuchen, NJ) to obtain fine powders that were passed through a 60 mesh (250 μm) sieve to obtain a uniform particle size.

2.6. ASD Preparation via Hot-Melt Extrusion. Hot-melt extruded (HME) ASDs of *RS*-PZQ and HPMCAS-MF with DLs of 20 and 30% were prepared using an Xplore PME extruder (Geleen, The Netherlands) equipped with a 5 mL volume barrel set and conveying screws. A temperature of 145 ± 1 °C, screw speed of 50 rpm, and residence time of 5 min were employed for extrudate preparation. All extrudates were cryomilled and passed through a 60 mesh (250 μm) sieve to obtain a uniform particle size.

2.7. X-ray Powder Diffraction. The crystallinity of starting *R*-PZQ/*RS*-PZQ and polymer materials as well as SE and HME ASDs was assessed using a Rigaku SmartLab diffractometer (Rigaku Americas, The Woodlands, TX) equipped with a Cu Kα radiation source and D/tex ultradetector. Samples were added to glass sample holders, and X-ray powder diffraction (XRPD) patterns were recorded over the range of 4−40° 2θ at a scanning speed of 0.6 or 4° per min and a 0.02° step size with the voltage and current set to 40 kV and 44 mA, respectively. XRPD was also used to monitor the physical stability of select ASDs stored under accelerated-stability conditions of 40 °C and 75% RH.

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Mol. Pharmaceutics 2024, 21, 5285−5296

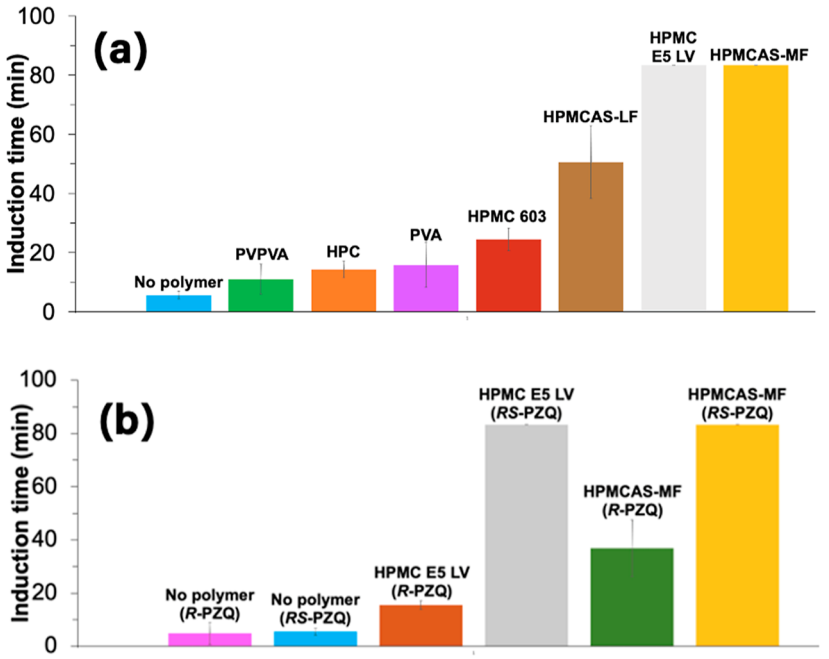


Figure 2. (a) Impact of the polymer type on the nucleation induction time of *RS*-PZQ in PBS (pH 6.5). The concentration of each polymer in solution was 300 μg/mL. (b) Comparison of crystallization induction time for *RS*-PZQ and *R*-PZQ in the presence of HPMCAS-MF and HPMC E5 LV. Error bars indicate standard deviation with n = 3 for *RS*-PZQ samples and n = 2 for *R*-PZQ samples.

2.8. Accelerated-Stability Studies of ASDs at 40 °C and 75% RH. Select ASDs were stored in loosely capped glass scintillation vials and placed in a sealed container kept inside a temperature-controlled oven. The humidity in the container was maintained at the target level using a saturated solution of NaCl. At predetermined time intervals, the ASDs were removed from storage, and their XRPD patterns were collected to check for the emergence of crystalline peaks.

2.9. Powder Dissolution Studies. Powder dissolution studies were conducted in triplicate in single- or two-stage experiments using a USP II dissolution apparatus (Hanson Vision G2 Classic 6, Teledyne Hanson Research, Chatsworth, CA). For single-stage experiments, ASD powders of *R*-PZQ and *RS*-PZQ were added to 50 mL PBS (pH 6.5) and monitored for ∼2 h at 37 °C with 100 rpm of paddle stirring. The target drug concentration for release in single-stage experiments with ASDs was either 667 μg/mL or 1.5 mg/mL. In single-stage experiments involving 600 mg tablets, PZQ tablets, USP and Biltricide tablets were added to 400 mL PBS (pH 6.5) and monitored for ∼2 h at 37 °C with 100 rpm of stirring and a target drug concentration of 1.5 mg/mL. For two-stage experiments, release in gastric pH conditions for ASDs was conducted in 45 mL HCl solution (pH 1.6) for 1 h followed by addition of 5 mL concentrated PBS (pH 7.3) to adjust the pH of the solution to pH 6.5, and drug release was monitored for an additional ∼30 min. In two-stage tablet experiments, the release in acid was conducted in 360 mL of HCl solution (pH 1.6) for 1 h and 40 mL of PBS (pH 7.3) was added to shift the pH to 6.5. The target drug concentration in all two-stage experiments was 1.5 mg/mL. An in situ Rainbow fiber optic ultraviolet spectrometer coupled with 5 mm fiber optic dip probes (Pion, Billerica, MA) was used to monitor the drug concentration over time. Second derivative analysis was applied to correct the spectral baseline, and a calibration curve of area under curve (AUC) of the range 278−285 nm was used to calculate the drug concentration. Calibration curves in PBS (pH 6.5) and HCl solution (pH 1.6) were built over the concentration range of 10−1500 μg/mL.

3. RESULTS

3.1. Crystalline Solubility of Enantiopure and Racemic PZQ in Aqueous Media. The crystalline solubilities of *R*-PZQ and *RS*-PZQ in PBS (pH 6.5) at 37 °C were found to be 282.6 ± 3.3 and 196.4 ± 0.3 μg/mL, respectively, in good agreement with previously reported solubility profiles of enantiopure and racemic PZQ in aqueous media.[50]

3.2. Amorphous Solubility of Enantiopure and Racemic PZQ in Aqueous Media. The amorphous solubility of *R*-PZQ in PBS (pH 6.5) and HCl solution (pH 1.6) at 37 °C was found to be 1.4 ± 0.1 and 1.4 ± 0.2 mg/mL, respectively. For *RS*-PZQ, the amorphous solubility in PBS and HCl solution was found to be 1.1 ± 0.1 and 1.4 ± 0.1 mg/mL, respectively.

3.3. Induction Time Experiments for ASD Polymer Carrier Selection. Polymers are known to effectively inhibit the crystallization of drugs in solution by forming drug−polymer intermolecular interactions that help suppress nucleation and/or crystal growth.[51,52] In this work, the propensity of different polymers to inhibit the crystallization of *RS*-PZQ and *R*-PZQ in PBS (pH 6.5) was investigated at a polymer concentration of 300 μg/mL to identify suitable polymer carriers for formulating stable ASDs. At a drug concentration corresponding to the amorphous solubility of *RS*-PZQ, HPMCAS-MF and HPMC E5 LV were the most potent inhibitors, preventing crystallization for at least 83 min (Figure 2a), which was the duration of the experiment. In control experiments featuring no polymer, the drug crystallized within 5.5 ± 1.3 min. HPMCAS-LF and HPMC PHARMACOAT 603 yielded induction times of 50.5 ± 12.3 and 24.5 ± 3.9 min, respectively. The respective induction times for PVA, HPC, and PVPVA were 15.7 ± 7.6, 14.3 ± 2.9, and 10.9 ± 5.1 min, respectively. Based on the induction time data obtained,

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Mol. Pharmaceutics 2024, 21, 5285−5296

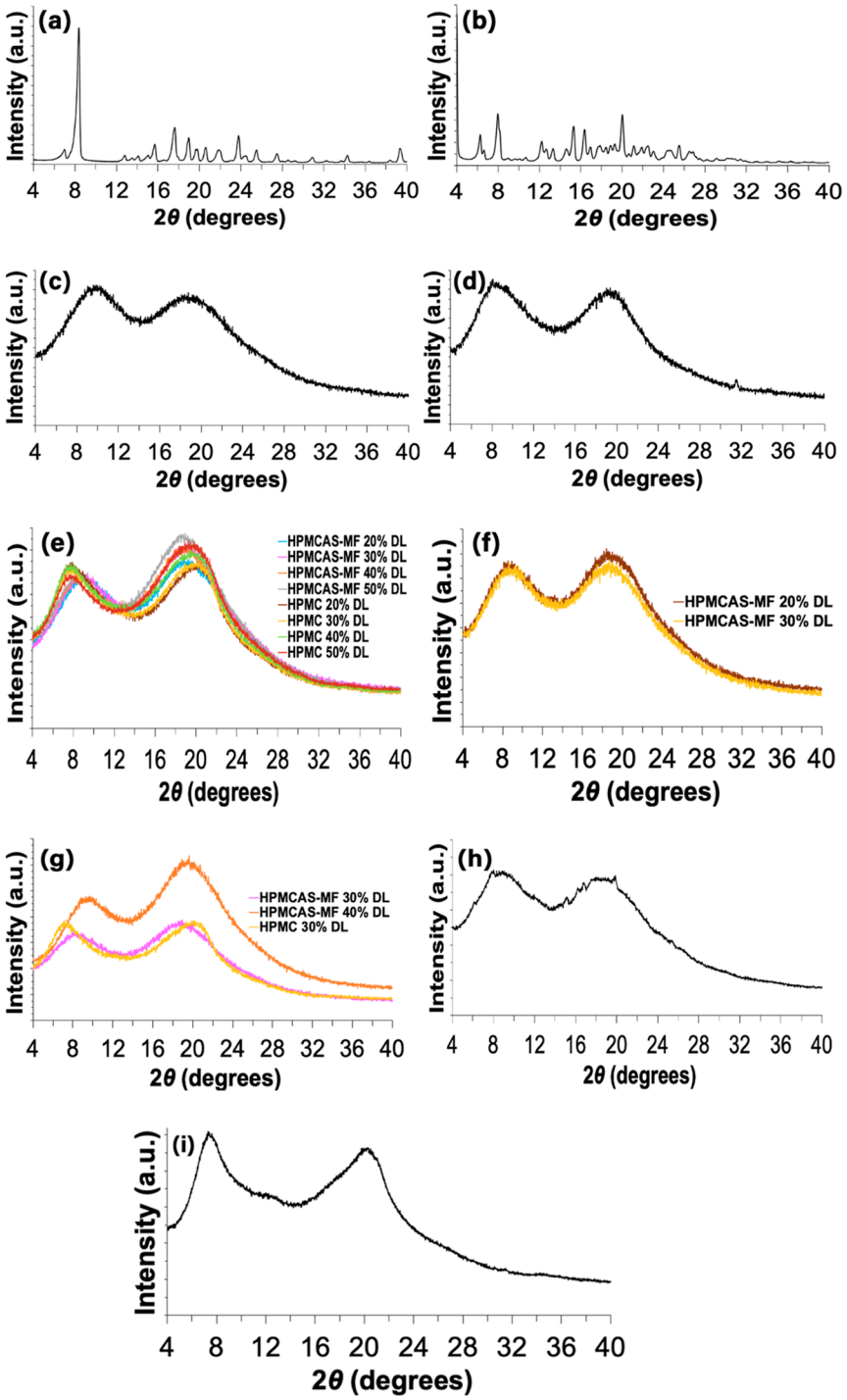


Figure 3. XRPD patterns of (a) *R*-PZQ, (b) *RS*-PZQ, (c) HPMCAS-MF, (d) HPMC E5 LV, (e) SE ASDs of *RS*-PZQ, (f) HME ASDs of *RS*-PZQ, (g) SE ASDs of *R*-PZQ, (h) 20% DL SE ASD of *RS*-PZQ with HPMCAS-MF after 21 weeks of storage, and (i) 20% DL SE ASD of *RS*-PZQ with HPMC E5 LV after 23 weeks of storage.

HPMCAS-MF and HPMC E5 LV were selected as the most suitable polymers for formulating stable ASDs of *RS*-PZQ via solvent evaporation and hot-melt extrusion and were also investigated with regards to their propensity to inhibit crystallization of *R*-PZQ. HPMCAS-MF was significantly less potent in inhibiting *R*-PZQ crystallization, with an average induction time of 37 ± 11 min (Figure 2b). HPMC E5 LV's propensity as a crystallization inhibitor was also significantly less for *R*-PZQ than *RS*-PZQ, with the average induction time for *R*-PZQ being 15.5 ± 1.6 min. No significant differences in the induction times of *RS*-PZQ and *R*-PZQ in the absence of polymer were observed in control experiments.

3.4. XRPD Analysis of PZQ ASDs. ASDs of *RS*-PZQ and *R*-PZQ prepared via rotary evaporation or hot-melt extrusion were subjected to XRPD analysis to check for signs of residual crystallinity. The XRPD patterns collected for all ASDs (Figure 3e−i) revealed the presence of only broad halo peaks characteristic of amorphous materials, confirming the absence of crystalline content within the limit of detection of the technique. HPMCAS-MF ASDs stored under accelerated-

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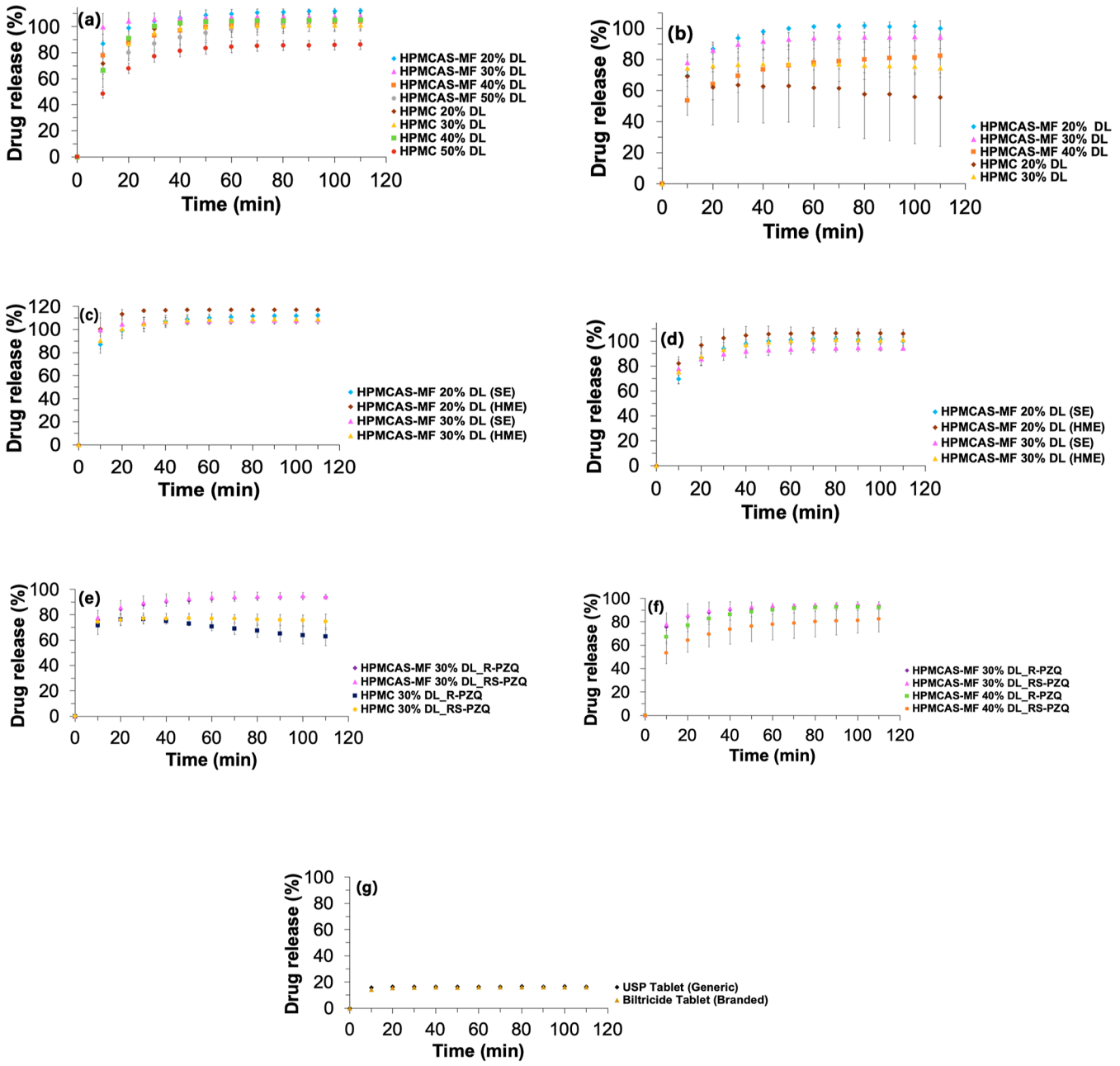


Figure 4. Release profiles of (a) SE ASDs of *RS*-PZQ with HPMCAS-MF and HPMC E5 LV; target drug concentration = 667 μg/mL. (b) SE ASDs of *RS*-PZQ with HPMCAS-MF and HPMC E5 LV; target drug concentration = 1.5 mg/mL. (c) SE and HME ASDs of *RS*-PZQ with HPMCAS-MF; target drug concentration = 667 μg/mL. (d) SE and HME ASDs of *RS*-PZQ with HPMCAS-MF; target drug concentration = 1.5 mg/mL. (e) SE ASDs of *RS*-PZQ and *R*-PZQ with HPMCAS-MF and HPMC E5 LV; target drug concentration = 1.5 mg/mL. (f) SE ASDs of *RS*-PZQ and *R*-PZQ with HPMCAS-MF at different DLs; target drug concentration = 1.5 mg/mL. (g) USP and Biltricide tablets; target drug concentration = 1.5 mg/mL. Error bars indicate standard deviation (n = 3).

stability conditions of 40 °C and 75% RH exhibited small crystalline peaks within 21 weeks (Figure 3h), while HPMC-based ASDs remained XRPD amorphous for at least 23 weeks (Figure 3i).

3.5. Powder Dissolution Studies of PZQ ASDs. *3.5.1. Single-Stage Dissolution.* At a target drug concentration of 667 μg/mL, SE ASDs of *RS*-PZQ prepared with HPMCAS-MF showed complete release regardless of the DL used (Figure 4a). Complete release from low-DL (20 and 30%) ASDs was achieved within 10−21 min. In contrast, ASDs prepared using HPMC E5 LV showed complete release with a DL up to 40%. Complete release from HPMC-based ASDs was slower than that from HPMCAS-MF ASDs and was achieved within 28−53 min. At 50% DL, the maximum release for HPMC-based ASDs dropped to 86%. When the target drug concentration was increased to 1.5 mg/mL (Figure 4b), complete release was observed within 51 min for HPMCAS-MF ASDs with 20% DL, whereas at 30 and 40% DL, the release dropped to 94 and 83%, respectively. HME ASDs with HPMCAS-MF gave complete release at both low (Figure 4c) and high (Figure 4d) target drug concentration, and the time required for complete release to be achieved was comparable to that noted for SE ASDs. SE HPMCAS-MF ASDs of *R*-PZQ with 30% DL were found to exhibit a higher maximum release

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Mol. Pharmaceutics 2024, 21, 5285−5296

(94%) than enantiopure HPMC ASDs (77%) of the same DL at a target concentration of 1.5 mg/mL (Figure 4e). Release from HPMC-based ASDs peaked at ∼25 min and later dropped to 62%, likely due to crystallization. Enhanced release of *R*-PZQ over *RS*-PZQ was noted for SE HPMCAS-MF ASDs with a 40% DL (Figure 4f). Maximum drug release from both generic USP tablets and branded Biltricide tablets did not exceed 16% (Figure 4g), indicating that the preparation of PZQ ASDs with HPMCAS-MF and HPMC E5 LV can notably enhance the dissolution profile of the drug in both racemic and enantiopure forms, leading to supersaturated solutions.

3.5.2. Two-Stage Dissolution. In two-stage powder dissolution studies (Figure 5), maximum drug release of *RS*-PZQ from HPMCAS-MF ASDs was 18−25% in the acidic stage and 71−90% following the shift from pH 1.6 to pH 6.5. In the case of HPMC-based ASDs, maximum release of *RS*-PZQ on the order of 81% was observed in the acidic stage which decreased to 75% following the pH shift. For both USP and Biltricide tablets, release did not exceed 15% in the acidic stage and kept constant after the pH shifted. Both types of tablets were found to release faster than the ASDs in the acidic stage, an expected outcome given the poor solubility of HPMCAS-MF in aqueous media with pH below 6.[53−55]

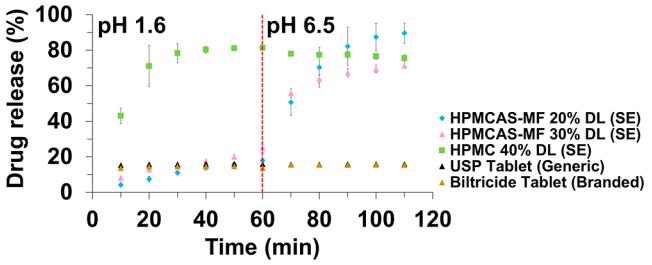


Figure 5. Two-stage dissolution testing of SE ASDs of *RS*-PZQ with HPMCAS-MF and HPMC E5 LV, USP tablets, and Biltricide tablets; target drug concentration = 1.5 mg/mL. Error bars indicate standard deviation (n = 3). Dashed red line represents the transition from gastric pH (1.6) to intestinal pH (6.5).

4. DISCUSSION

4.1. Polymer Selection for Formation of Stable PZQ ASDs. As a BCS class II drug with poor aqueous solubility and oral bioavailability,[5−9] PZQ is a fitting candidate for ASD preparation. A key consideration in selecting suitable polymeric carriers for preparing ASDs is the ability of polymers to effectively inhibit crystallization of amorphous drugs by suppressing nucleation and/or crystal growth.[51,52] In this work, *RS*-PZQ and *R*-PZQ were found to crystallize quickly in aqueous media in the absence of predissolved polymers (Figure 2a,b). In the presence of various pharmaceutically relevant polymers, the induction time for *RS*-PZQ was always prolonged, with cellulose-based polymers HPMCAS-MF and HPMC E5 LV found to suppress crystallization for the longest period of time (≥83 min) during data collection. Other grades of HPMCAS (HPMCAS-LF) and HPMC (HPMC PHARMACOAT 603) investigated with regards to their potency as crystallization inhibitors yielded shorter induction times than HPMCAS-MF and HPMC E5 LV, likely due to differences in functional group content and amphiphilicity between the different grades of the two polymers which affected their tendency to interact with nascent crystals. Based on these findings, HPMCAS-MF and HPMC E5 LV were identified as the most potent crystallization inhibitors for *RS*-PZQ and used to formulate ASDs via rotary evaporation and HME.

The propensity of HPMCAS and HPMC to be effective crystallization inhibitors for amorphous pharmaceutical systems is well established[52,56−59] and these polymers have commonly demonstrated superior inhibition profiles compared to noncellulose-based polymers. HPMCAS and HPMC have both proven to be effective crystallization inhibitors across a broad range of drugs with distinct physicochemical properties[60−63] and the results obtained herein further highlight their effectiveness for the purpose of suppressing drug crystallization. In addition to successfully inhibiting the crystallization of *RS*-PZQ in solution, HPMCAS-MF and HPMC E5 LV also proved to be potent crystallization inhibitors in the solid state as ASDs of *RS*-PZQ prepared using these two polymer systems remained physically stable for several months under accelerated-stability conditions of 40 °C and 75% RH (Figure 3h,i).

Due to their ability to suppress crystallization of *RS*-PZQ in aqueous solution more effectively than the rest of the polymers utilized in induction time experiments, as well as providing physical stabilization following ASD preparation, HPMCAS-MF and HPMC E5 LV were also investigated with regards to their ability to inhibit crystallization of *R*-PZQ (Figure 2b). While an inhibition effect was identified for both polymers in induction time experiments involving *R*-PZQ, the inhibition effect was significantly less pronounced relative to that observed in *RS*-PZQ experiments. The less-pronounced crystallization inhibition noted for HPMCAS-MF and HPMC E5 LV in the case of *R*-PZQ may be attributed to differences in the structural properties of *R*-PZQ and *RS*-PZQ. The most thermodynamically stable, commercial form of *RS*-PZQ is an anhydrate crystallizing in the triclinic *P*1 space group and all PZQ molecules present in the crystal structure exhibit the *syn* conformation with regards to the positioning of the carbonyl groups.[12] On the contrary, *R*-PZQ is only known to exist in hemihydrate and monohydrate forms crystallizing in the monoclinic *C*2 group and the PZQ molecules in the hydrated structures exhibit the *anti* conformation.[3,64] These conformational differences between the racemic and enantiopure forms of PZQ could directly impact the crystallization behavior of the compound in the presence of polymers by impacting the ability of the polymers to interact with the drug. Alternatively, interactions between one of the carbonyl groups of each *R*-PZQ molecule and water may reduce the ability of the drug molecules to interact with the polymer, subsequently reducing their ability to inhibit crystallization. In addition, chiral polymers such as HPMCAS and HPMC have been shown to interact stereoselectively with enantiomers in amorphous formulations.[65,66] Therefore, it is not unreasonable to speculate that these polymers interact more with *S*-PZQ, thereby better inhibiting crystallization of the racemic compound relative to *R*-PZQ.

4.2. Release Performance of PZQ ASDs. Powder dissolution studies of *RS*-PZQ ASDs prepared using HPMCAS-MF and HPMC E5 LV were performed using both single-stage and two-stage experimental protocols to develop an understanding of the impact of polymer type, ASD DL, drug concentration, sample preparation method, dissolution medium pH, and PZQ chirality on drug release from the selected polymer carriers.

4.2.1. Impact of Polymer Type, ASD DL, and Drug Concentration. At a target concentration of 667 μg/mL

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Mol. Pharmaceutics 2024, 21, 5285−5296

(Figure 4a), ASDs of *RS*-PZQ formulated with HPMCAS-MF consistently showed complete drug release in PBS (pH 6.5) when DLs of 20−50% were utilized. ASDs formulated using HPMC E5 LV also resulted in robust release of the racemic form of PZQ, with complete release achieved using DLs in the range of 20−40%. A drop in release performance was observed for HPMC-based ASDs when the DL was pushed to 50% although those ASDs still allowed for ∼86% of drug to be released. While complete drug release was noted for most of the ASD samples studied regardless of the polymer carrier used, release from HPMCAS-MF ASDs was generally faster, particularly at lower DLs (20 and 30%). The results obtained for the release of *RS*-PZQ from HPMCAS-MF and HPMC E5 LV clearly illustrates the propensity of these two polymer systems to act as carriers capable of facilitating the effective release of the drug. Furthermore, no "falling-of-the-cliff" effect[67] was noted as drug release never declined massively when the DL was increased for both types of *RS*-PZQ ASDs.

At a target concentration of 1.5 mg/mL (Figure 4b), which approximately corresponds to the amorphous solubility of *R*-PZQ, the release performance of HPMCAS-based ASDs of *RS*-PZQ gradually decreased from complete release to ∼83% as the DL increased from 20 to 40%. The observation of gradual decrease in drug release from HPMCAS-MF is in line with past observations[68] and suggests that the release is polymer controlled. For *R*-PZQ, overall release from HPMCAS-MF did not decrease with increasing DL but the release got slower during the early stages of dissolution as DL increased (Figure 4e,f). No evidence of a "falling-of-the-cliff" effect was observed with either *RS*-PZQ or *R*-PZQ HPMCAS-based ASDs.

4.2.2. Impact of the Sample Preparation Method. HME offers a cheaper and greener preparation route for the development of ASD formulations compared to solvent-based methods and is most suitable for preparing ASDs with components that are not sensitive to heat.[69] *RS*-PZQ has a melting point of ∼142 °C and does not degrade thermally upon melting,[70,71] making it an ideal candidate for formulating ASDs using HME. In order to achieve the highest possible degree of molecular mixing between *RS*-PZQ and HPMCAS-MF in this study, the drug and polymer were heated above their respective melting point and glass transition temperature[53] during ASD preparation.[72] The resulting ASDs exhibited complete release at 20 and 30% DL and this observation applied to target drug concentrations of both 667 μg/mL and 1.5 mg/mL (Figure 4c,d). At a high target concentration, the extruded ASDs showed slightly better release than SE ASDs at both DLs investigated. Our results highlight the potential of HME as an appropriate manufacturing method for the preparation of PZQ ASDs with robust release profiles. Although not investigated herein, we note that *R*-PZQ has a lower melting point than the racemic crystal (∼110 °C).[50]

4.2.3. Impact of Dissolution Medium pH. Two-stage dissolution experiments were pursued in this work to assess the impact of dissolution medium pH on the release profiles of *RS*-PZQ from HPMCAS-MF ASDs, HPMC E5 LV ASDs, and commercial tablets (Figure 5). These experiments were meant to simulate pH conditions applicable to oral drug administration via the gastrointestinal tract.[73] In the first stage of those experiments, which were all performed using a target drug concentration of 1.5 mg/mL, drug release was monitored under pH conditions simulating those of fasted-state gastric media (pH = 1.6), whereas in the second stage, the pH was shifted toward intestinal pH conditions (pH = 6.5). *RS*-PZQ ASDs comprising HPMCAS-MF showed poor release which did not exceed 25% under gastric conditions, an expected outcome considering that HPMCAS-MF is an enteric polymer with rather hydrophobic nature and limited solubility in solutions with a pH below 6.[53−55] Shifting the pH toward intestinal conditions allowed for improved release of HPMCAS-based ASDs up to 90% which is a small decrease compared to the complete or near-complete release observed for these ASDs in single-stage dissolution tests conducted at a pH of 6.5. The slightly worse release performance under intestinal conditions in the two-stage experiments might be attributable to a small extent of drug crystallization of undissolved ASD particles following their prolonged suspension in the acidic medium, a previously noted failure mechanism for HPMCAS-based ASDs.[74,75] This speculation requires further investigation. Unlike HPMCAS-MF ASDs, HPMC-based ASDs of *RS*-PZQ exhibited significantly better release in the acidic medium, which ultimately peaked at 81% within 50 min of dissolution testing. HPMC is known to be readily soluble in acidic conditions simulating the pH of the stomach;[76] therefore, the observation of improved PZQ release from HPMC E5 LV at a pH of 1.6 is not surprising. Given that PZQ is dosed with food, where the gastric pH is higher, the slightly impaired release observed from HPMCAS-based ASDs following an initial low pH stage may not be of concern, although future studies should be performed to better explore the pH sensitivity of the release.

4.2.4. Impact of Chirality. Chirality is a property of significant importance in the context of pharmaceutical manufacturing since more than half of all pharmaceuticals on the market are known to exhibit chirality.[77,78] While the vast majority of chiral pharmaceuticals in the past have reached the market in racemic form,[79] as is the case with PZQ, the adoption of enantiomerically pure drug products has become more prevalent in recent years.[80] Developing suitable and cost-effective formulations for commercial use of the therapeutically active enantiomer of PZQ has been identified as a priority[3] because of the advantages that a potential formulation of *R*-PZQ could offer in the context of improved biopharmaceutical performance, taste, and reduced side-effect occurrence. In this work, *R*-PZQ ASDs were formulated and compared with *RS*-PZQ ASDs to evaluate the ability of polymers to release the therapeutic enantiomer more efficiently than that of the commercial racemic form. Indeed, an enhanced release of *R*-PZQ from HPMCAS-MF ASDs was observed when a DL of 40% was used (Figure 4f). Promising results were also obtained at a lower DL of 30%, with *R*-PZQ and *RS*-PZQ ASDs with HPMCAS-MF showing similar release profiles. Enhanced release of *R*-PZQ could not be observed when HPMC-based ASDs were utilized and a notable drop in release (Figure 4e), which became apparent following 40 min of testing, hinted toward the occurrence of drug crystallization, an observation aligning well with the reduced crystallization inhibition propensity shown by HPMC E5 LV when used in induction time studies of *R*-PZQ. Thus, HPMCAS-MF was identified as the preferred polymer system for the purpose of achieving robust release of *R*-PZQ. The effect of chirality on the release properties of drugs from ASDs has not been investigated extensively, and, while the mechanism resulting in an improved release of *R*-PZQ from HPMCAS-MF at 40% DL requires further investigation, our results highlight the potential of HPMCAS-MF as a suitable carrier for the

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Mol. Pharmaceutics 2024, 21, 5285−5296

development of commercially viable formulations of the therapeutic enantiomer of PZQ.

4.2.5. Enhanced Release of PZQ ASDs over Commercial PZQ Tablets. The main goal of this work was to prepare ASDs of PZQ capable of releasing the drug more efficiently than commercial PZQ formulations. Through our experimental efforts, we were able to successfully formulate ASDs of both *RS*-PZQ and *R*-PZQ which showed notably enhanced drug release profiles compared to both generic and branded (Biltricide) PZQ tablets, which are currently available on the market. The commercial tablets investigated as part of our dissolution studies exhibited limited release which did not exceed 16% in single-stage experiments at pH 6.5 and nonsink conditions (Figure 4g). In similar studies performed using various HPMCAS-MF and HPMC-based ASDs prepared using *RS*-PZQ and *R*-PZQ (Figure 4a−f), complete or near-complete release (>90%) was observed with DLs as high as 40% (in the case of *R*-PZQ) at a target concentration corresponding roughly to the amorphous solubility of the therapeutic enantiomer, indicating a maximum PZQ release increase in the order of 6.25 times compared to commercial tablets. This is in line with the amorphous solubility advantage, which is around fivefold. While enhanced release of PZQ from solid dispersions had previously been noted in several studies,[9,45−48] this is the first instance where significant improvement in the release profile of the drug has been observed using ASDs comprising solely of the therapeutic *R*-enantiomer. Although pharmacokinetic studies aiming to assess the in vivo performance of PZQ ASDs are not reported herein, the expectation is that the improvement in the dissolution properties exhibited by PZQ ASDs will translate to an enhanced pharmacokinetic profile for the drug and ultimately lead to improved oral bioavailability. In the case of *R*-PZQ ASDs, that could lead to the establishment of an attractive formulation for commercial application since enantiopure ASD formulations may help overcome the known biopharmaceutical and compliance challenges associated with commercial PZQ tablets.

5. CONCLUSIONS

This work sought to identify suitable polymer systems for the development of ASD formulations of racemic and enantiopure PZQ with enhanced drug release profiles and to investigate the impact of various parameters on PZQ release. Crystallization induction time studies performed using a variety of pharmaceutical polymers assisted in identifying the cellulose-based polymers HPMCAS-MF and HPMC E5 LV as the most potent crystallization inhibitors of *RS*-PZQ. SE ASDs of *RS*-PZQ formulated with the above-mentioned polymers remained physically stable for several months upon storage under accelerated-stability conditions and yielded robust release profiles that were up to 6 times more favorable than those exhibited by both generic and branded PZQ tablets currently available on the market. *RS*-PZQ ASDs with HPMCAS-MF generally released the drug faster than HPMC-based ASDs did. HPMCAS-MF ASDs formulated using the therapeutic enantiomer *R*-PZQ were found to release either similarly well or better than HPMCAS-MF ASDs of *RS*-PZQ at DLs of 30 and 40%. While the exact mechanism behind the improved release performance of enantiopure PZQ ASDs and their long-term physical stability was not determined, the improved release performance exhibited by these ASDs under nonsink conditions has significant implications for the development of novel PZQ formulations of commercial interest. It is anticipated that *R*-PZQ ASDs will show improved pharmacokinetic and oral bioavailability properties compared to commercial PZQ tablets, and, because *R*-PZQ is mainly responsible for the drug's therapeutic efficacy and is generally not associated with its unwanted side effects, the development of commercial ASD formulations comprising the *R*-enantiomer could help overcome compliance issues that have plagued millions of people needing to receive PZQ to be treated and lead to improved treatment regimen for schistosomiasis.

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Notes

The authors declare no competing financial interest.

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