Balancing Solid-State Stability and Dissolution Performance of Lumefantrine Amorphous Solid Dispersions: The Role of Polymer Choice and Drug–Polymer Interactions

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ABSTRACT: Amorphous solid dispersions (ASDs) are of great interest due to their ability to enhance the delivery of poorly soluble drugs. Recent studies have shown that, in addition to acting as a crystallization inhibitor, the polymer in an ASD plays a role in controlling the rate of drug release, notably in congruently releasing formulations, where both the drug and polymer have similar normalized release rates. The aim of this study was to compare the solid-state stability and release performance of ASDs when formulated with neutral and enteric polymers. One neutral (polyvinylpyrrolidone−vinyl acetate copolymer, PVPVA) and four enteric polymers (hypromellose acetate succinate; hypromellose phthalate; cellulose acetate phthalate, CAP; methacrylic acid−methyl methacrylate copolymer, Eudragit L 100) were used to formulate binary ASDs with lumefantrine, a hydrophobic and weakly basic antimalarial drug. The normalized drug and polymer release rates of lumefantrine−PVPVA ASDs up to 35% drug loading (DL) were similar and rapid. No drug release from PVPVA systems was detected when the DL was increased to 40%. In contrast, ASDs formulated with enteric polymers showed a DL-dependent decrease in the release rates of both the drug and polymer, whereby release was slower than for PVPVA ASDs for DLs < 40% DL. Drug release from CAP and Eudragit L 100 systems was the slowest and drug amorphous solubility was not achieved even at 5% DL. Although lumefantrine−PVPVA ASDs showed fast release, they also showed rapid drug crystallization under accelerated stability conditions, while the ASDs with enteric polymers showed much greater resistance to crystallization. This study highlights the importance of polymer selection in the formulation of ASDs, where a balance between physical stability and dissolution release must be achieved.

KEYWORDS: amorphous solid dispersions, lumefantrine, polymer release, neutral polymer, enteric polymer

INTRODUCTION

Drug solubility is important for orally administered dosage forms to ensure that the desired plasma concentration to achieve therapeutic efficacy is reached. While 40% of new chemical entities in the current market are poorly soluble, approximately 90% of drugs in the development pipeline are classified as poorly soluble based on the Biopharmaceutics Classification System. This creates a significant challenge in the formulation of oral dosage forms. One example of a poorly soluble drug is lumefantrine, which has a reported crystalline solubility of 2.6 ng/mL in fasted state simulated intestinal fluid. Lumefantrine is an antimalarial drug used in combination with artemether for the treatment of multidrug resistant strains of Plasmodium falciparum malaria. Artemether serves as the rapid-acting drug to reduce the parasite biomass, while lumefantrine acts over a longer period to eliminate the residual parasites, thereby minimizing the risk of recrudescence. Approved by the United States Food and Drug Administration in 2008 and marketed as a fixed-dose oral combination of lumefantrine (120 mg) and artemether (20 mg) under the brand name Coartem, the treatment regimen consists of a three-day treatment schedule with a total of six doses. Four tablets are taken as a single initial dose, followed by four tablets again after 8 h, and then four tablets twice daily for the subsequent 2 days, to be taken with food. Overall, the treatment regime with Coartem involves a rather high pill burden, which could potentially contribute to patient non-adherence, therefore exacerbating the prevalence of drug-resistant malaria.

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A more pressing problem concerning the treatment of falciparum malaria with Coartem is treatment failure. Lumefantrine was reported to be slowly and erratically absorbed,\(^4\) with low and variable bioavailability contributing to interindividual fluctuations in pharmacokinetic profiles.\(^5,8\) Relative bioavailability of lumefantrine was noted to increase by a factor of 16 when taken with a high-fat meal compared to when taken in the fasted state.\(^7,8\) When administered incorrectly on an empty stomach, poor absorption and low plasma concentration of lumefantrine resulted in treatment failure.\(^7,8\) Additionally, with nausea and vomiting as common symptoms in malaria patients, the dependence of bioavailability on food intake could also increase the likelihood of treatment failure due to poor absorption.

Attempts to improve the bioavailability of lumefantrine have been made by formulating it into a self-nanoemulsifying delivery system,\(^3,9\) nanoparticles for oral and transdermal delivery,\(^1,4,11\) solid lipid microparticles,\(^12\) and solid lipid nanoparticles.\(^13\) A study with healthy volunteers reported a delivery,\(^10,11\) solid lipid microparticles,\(^12\) and solid lipid nanoparticles.\(^13\) A study with healthy volunteers reported a 24–48 fold increase in bioavailability when solid dispersion formulations of lumefantrine produced via hot-melt extrusion were administered in place of the marketed formulation.\(^2\) Additionally, higher bioavailability was also reported in subjects who were administered the medication in the fasted state. This suggests that lumefantrine could benefit from being reformulated as an amorphous solid dispersion (ASD) to be less dependent on food intake, thereby reducing the interindividual variability in bioavailability, achieving better treatment outcomes.

ASDs are comprised of an amorphous drug molecularly dispersed in a hydrophilic polymer matrix. This formulation approach holds great promise in dealing with solubility-limited absorption, and typically confers a bioavailability advantage in comparison to the crystalline drug. The dissolution of the higher energy amorphous form of the drug enables the formation of a supersaturated solution, which is maintained by the aid of a polymer acting as the crystallization inhibitor.\(^14\) The use of polymers with high glass transition temperatures (\(T_g\)) is especially beneficial when paired with drugs with low \(T_g\) to increase the overall \(T_g\) of the resultant dispersion through an antiplasticizing effect, so as to lower its molecular mobility and improve physical stability.\(^15\) However, the bioavailability of a given ASD is formulation dependent,\(^16,17\) where optimization of factors such as choice of polymer, manufacturing method and drug loading (DL) through thorough mechanistic understanding of the drug–polymer interactions at the molecular level is key to successful ASD formulation.

The two important aspects of an ASD formulation are its solid-state stability and the ability to achieve and maintain drug supersaturation upon ASD dissolution. Drugs in the metastable amorphous state are susceptible to recrystallization as the crystalline form is more thermodynamically stable. However, studies have shown that the risk of drug recrystallization can be mitigated through appropriate selection of the polymer\(^1\) and kinetic stabilization is conferred by formation of a miscible blend with a higher \(T_g\) polymer.\(^19,20\) In the case of drug release from ASBs, fast dissolution to yield supersaturated solutions results in an elevated free drug concentration and bioavailability enhancement. Additionally, the concentration of drug released from some formulations can exceed its amorphous solubility. In this case, the drug molecules can no longer exist as molecularly dissolved species in the bulk aqueous phase; rather, phase separation occurs to yield colloidal drug-rich droplets via liquid–liquid phase separation (LLPS).\(^21\) LLPS is desirable as the drug-rich droplets serve as a drug reservoir to replenish the drug removed through transport across a membrane to ensure that the maximum drug concentration in the bulk aqueous phase is always maintained.\(^22\) However, LLPS is typically observed only in formulations with low DL. Recent studies have reported that at low DL, drug release from an ASD is polymer-controlled, where the normalized release rates of both the drug and polymer are congruent and similar to one another.\(^23,24\) As the DL increases, a transition from polymer-controlled to drug-controlled dissolution results in an abrupt decrease in the drug release rate. In this case, the drug and polymer release are incongruent. The highest DL where congruent release is maintained is known as the limit of congruency (LoC).\(^25\) In previous studies, the LoC of drugs when formulated as ASBs with polyvinylpyrrolidone–vinyl acetate copolymer (PVPVA) ranged between 5–25% DL.\(^23–27\) The precise nature of this transition from congruent to incongruent release remains poorly understood, but recent studies have suggested that hydrogen bonding between drug and polymer in PVPVA-based ASD may be detrimental to dissolution performance relative to a comparable system where specific drug–polymer interactions are absent.\(^28,29\) Moreover, most studies evaluating the LoC concept to date have only evaluated binary ASBs formulated with PVPVA, and the applicability to ASBs with other polymers remains an outstanding question.

Herein, the suitability of enteric polymers as candidates to formulate ASDs of lumefantrine was evaluated and compared to ASDs prepared with the neutral polymer, PVPVA. Lumefantrine is a lipophilic (log \(P = 8.34\))\(^29\) and weakly basic drug (\(pK_a\) of tertiary amine = 8.73)\(^30\) with one hydrogen bond donor and two acceptor groups. ASDs of different DLs were prepared using the solvent evaporation method. The Wood’s intrinsic dissolution apparatus was used to monitor the release of lumefantrine and the polymer. The surface of the compacts after partial dissolution was characterized using Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy. Dynamic light scattering measurements were performed to detect the presence of drug-rich droplets. Solid-state stability of the ASBs under accelerated stability storage conditions was monitored using powder X-ray diffraction.

### MATERIALS AND METHODS

#### Materials

Lumefantrine was purchased from Gojira Fine Chemicals (Bradford Heights, OH). Hypromellose phthalate (HPMCP; HP-50) and hypromellose acetate succinate (HPMCAS; AQOAT AS-MF) were supplied by Shin-Etsu Chemicals (Tokyo, Japan). PVPVA (Kollidon VA 64) was supplied by BASF Corporation (Ludwigshafen, Germany). Methacrylic acid–methyl methacrylate copolymer (Eudragit L 100) was supplied by Evonik (Darmstadt, Germany), while cellulose acetate phthalate (CAP), phenol, and pyrene were purchased from Sigma-Aldrich (St. Louis, MO). Dichloromethane (DCM), methanol (MeOH), acetonitrile (ACN), dimethyl sulfoxide (DMSO), potassium phosphate monobasic, sodium hydroxide (NaOH), hydrochloric acid (HCl), potassium hydroxide (KOH), potassium chloride (KCl), and concentrated sulfuric acid were procured from Fisher Chemical (Fair Lawn, NJ). Ethanol (EtOH), 200 proof, was procured from Decon Laboratories (King of Prussia, PA). Trifluoro-
Acetic acid (TFA) was purchased from Acros Organics (Fair Lawn, NJ). The medium for all solubility and dissolution studies of lumefantrine was 50 mM pH 6.8 phosphate buffer, prepared by mixing 6.8 g of potassium phosphate monobasic and 112 mL of 0.2 M NaOH in ultrapure water to make up a final volume of 1 L, followed by titration with 1 M NaOH to pH 6.8. For quantification of PVPVA and Eudragit L 100, pH 7.4 phosphate buffer was prepared by dissolving phosphate buffer saline tablets (Research Products International, Mount Prospect, IL) in ultrapure water. The chemical structures of lumefantrine and the polymers used to prepare the ASDs are shown in Figure 1.

**METHODS**

**Crystalline and Amorphous Solubility Determination.**

**Crystalline Solubility Determination.** The crystalline solubility of lumefantrine was determined in 50 mM pH 6.8 phosphate buffer. Briefly, an excess amount of lumefantrine was added to the buffer equilibrated to 37 °C and stirred for 48 h. The excess solid was removed from the solution via ultracentrifugation at 35 000 rpm for 30 min at 37 °C using an Optima L-100 XP centrifuge (Beckman Coulter, Brea, CA) equipped with an SW 41 Ti swinging-bucket rotor. The concentration at which an increase in scattering was observed was noted as the amorphous solubility of lumefantrine.

**Amorphous Solubility Determination.** The amorphous solubility of lumefantrine was determined via the UV extinction and fluorescence spectroscopy methods.

**UV Extinction.** A scintillation vial containing 15 mL of 50 mM pH 6.8 phosphate buffer was placed in a water-jacketed beaker and pre-equilibrated to 37 °C. A 1 mg/mL stock solution of lumefantrine in DMSO was added to the buffer using a syringe pump (Harvard Apparatus, Holliston, MA) at a rate of 300 μL/min, with a stirring rate of 300 rpm employed to ensure homogeneity. A 1 cm path length dip probe attached to a 400 UV/vis spectrophotometer (SI Photonics, Tucson, AZ) was used to monitor for changes in scattering at 450 nm. The concentration at which an increase in scattering was observed was noted as the amorphous solubility of lumefantrine.

**Fluorescence Spectroscopy.** A 1 mg/mL lumefantrine stock solution was prepared with DMSO and added to 10 mL of 50 mM pH 6.8 phosphate buffer containing 0.2 μg/mL pyrene as the stationary phase, while the mobile phase comprised of ACN and 0.1% TFA in water prepared at a ratio of 70:30, v/v and eluted at a flow rate of 1.5 mL/min with the isocratic elution mode. For every analysis, 80 μL of the sample was injected. The column was maintained at 25 °C during analysis, and the detection was carried out using an ultraviolet (UV) detector at a wavelength of 335 nm. Under these conditions, the retention time of lumefantrine was approximately 4.8 min. A standard curve built with a linear regression model for the concentration range of 0.05–10 μg/mL yielded an R² value of 0.999.

![Figure 1. Chemical structures of (a) lumefantrine and the polymers used, (b) CAP, (c) HPMCP, (d) HPMCAS, (e) Eudragit L 100, and (f) PVPVA.](https://doi.org/10.1021/acs.molpharmaceut.1c00481)
the environmentally sensitive fluorescence probe. The buffer solution was pre-equilibrated to 37 °C. A series of lumefantrine supersaturated solutions was prepared to cover a final lumefantrine concentration range between 1 and 14 μg/mL. The solutions were then filled into a 1 cm quartz cuvette for measurement. Fluorescence spectroscopy measurements were performed using an RF-5301 PC spectrofluorometer (Shimadzu, Kyoto, Japan). The excitation wavelength used was 322 nm, while the emission range was between 350 to 450 nm. The excitation and emission slits were set to 10 and 3 nm, respectively.

Preparation of Lumefantrine ASDs via Rotary Evaporation. Lumefantrine–polymer binary ASDs were prepared by solvent evaporation using a Hei-VAP Core rotary evaporator (Heidolph Instruments, Schwabach, Germany) equipped with a water bath set to 45 °C. For ASDs containing PVPVA, lumefantrine and PVPVA were dissolved in DCM to prepare ASDs of 5, 10, 15, 20, 25, 35, 40, 45, and 50%, w/w DL. With HPMCAS and HPMCP, ASDs of 5, 10, 15, 20, 25, and 50%, w/w DL were prepared. ASDs of 5, 10, 25, and 50%, w/w DL were prepared for CAP and Eudragit L 100. Drug–polymer powder blends containing HPMCP and CAP were dissolved in 8:2 DCM/MeOH, v/v, while blends containing HPMCAS and Eudragit L 100 were dissolved in 1:1 DCM/MeOH, v/v and 1:1 DCM/EtOH, v/v, respectively. The solid content of all the samples was 20 mg/mL. Upon evaporation of the solvent, the ASD was subjected to a secondary drying step in a vacuum oven for at least 24 h. The ASD was subsequently transferred into a grinding vial and pulverized with a 6750 Freezer/Mill cryogenic impact mill (SPEX SamplePrep, Metuchen, NJ). The pulverized ASD powder was passed through a 250 μm sieve, and the undersize fraction was collected for further analysis.

Thermal Analysis. Crystalline lumefantrine and the binary ASDs prepared were analyzed using a Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE) connected to an RCS 90 refrigerated cooling system (TA Instruments, New Castle, DE). Dry nitrogen was purged into the sample chamber at 50 mL/min. The differential scanning calorimeter was calibrated for temperature using indium and tin, while enthalpy calibration was performed with indium. For each analysis, approximately 3–5 mg of the sample was accurately weighed and sealed in a Tzero aluminum sample pan (TA Instruments, New Castle, DE). Crystalline lumefantrine was first equilibrated to 25 °C, then heated to 150 °C, cooled to −30 °C, and reheated to 150 °C at 10 °C/min to determine its melting point and θf.

Modulated differential scanning calorimetry (DSC) was used to analyze the rotary-evaporated ASDs. Each sample was first equilibrated to −10 °C, followed by heating at a rate of 2 °C/min to 220 °C with a modulation of 1 °C every 60 s. Using the TA Universal Analysis software (TA Instruments, New Castle, DE), the reversible heat flow data was separated from the irreversible signal and used to determine the Tgs of the ASDs.

Release Studies of Lumefantrine ASDs. Surface Normalized Dissolution of Lumefantrine ASD Compacts. Surface normalized dissolution of lumefantrine ASD compacts was performed using the Wood’s intrinsic dissolution apparatus (Quality Lab Accessories, Telford, PA) in 50 mM pH 6.8 phosphate buffer. For each DL, at least three individual compacts were analyzed, and the results averaged. The dissolution apparatus consists of an 8 mm die, a punch, a surface plate, as well as a shaft and die holder to mount the die onto a stirrer. To prepare the ASD compact for dissolution studies, the die was secured to the surface plate, and 50 mg of ASD powder was carefully weighed and poured into the die cavity. The punch was then inserted into the die cavity, and the powder was compressed at 1500 psi for 1 min using a benchtop manual hand press (Carver, Wabash, IN). The die was subsequently removed from the surface plate and mounted onto the die holder. The release experiments were performed using a Vision G2 Classic 6 dissolution tester (Teledyne Instruments, Chatsworth, CA) equipped with a thermostatically controlled water bath set to 37 °C. The exposed surface of the compact was immersed in 100 mL of deaerated dissolution medium pre-equilibrated to 37 °C, and the shaft was set to rotate at 100 rpm. At predetermined time points, aliquots of dissolution medium were withdrawn and replenished with an equal volume of fresh medium. The aliquots were analyzed for drug and polymer concentrations. The concentration of lumefantrine was determined using reversed-phase HPLC. Dissolution experiments were also carried out on neat amorphous lumefantrine and the five polymers for reference.

Preparation of Neat Amorphous Lumefantrine. Approximately 20 mg of crystalline lumefantrine powder was melted in a hot air oven at 180 °C for 5 min and immediately poured into the die cavity of the intrinsic dissolution apparatus die. The die was then placed under reduced pressure prior to dissolution.

Quantification of Polymers. PVPVA and Eudragit L 100 were quantified using size exclusion chromatography (SEC–HPLC), while HPMCAS, HPMCP, and CAP were quantified using colorimetric analysis.

Quantification of PVPVA and Eudragit L 100 Release. PVPVA was quantified with an A2500, aqueous GPC/SEC column (6 μm particle size, 8 mm × 300 mm, molecular weight exclusion limit of 10 000 Da for pullulan, Malvern Panalytical, Worcestershire, UK) as the stationary phase. The mobile phase comprised of 80% 50 mM pH 7.4 buffer and 20% MeOH, v/v eluted at a flow rate of 0.5 mL/min. The injection volume used was 10 μL, and PVPVA, with a retention time of approximately 10.8 min, was detected using a UV detector at a detection wavelength of 210 nm. A calibration curve encompassing the concentration range of 1–1000 μg/mL of PVPVA yielded an R² value of 0.999 when modeled with the linear regression model.

For the quantification of Eudragit L 100, the mobile phase used was 75% 25 mM pH 7.4 buffer and 25% ACN, v/v, eluted at a flow rate of 1 mL/min. For quantification, 20 μL of the sample was injected, and a detection wavelength of 210 nm was used to detect the peak corresponding to Eudragit L 100 at a retention time of 5 min. A calibration curve ranging from 1–200 μg/mL of Eudragit L 100 (R² = 0.999) was used to quantify the amount of polymer released during dissolution.

Quantification of HPMCAS, HPMCP, and CAP Release. Colorimetric analysis was performed on aliquots withdrawn from the dissolution medium to quantify the release of HPMCAS, HPMCP, and CAP from the ASD compacts. Briefly, 10 μL of phenol was added to 400 μL of dissolution sample, followed by the rapid addition of 1 mL of concentrated sulfuric acid. The sample was then mixed using a vortex mixer and left to stand for at least 1 h before colorimetric analysis with a UV-1600 PC UV/vis spectrophotometer (VWR International, Radnor, PA) at 490 nm.
calibration curve ranging from 1–100 μg/mL (R² = 0.999) was prepared. Samples containing polymer concentrations higher than 100 μg/mL were diluted appropriately with buffer before the addition of phenol and concentrated sulfuric acid.

**Fourier Transform Infrared (FTIR) Spectroscopy.** Attenuated Total Reflectance Spectroscopic (ATR) Analysis of Neat Polymers and ASD Powders. FTIR analysis was performed with a Vertex 70 IR spectrophotometer (Bruker Optics, Billerica, MA) equipped with a Golden Gate ATR accessory (Specac, Fort Washington, PA). Spectra of samples were collected between 4500 and 600 cm⁻¹ at a resolution of 4 cm⁻¹. Dry, carbon dioxide (CO₂)-free air was continuously flushed through the ATR unit and sample chamber to avoid interference from moisture and CO₂. A background scan was taken before sample measurement. For each measurement, 32 scans were coadded by the OPUS software (Version 7.2, Bruker Optics, Billerica, MA) to produce the final spectrum. Triplicate measurements were performed for each sample, and the results were averaged.

**Preparation of Thin Films for FTIR Spectroscopy.** Lumefantrine and PVPVA were separately dissolved in DCM and MeOH to prepare 100 mg/mL stock solutions. Lumefantrine–PVPVA solution mixtures containing 10, 20, and 50% drug were prepared by combining fixed volumes of lumefantrine and PVPVA stock solutions to achieve a final solution with a 100 μg/mL solid content. The mixtures were spin-coated on zinc selenide (ZnSe) windows (Harrick Scientific Corporation, Ossining, NY) using a KW-4A spin coater (Chemat Technology, Northridge, CA). To each ZnSe window, 50 μL of the PVPVA or lumefantrine–PVPVA solution was deposited and spun for 15 s at 500 rpm followed by 45 s at 2000 rpm. For each sample, 128 scans were collected between 4500 and 600 cm⁻¹ for both the background and samples at a resolution of 4 cm⁻¹. To ensure that the spin-coated films were completely dry and devoid of water, repeated measurements of the thin films were made, and the wavenumbers corresponding to the carbonyl groups of PVPVA (1736 and 1684 cm⁻¹, which correspond to the vinyl acetate and vinlypyrrolidone carbonyl groups, respectively) were continuously monitored until no further change was observed for at least three continuous measurements taken at least 5 min apart.

**Powder X-ray Diffraction (PXRD).** A Rigaku SmartLab diffractometer (Rigaku Americas, The Woodlands, TX) operating at 40 kV and 44 mV was used to collect PXRD patterns in Bragg–Brentano mode with a Cu-κα radiation source and D/tek ultra detector. Each sample was placed on a glass sample holder, and measurements were performed from 4°–40° 2θ using a step size of 0.02° and a scan rate of 4°/min.

**Dynamic Light Scattering (DLS).** The particle size of the drug-rich colloidal species generated during the ASD release studies was measured using DLS. A 1.5 mL aliquot of dissolution medium was transferred into a polystyrene disposable cuvette after 2 h and analyzed using a Nano-ZS Zetasizer (Malvern Instruments, Worcestershire, UK). Particle size measurements were performed via DLS with a backscatter detector set at an angle of 173°. Triplicate measurements were obtained, and the results averaged. For all the measurements reported, the polydispersity index (PDI) was less than 0.2.

**X-ray Photoelectron Spectroscopy (XPS).** The compacts prepared with 25% DL ASDs before and after dissolution (30 min for ASDs containing enteric polymers and 10 min for PVPVA-based ASD) were manually ejected from the die, and the chemical composition of the compact surface was evaluated using XPS.

XPS data were obtained using a Kratos Axis Ultra DLD imaging spectrometer with monochromatic Al Kα radiation (1486.6 eV) at the constant pass energies (PE) of 20 and 160 eV for high-resolution and survey spectra, respectively. A commercial Kratos charge neutralizer was used to avoid the nonhomogeneous electric charge of the nonconducting sample and to achieve better resolution. Binding energy (BE) values refer to the Fermi level, and the energy scale was calibrated using Au 4f7/2 at 840.6 eV and Cu 2p3/2 at 932.67 eV. The compacts were placed on a stainless-steel sample holder bar using a double-sided adhesive Cu tape. XPS data were analyzed with the CasaXPS software (www.casaxps.com). Prior to data analysis, the C–C component of the C 1s peak was set to a binding energy of 284.8 eV to correct for charge on each sample. Curve-fitting was performed following a Shirley background subtraction using Gaussian/Lorentzian peak shape (the protonated N 1s component) and the peak obtained from the reference compounds (the N 1s peak of lumefantrine and PVPVA). The atomic concentrations of the elements in the near-surface region were estimated after a Shirley background subtraction adjusting on the corresponding Scafiled atomic sensitivity factors and inelastic mean free path (IMFP) of photoelectrons using standard procedures in the CasaXPS software assuming a homogeneous mixture of the elements within the information depths (~10 nm).

**Potentiometric Titration of the Enteric Polymers.** HPMCAS, HPmCp, and Eudragit L 100 were oven-dried at 105 °C for 30 min and cooled overnight in a desiccator over calcium sulfate under reduced pressure. CAP was similarly dried in a desiccator over calcium sulfate under reduced pressure. The polymers were dispersed in 40 mL of deionized water. The amount of polymer added was calculated based on their respective theoretical acid content so that the concentration of the acid moiety present corresponded to ~2.5 mmol/L. To each sample, 260 μL of 0.5 M NaOH was added and stirred overnight to completely dissolve the polymer. Potentiometric titration was performed with a calibrated sympHony combination pH probe (VWR International, Radnor, PA) connected to a B10P benchtop pH meter (VWR International, Radnor, PA) with 0.1 M HCl as the titrant. The pH probe was immersed in the polymeric solution, and a fixed amount of titrant was added. With continuous stirring, the change in pH value was monitored after each titrant addition until no further change was observed for at least 5 min. The value was then recorded as the equilibrium pH value corresponding to the amount of titrant added.

To determine the titration end point, at least five equilibration points were fitted to a polynomial equation (R² = 0.999) using the Curve Fitting app in Matlab (R2020b, The MathWorks, Natick, MA). A second derivative was then applied to the fitted equation. Through a plot of the second derivative (Δ(ΔpH)/ΔV²) against the volume of titrant added, the volume corresponding to the point where the second derivative curve crossed the abcissa was taken as the titration end point. The total amount of 0.1 M HCl required to neutralize the carboxylic acid groups in each polymer was determined by subtracting the volume corresponding to the second titration end point from the first. The first end point corresponded to the neutralization of excess NaOH added. The data points from between the two titration end points were further converted to the fraction of ionized group, with
the first end point and second end point corresponding to the pH where the polymer was fully ionized and un-ionized, respectively. For each polymer, the pH value was taken as the pH where 50% of the ionizable groups of the polymer were neutralized.

Preparation of Polymer Solutions At Different pH Conditions. The pH-dependent solubility of the enteric polymers was determined from pH 1.7 to pH 5.5. A stock solution of ~1 mg/mL polymer was prepared by dissolving a preweighed amount of polymer in basified 0.15 M KCl. 0.5 M KOH was used as the base to dissolve the polymers. The solution was stirred overnight to ensure that the polymer was fully dissolved. The polymer solution was aliquoted into 20 mL scintillation vials and stirred at 300 rpm. A calibrated symphony combination pH probe (VWR International, Radnor, PA) connected to a B10P benchtop pH meter (VWR International, Radnor, PA) was added in the polymer solution, and 0.1 M HCl was added gradually until the desired pH was achieved on stirring for at least 5 min. Stirring was then stopped, and the pH was monitored for another 5 min. This process was repeated until no change in pH was observed for at least 5 min with and without stirring, respectively. The polymer solution (or suspension, if precipitation of the polymer was observed) was then centrifuged with a mySPIN12 mini centrifuge (Thermo Fischer Scientific, Waltham, MA) at 10 000 rpm for 5 min. The supernatant was carefully withdrawn with a syringe and filtered through a 25 mm diameter 0.2 μm PTFE syringe filter (VWR International, Radnor, PA) before quantification. A standard curve built with a linear regression model for the concentration range of 1–200 μg/mL yielded an R² value of 0.999 for all the polymers.

Quantification of HPMCAS and Eudragit L 100. HPMCAS and Eudragit L 100 were quantified using the methods used for polymer quantification in the ASD release studies.

Quantification of HPMCP and CAP. HPMCP and CAP were quantified spectrophotometrically with a Cary 300 UV/vis spectrophotometer (Agilent Technologies, Santa Clara, CA) at 281 nm.

Results

Crystalline and Amorphous Solubility of Lumefantrine. The crystalline solubility of lumefantrine in 50 mM pH 6.8 phosphate buffer at 37 °C was <50 ng/mL (which was the quantification limit of the analytical method used). The amorphous solubility value of lumefantrine using the UV extinction method was 6.6 ± 0.5 μg/mL and was in good agreement with the value obtained through fluorescence spectroscopy (~6 μg/mL).

Thermal Analysis. DSC was used to classify the crystallization tendency of lumefantrine. Based on the DSC thermogram, lumefantrine was found to exhibit Class III behavior,33 where observable crystallization was absent during a heating/cooling/heating cycle. The onset melting temperature of lumefantrine was 127.9 °C, and the onset Tg was 19.7 ± 0.2 °C.

The Tg of the various dispersions are summarized in Table 1. Apart from the HPMCAS ASD with 50% DL, all the ASDs prepared showed a single Tg with no melting events, indicating that the drug and polymer were in a molecularly dispersed amorphous state. The melting endotherm observed for the 50% DL HPMCAS dispersion suggests some recrystallization during heating in the differential scanning calorimeter.

Dispersion Crystallinity. The PXRD patterns of the ASDs showed that all the dispersions were X-ray amorphous after preparation (Figure 2a,e,g,i). When the dispersions were stored in open dish accelerated stability conditions of 40 °C/75% RH, ASDs formulated with PVPVA were least stable under the accelerated stability conditions, with dispersions of 50%, 25%, 10%, and 5% DL showing small peaks corresponding to crystalline lumefantrine after 1, 2, 4, and 8 weeks, respectively (Figure 2b). Small lumefantrine crystalline peaks were also observed in the HPMCAS, HPMCP, and Eudragit L 100 ASDs with 50% DL after 1 week (Figure 2d), 32 weeks (Figure 2f), and 8 weeks (Figure 2j), respectively. For lumefantrine–CAP ASDs, peaks were observed in 5% DL ASDs after 1 week of storage, while ASDs with 10 and 25% DL also showed crystalline peaks after 4 and 16 weeks, respectively (Figure 2h). This observation was intriguing for two reasons: first, the peak positions did not coincide with those found in crystalline lumefantrine, and second, the appearance of crystalline peaks indicative of product failure first occurred in the ASD with the lowest DL. To investigate further, neat CAP pellets were pulverized into a fine powder with a cryogenic impact mill, and the PXRD pattern was collected. As shown in Figure 2h, the cryomilled neat CAP contained crystalline material, where the peaks coincided with those observed in the ASDs. Given that these diffraction peaks arise from the neat polymer, they are clearly not related to drug crystallization. For ASDs, no crystalline drug peaks were observed, except in the 50% DL ASD, which showed a small crystalline peak at 23.3° after 40 weeks. All lumefantrine–CAP ASDs stored at room temperature with desiccant remained X-ray amorphous for up to 36 weeks (data not shown).

Release Profiles of Lumefantrine ASDs. The release profiles of both lumefantrine and polymer from ASDs at different DLs are shown in Figure 3. For neat amorphous lumefantrine, no release was detected in solution up to 2 h. Given that the HPLC detection limit for lumefantrine was approximately 50 ng/mL, the dissolution rate of amorphous lumefantrine is <0.08 μg·min⁻¹·cm⁻².

Surface Normalized Dissolution of Lumefantrine–PVPVA ASDs. For lumefantrine–PVPVA ASDs ranging from 5–35%
Figure 2. X-ray diffraction patterns of lumefantrine binary ASDs formulated with (a) PVPVA, (c) HPMCAS, (e) HPMCP, (g) CAP, and (i) Eudragit L 100 immediately after rotary evaporation. Some formulations of (b) PVPVA, (d) HPMCAS, (f) HPMCP, (h) CAP, and (j) Eudragit L 100 showed crystalline drug peaks after storage at 40 °C/75% RH.
Figure 3. Release profiles of (a) lumefantrine and (b) PVPVA from lumefantrine−PVPVA ASDs, (c) lumefantrine and (d) HPMCAS from lumefantrine−HPMCAS ASDs, (e) lumefantrine and (f) HPMCP from lumefantrine−HPMCP ASDs, (g) lumefantrine and (h) CAP from lumefantrine−CAP ASDs, and (i) lumefantrine and (j) Eudragit L 100 from lumefantrine−Eudragit L 100 ASDs with different DLs. The red dashed line represents the amorphous solubility of lumefantrine.
DL, drug release was rapid and led to a released concentration higher than amorphous solubility, with the extent of release reaching a plateau at around 25 min (Figure 3a). The release extent was $\sim 70\%$ or greater for all DLs up to 35\% DL. It was also observed that the ASD with 35\% DL showed a short lag time of about 10 min, followed by rapid drug release to a concentration in excess of the amorphous solubility. At this DL, the amount of lumefantrine released after 25 min was approximately 20 times higher than its amorphous solubility. The dissolution medium changed with time from a clear solution to having a cloudy appearance with a bluish tinge, which is characteristic of the formation of drug-rich colloid particles.21 Thus, the measured solution concentration reflected both molecularly dissolved lumefantrine and lumefantrine present in drug-rich colloids.

| polymer | % DL | polymer (mg·min$^{-1}$·cm$^{-2}$) | lumefantrine (mg·min$^{-1}$·cm$^{-2}$) | ratio (polymer/drug) |
|---------|------|---------------------------------|--------------------------------------|----------------------|
| PVPVA   |      |                                 |                                      |                      |
| PVPVA alone | 4.58 (0.06) | N/A                              | N/A                                  | N/A                  |
| 5       | 4.49 (0.25) | 3.68 (0.39)                      | 1.22                                 |                      |
| 10      | 4.89 (0.25) | 3.15 (0.06)                      | 1.55                                 |                      |
| 15      | 4.68 (0.27) | 3.92 (0.24)                      | 1.19                                 |                      |
| 20      | 4.78 (0.18) | 3.79 (0.07)                      | 1.26                                 |                      |
| 25      | 4.88 (0.30) | 3.75 (0.25)                      | 1.30                                 |                      |
| 35      | 4.91 (0.75) | 3.64 (0.37)                      | 1.35                                 |                      |
| 40      | 0.21 (0.01) | below quantification limit       | N/A                                  |                      |
| 45      | 0.04 (0.03) | below quantification limit       | N/A                                  |                      |
| 50      | 0.004 (0.001) | below quantification limit   | N/A                                  |                      |
| HPMCAS  |      |                                 |                                      |                      |
| HPMCAS only | 0.79 (0.0004) | N/A                              | N/A                                  | N/A                  |
| 5       | 0.67 (0.03) | 0.61 (0.05)                      | 1.09                                 |                      |
| 10      | 0.42 (0.03) | 0.38 (0.02)                      | 1.11                                 |                      |
| 15      | 0.15 (0.01) | 0.15 (0.01)                      | 1                                    |                      |
| 20      | 0.10 (0.01) | 0.06 (0.01)                      | 1.67                                 |                      |
| 25      | 0.048 (0.002) | 0.033 (0.002)                  | 1.45                                 |                      |
| 50      | 0.001 (0.001) | 0.002 (0.001)                 | 5                                    |                      |
| HPMCP   |      |                                 |                                      |                      |
| HPMCP only | 0.87 (0.02) | N/A                              | N/A                                  | N/A                  |
| 5       | 0.72 (0.15) | 0.72 (0.05)                      | 1                                    |                      |
| 10      | 0.46 (0.05) | 0.45 (0.11)                      | 1.02                                 |                      |
| 15      | 0.27 (0.002) | 0.26 (0.01)                    | 1.04                                 |                      |
| 20      | 0.074 (0.003) | 0.071 (0.002)                  | 1.04                                 |                      |
| 25      | 0.021 (0.006) | 0.017 (0.001)                 | 1.24                                 |                      |
| 50      | 0.007 (0.004) | 0.002 (0.0006)               | 5                                    |                      |
| CAP     |      |                                 |                                      |                      |
| CAP only | 0.56 (0.03) | N/A                              | N/A                                  | N/A                  |
| 5       | 0.25 (0.08) | 0.15 (0.005)                     | 1.67                                 |                      |
| 10      | 0.19 (0.03) | 0.09 (0.02)                      | 2.11                                 |                      |
| 15      | 0.021 (0.003) | 0.021 (0.003)                 | 1                                    |                      |
| 25      | below quantification limit | below quantification limit       | N/A                                  |                      |
| 50      | below quantification limit | below quantification limit       | N/A                                  |                      |
| Eudragit L 100 | 0.23 (0.002) | N/A                              | N/A                                  | N/A                  |
| Eudragit L 100 only | 0.23 (0.002) | N/A                              | N/A                                  | N/A                  |
| 5       | 0.09 (0.04) | 0.07 (0.03)                      | 1.29                                 |                      |
| 10      | 0.038 (0.009) | 0.031 (0.008)                  | 1.23                                 |                      |
| 15      | 0.015 (0.002) | 0.013 (0.001)                 | 1.15                                 |                      |
| 25      | below quantification limit | below quantification limit       | N/A                                  |                      |
| 50      | below quantification limit | below quantification limit       | N/A                                  |                      |

aStandard deviations are shown in parentheses, where $n = 3$. DL, drug release was rapid and led to a released concentration higher than amorphous solubility, with the extent of release reaching a plateau at around 25 min (Figure 3a). The release extent was $\sim 70\%$ or greater for all DLs up to 35\% DL. It was also observed that the ASD with 35\% DL showed a short lag time of about 10 min, followed by rapid drug release to a concentration in excess of the amorphous solubility. At this DL, the amount of lumefantrine released after 25 min was approximately 20 times higher than its amorphous solubility. The dissolution medium changed with time from a clear solution to having a cloudy appearance with a bluish tinge, which is characteristic of the formation of drug-rich colloid particles.21 Thus, the measured solution concentration reflected both molecularly dissolved lumefantrine and lumefantrine present in drug-rich colloids. The surface normalized dissolution rate of lumefantrine in these ASDs was between 3.1–3.9 mg·min$^{-1}$·cm$^{-2}$ (Table 2). Upon increasing the DL to 40%, drug release was minimal and unquantifiable.

The surface normalized dissolution rate of neat PVPVA was 4.58 ± 0.06 mg·min$^{-1}$·cm$^{-2}$. The PVPVA release rate for lumefantrine–PVPVA ASDs ranging from 5–35\% DL was between 4.5–4.9 mg·min$^{-1}$·cm$^{-2}$. Similar to previous findings,24,25,34 the polymer release rates from the ASDs remained similar to that of the neat PVPVA (Figure 4a). A drastic reduction in polymer release rate was observed for ASDs with
40, 45, and 50% DL (Table 2). For the ASDs ranging from 5−35% DL, the ratio between the surface normalized release rates of polymer and drug ranged from 1.2−1.6. The similarity in the normalized release rates between lumefantrine and PVPVA suggests that, at these DLs, the overall dissolution of the ASD was controlled by PVPVA, otherwise known as polymer-controlled dissolution.

Surface Normalized Dissolution of Lumefantrine−HPMCAS and Lumefantrine−HPMCP ASDs. As shown in Figure 3c,e, drug release from lumefantrine−HPMCAS and lumefantrine−HPMCP ASDs increased linearly with time over 2 h. Drug release exceeded the amorphous solubility for both ASDs with 5, 10, 15, and 20% DL. At 5, 10, and 15% DL, lumefantrine−HPMCP ASDs consistently outperformed lumefantrine−HPMCAS, where a higher release of lumefantrine was observed for ASDs of the same DL. For lumefantrine−HPMCP ASDs, the extent of drug release was ∼78%, 62%, and 26% for 5, 10, and 15% DL formulations, respectively, while...
∼64%, 40%, and 16% of lumefantrine were released from lumefantrine–HPMCAS ASDs after 2 h. However, at 20% DL, the amount of drug released from the lumefantrine–HPMCP ASD after 2 h of dissolution was slightly lower than that of the lumefantrine–HPMCAS ASD (∼10% vs ∼7%). Drug release from both types of ASDs with 25 and 50% DL was slow and did not reach the amorphous solubility. For 50% DL ASDs, drug release could only be quantified after 1 h of dissolution.

**Table 3. Z-Average Diameter of the Drug-Rich Droplets Generated during ASD Dissolution**

| ASD sample | 5% DL   | 10% DL  | 15% DL  | 20% DL  | 25% DL  | 35% DL  |
|------------|---------|---------|---------|---------|---------|---------|
| HPMCAS     | 128 (2) | 122 (2) | 123 (6) | 141 (7) | c       | b       |
| HPMCP      | 80 (2)  | 86.5 (0.2) | 92 (1)  | 91 (4)  | c       | b       |
| PVPVA      | 209.4 (0.8) | 194.9 (0.9) | 238 (10) | 232 (7) | 193 (1) | 244 (12) |

*Standard deviations are shown in parentheses, where n = 3. ASD not prepared. PDI was too high for data to be meaningful as drug concentration was lower than amorphous solubility.*

**Figure 5.** ATR-FTIR spectra of the carbonyl region of (a) PVPVA, (b) HPMCAS, (c) HPMCP, (d) CAP, and (e) Eudragit L 100 lumefantrine binary ASDs, with neat polymer and amorphous lumefantrine spectra as a reference. The dashed black line denotes the peak position of the neat polymer.
Overall, the surface normalized dissolution rates of these binary ASDs showed a DL-dependent decrease (Figure 4b,c). When formulated as binary ASDs with lumefantrine, the surface normalized dissolution rate of both HPMCAS and HPMCP showed a decline as DL increased (Figure 4b,c). A comparison of the drug and polymer normalized release rates for these binary ASDs showed that a ratio of ∼1 was maintained for lower DL ASDs (Table 2). In the case of lumefantrine–HPMCP ASDs, this was observed when the DL was between 5−20%. This suggests that despite the steep decline in the release rates of both drug and polymer as DL was increased, the drug and polymer were still releasing at similar normalized rates. However, as DL increased, the ratio between the surface normalized release rates of polymer and drug increased, indicating that the release of HPMCP was much faster compared to that of lumefantrine. In the case of HPMCAS ASDs, the ratio between the surface normalized release rates of polymer and drug started deviating from ∼1 when DL was increased to 20% and beyond.

Surface Normalized Dissolution of Lumefantrine–CAP and Lumefantrine–Eudragit L 100 ASDs. As shown in Figure 3g,i, drug release from all the ASDs formulated with CAP and Eudragit L 100 did not reach amorphous solubility after 2 h. Drug release from 25 and 50% DL was below the quantification limit. Likewise, the polymer release from the ASDs at these DLs was also below the quantification limit. The normalized release rates of neat CAP and Eudragit L 100 were much lower than those of HPMCP and HPMCAS; when formulated as binary ASDs, a further decrease in the normalized release rates of the polymers was observed (Figure 4d,e). The normalized release rates of both polymers were consistently higher than that of the drug, even at a low DL of 5%.

Particle Size of The Drug-Rich Droplets Formed during Dissolution. Dynamic light scattering analysis of the dissolution medium was performed to assess the size of any drug-rich droplets present. Drug-rich droplets formed as a result of LLPS have been reported to have initial sizes in the range of 50−500 nm. DLS analysis of the dissolution

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**Figure 6.** FTIR spectra of the carbonyl region of (a) PVPVA, (b) HPMCAS, (c) HPMCP, (d) CAP, and (e) Eudragit L 100 ASD (dashed line) and the compacts after 2 h dissolution (solid line). The spectrum of neat amorphous lumefantrine is shown for comparison.
medium after 2 h showed that the hydrodynamic diameter of the drug-rich phase generated from lumefantrine−PVPVA ASDs was around 200−250 nm, while the drug-rich droplets generated from lumefantrine−HPMCAS and lumefantrine−HPMCP ASDs were smaller (Table 3). The size of the drug-rich droplets generated from lumefantrine−HPMCP ASDs was between 80−90 nm, while lumefantrine−HPMCAS ASDs generated drug-rich droplets ranging from 120−140 nm in size. For lumefantrine−CAP and lumefantrine−Eudragit L 100 ASDs, a high PDI was reported in all DLS measurements, which indicated the absence of drug-rich droplets, consistent with release studies which showed that the amorphous solubility was not reached over the experimental period.

FTIR Analysis. The region corresponding to the carbonyl stretching of the polymers is shown in Figure 5, for spectra obtained using ATR sampling. Different extents of blue shifts were observed in the carbonyl region of all the dispersions prepared. The peaks at 1730 and 1670 cm\(^{-1}\) corresponded to the vinyl acetate and vinylpyrrolidone groups in PVPVA, respectively. For lumefantrine−PVPVA ASDs, a modest 2 cm\(^{-1}\) blue shift was observed for the peak corresponding to the vinyl acetate group when DL was increased to 25%. No further peak shift was observed when DL was further increased. A gradual blue shift was observed for the peak corresponding to the vinylpyrrolidone group when DL was increased, where a 6 cm\(^{-1}\) shift in wavenumber was recorded for the 50% DL ASD. This blue shift most likely reflected a decrease in water content with increased DL.

To eliminate the contribution of water−PVPVA interactions, which may impact the ATR measurements, thin films containing lumefantrine−PVPVA were prepared and continuously purged with dry, CO\(_2\)-free air during measurement to rigorously dry the samples. As shown in Figure S1, the peak positions of the vinylpyrrolidone and vinyl acetate carbonyl groups did not shift as DL was increased. This shows that lumefantrine does not interact with PVPVA via hydrogen bonding with the carbonyl groups.

A single well-resolved peak was observed in the carbonyl region for HPMCAS, HPMCP, and CAP. In the case of Eudragit L 100, a broad band spanning approximately 20 cm\(^{-1}\) was observed. The broad band observed in the FTIR spectrum of Eudragit L 100 is postulated to be the result of an overlap of the poorly resolved carboxylic acid and ester carbonyl bands. A peak shift to higher wavenumbers in the carbonyl region was also observed for the binary ASDs with enteric polymers. As these polymers contain carboxylic acid moieties, they are likely able to self-associate via the formation of hydrogen bonds. The blue shift observed with the introduction of lumefantrine is therefore suggestive of a change in hydrogen bonding within the polymer through the incorporation of lumefantrine. A modest 2−6 cm\(^{-1}\) blue shift was observed in lumefantrine−HPMCAS and lumefantrine−HPMCP ASDs. Lumefantrine−CAP and lumefantrine−Eudragit L 100 ASDs showed a more marked blue shift compared to the other ASDs. Blue shifts of 8 and 21 cm\(^{-1}\) were recorded for 25 and 50% DL lumefantrine−CAP ASDs, respectively. With Eudragit L 100, 13 and 21 cm\(^{-1}\) blue shifts were observed for ASDs at 25 and 50% DL respectively. Interestingly, no shift in peak position was observed for the ASDs at 5 and 10% DL. This was different from lumefantrine−HPMCAS and HPMCP ASDs, where a well resolved 2 cm\(^{-1}\) blue shift was observed even at 5% DL.

The IR spectra of the ASDs were also monitored after 2 h of dissolution. The compacts were carefully removed from the die and dried overnight under reduced pressure. The compact surface of the ASD was then carefully scraped off with a spatula, and the ATR−FTIR spectrum was obtained. For high DL PVPVA ASDs (Figure 6a), it is apparent that the intensity

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**Figure 7.** Subtracted FTIR spectra of (a) HPMCAS, (b) HPMCP, (c) CAP, and (d) Eudragit L 100 25% DL ASD (solid line) and the spectra of the respective neat spectra (dashed line).
of the characteristic peaks of PVPVA was substantially diminished, relative to the intensity of the lumefantrine peaks. This is most apparent by considering the drug bands between 1600 and 1550 cm$^{-1}$ which can be attributed to the $\equiv$C=] aromatic carbons in lumefantrine. The bands in this region were present in amorphous lumefantrine, were weak in the initial dispersions, and became increasingly apparent after 2 h of immersion in the dissolution medium. These observations strongly suggest that the compact surface was enriched with the drug while the polymer concentration was markedly reduced.

For HPMCAS, HPMCP and CAP ASD compacts after 2 h immersion in the dissolution medium, minimal changes in spectra were obtained relative to the initial dispersions (Figure 6b--d). The similarity between the spectra before and after dissolution in terms of peak shape and position suggests that the surface composition of the ASD compacts in terms of drug and polymer ratio did not change drastically following partial release. The exception to this observation was the lumefantrine--Eudragit L 100 ASD, where an increase in the intensity of the lumefantrine peaks between 1600 and 1550 cm$^{-1}$ was observed after partial dissolution (Figure 6e).

To probe for possible proton exchange between lumefantrine and the enteric polymers, leading to the conversion of a carboxylic acid to a carbamate group, subtraction spectroscopy was used to identify regions of change in the ASD spectra. Using the ASD spectra collected from 25% DL formulations, the spectrum of amorphous lumefantrine was subtracted from all the ASD spectra, and the resultant spectrum was compared with the spectrum of the corresponding neat polymer. As shown in Figure 7, the subtracted spectra showed additional peaks between 1594−1560 cm$^{-1}$ and 1410−1343 cm$^{-1}$, which corresponded to the asymmetric and symmetric stretching frequencies of the carbamate group. This provides evidence of an acid–base interaction between lumefantrine and the enteric polymers.

X-ray Photoelectron Spectroscopy. X-ray photoelectron spectroscopy was used to further confirm the presence and extent of protonation of lumefantrine in the 25% DL ASDs. Protonation results in a shift of the corresponding photoemission emission peak of the affected functional group toward higher BE. Therefore, the protonated and unprotonated components can be distinguished in the N 1s spectra as demonstrated previously.$^{6,35}$ The area of the components is proportional to the amount, and, thus, the extent of protonation can be calculated. As shown in Figure 8 and summarized in Table 4, the extent of protonation varied between different enteric polymers, while no protonation was observed with PVPVA-based ASDs. Among the enteric polymers, the largest extent of protonation was observed with CAP, while HPMCAS showed the least protonation. After dissolution, the extent of protonation was found to decrease for the ASDs except for CAP, where negligible change was observed. The change in percentage protonation of lumefantrine after dissolution suggests that the surface composition of the compact changed during dissolution. The decrease in percentage protonation for HPMCAS, HPMCP, and Eudragit L 100 ASDs is consistent with drug enrichment on the compact surface.

To probe for more evidence of lumefantrine surface enrichment following partial dissolution, the change in the ratio between C and Cl, C/Cl was evaluated. As C is present in the drug and polymers, while Cl is only present in lumefantrine, a reduction in C/Cl after dissolution is indicative of drug enrichment. The XPS measured C/Cl ratio of neat lumefantrine was 12 ± 1. Using this value, the atomic percentages of C corresponding to lumefantrine and the respective polymers were calculated from the C 1s spectra. As shown in Figure 9, the atomic percent of C corresponding to lumefantrine increased after 10 (PVPVA) and 30 min (enteric polymers) of immersion in the dissolution medium. This is consistent with the observation that the normalized polymer release rate was slightly higher than that of the drug in the 25% DL ASDs (Table 2). Therefore, drug release was still observed for PVPVA-, HPMCAS-, and HPMCP-based ASDs.

![Figure 8](https://doi.org/10.1021/acs.molpharmaceut.1c00481)

**Table 4. Percentage Protonation of Lumefantrine in the Presence of Different Polymers**

| polymer         | % protonation before dissolution | % protonation after dissolution |
|-----------------|---------------------------------|--------------------------------|
| PVPVA           | 0                               | 0                              |
| HPMCAS          | 19 (6)                          | 3 (8)                          |
| HPMCP           | 46 (4)                          | 21 (7)                         |
| CAP             | 55 (3)                          | 54 (4)                         |
| Eudragit L 100  | 49 (6)                          | 12 (4)                         |

*The samples analyzed were 25% DL ASDs. Standard deviations are shown in parentheses, where $n = 3$. 

Quantification of the Number of Carboxylic Acid Groups in Enteric Polymers via Potentiometric Titra-
Potentiometric titration was used to determine the number of carboxylic acid groups in the four enteric polymers. Two titration end points were observed for each titration curve (Figure 10), which were used to calculate the number of carboxylic acid groups in each polymer. Among the polymers, HPMCAS has the least amount of carboxylic acid groups per unit weight, followed by HPMCP, CAP, and Eudragit L 100 (Table 5). HPMCP has the lowest pK$_a$ among the polymers, followed by CAP, HPMCAS, and Eudragit L 100. At pH 6.8, HPMCP and CAP are fully ionized, HPMCAS is close to fully ionized, and Eudragit L 100 is partially ionized.

### DISCUSSION

The Impact of Polymer Selection on Dissolution Performance. Studies have shown that polymer-controlled dissolution in binary ASDs leads to the congruent release of the drug and polymer; that is, the two components release simultaneously at the same normalized rate. Consequently,
because the neat polymer dissolution rate is typically much faster than that of a lipophilic amorphous drug, the drug release rate from ASDs is enhanced in the polymer-controlled regime. This holds true if the normalized polymer release rate from the dispersion is similar to that of the neat polymer, which appears to be the case for a number of systems studied to date.\textsuperscript{23,24,26,27} Thus, to maximize the effectiveness of an ASD formulation, the release should ideally be polymer-controlled. Conversely, in drug-controlled dissolution, the release rate of the drug, and often that of the polymer, is much lower. Observations correlating drug and polymer release rates, or lack thereof, have mainly been made for PVPVA-based ASDs,\textsuperscript{23,24,26,27} while studies with other polymers commonly used to formulate ASDs are limited. PVPVA-based ASDs typically show an interesting pattern of release, whereby the drug release is rapid and congruent with that of the polymer at low DLs, occurring at approximately the same normalized rate as for the neat polymer, and then drastically drops when the DL is increased by a small increment, a phenomenon that has been called the “falling-off-the-cliff” effect.\textsuperscript{28} It is not currently well established if ASDs formulated with other polymers show a similar “falling-off-the-cliff” effect and if and how the polymer release rate is modulated by the presence of the drug. Clearly, the results of the current study suggest that the presence of a drug can have a notable impact on the polymer release rate (and vice versa), even when release is congruent.

Surface normalized release studies of the lumefantrine binary ASDs revealed different trends in the release profiles as DL was varied. In PVPVA systems, the release of the drug and polymer remained congruent until 35% DL, while an abrupt “falling-off-the-cliff” effect was observed when the DL was increased to 40% (Figure 4). In addition, ASDs with DL of 35% and below yielded drug-rich droplets, indicating that the concentration of lumefantrine in the dissolution medium exceeded its amorphous solubility. This is another indicator of polymer-controlled release, whereby the formulation can keep releasing drug, even when the solution concentration has reached the amorphous solubility; for drug-controlled dissolution, at this concentration, there is no thermodynamic driving force for dissolution. Thus, the LoC for the lumefantrine–PVPVA system is 35% DL. While the “falling-off-the-cliff” pattern of behavior observed for lumefantrine–PVPVA ASDs is similar to that observed for a number of other dispersions with this polymer, the LoC is higher than for other systems, which have been reported to be in the range of 5–25% DL.\textsuperscript{23–27} The higher LoC is consistent with a lack of specific interactions between lumefantrine and the polymer, which has been suggested to promote drug release at higher DLs.\textsuperscript{27} Alternatively, ionization of lumefantrine upon contact with the dissolution medium may play a role; lumefantrine has a pK$_a$ of 8.73.\textsuperscript{30}

In contrast, the “falling-off-the-cliff” effect was not observed for the ASDs formulated with enteric polymers. For these systems, the drug and polymer release rates declined continuously with increasing DL. For example, for HPMCP and HPMCAS ASDs, increasing the DL from 5 to 20% resulted in a 10-fold decrease in the drug release rate (Table 2). This is much larger than the approximately 2.5-fold decrease in release rate observed for felodipine–HPMCAS ASDs when increasing the DL from 10 to 40%,\textsuperscript{38} and the 4.2-fold decrease observed for loratadine–HPMCAS ASDs when increasing the DL from 5 to 50%.\textsuperscript{28} For the lumefantrine ASDs with HPMCP and HPMCAS, drug and polymer release occurred at a similar normalized rate for DLs up to 25%, while at a 50% DL, the polymer dissolution was very slow, but faster than that of the drug, where the release was undetectable. It is also clear that the release rate of the neat polymer is important in dictating the achievable release rate of the drug at a given DL. Hence, because HPMCAS and HPMCP have faster dissolution rates than Eudragit L 100 and CAP as neat polymers, the drug release rate is always faster from ASDs formulated with the former two polymers, for a given DL.

Given the importance of the polymer in dictating the drug release rate, at least in the polymer-controlled regimen, it was of interest to evaluate the impact of the DL on the polymer release rate. Clearly, while the drug did not impact PVPVA release in the congruent regimen (Figure 4), where the polymer released from the ASDs at a similar normalized rate as observed for the neat polymer, the same was not true for the enteric polymers. Figure 11 shows the normalized rates of the polymers plotted on a logarithmic scale with respect to DL. This type of plot, termed a Meyerhofer plot, has been used to evaluate the influence of additives on polymer dissolution rate in the area of photoresist performance.\textsuperscript{39} Figure 11 allows for a comparison of the dissolution rates of the neat polymers and the incremental impact of adding a drug. It is clear that a steeper slope is observed for the decline in CAP and Eudragit L 100 release rates relative to HPMCP and HPMCAS. Thus, lumefantrine appears to have a greater impact on reducing the dissolution rate of the former polymers. Further, the resultant performance of a given ASD as a function of DL has a high degree of dependency on the neat polymer dissolution rate. In other words, formulating an ASD using a polymer with a higher dissolution rate is advantageous to achieve higher DL systems with adequate release rates. By extrapolation, the release rates of CAP and Eudragit L 100 at 25% DL are expected to be similar to the release rates of HPMCP and HPMCAS at 50% DL. The low polymer dissolution rate, further impaired by the addition of the drug, likely explains why no drug release was detected at 25% DL for CAP and Eudragit L 100. Figure 11 also clearly highlights the very different release behavior of PVPVA-based ASDs versus those formulated with enteric polymers, although the polymer release rates of HPMCP, HPMCAS, and PVPVA eventually converged when the DL is approximately 50%. Given that the neat polymers had very different normalized dissolution rates
at lower DLs, this observation suggests that drug-controlled dissolution dominates at high DL.

The “falling-off-the-cliff” effect commonly observed in PVPVA ASDs has been attributed to water-induced phase separation, which leads to the formation of a drug-rich layer at the surface once a certain DL is reached. Here, penetration of water during hydration induces amorphous–amorphous phase separation (AAPS) and some extent of demixing of the drug and polymer. The more hydrophilic PVPVA-rich phase will initially dissolve in the dissolution medium, leaving behind the poorly soluble amorphous drug-rich phase, ultimately leading to the formation of a physical barrier in the form of a drug-enriched surface, thereby preventing further release of the drug and, in some instances, polymer from beneath the compact surface. With lumefantrine, studies with FTIR spectroscopy showed that at 40, 45, and 50% DL, the chemical composition of the lumefantrine–PVPVA compact surface changed and was enriched in drug and depleted in polymer. In comparison, FTIR spectra of ASDs formulated with enteric polymers did not show detectable surface enrichment, with the exception of Eudragit L 100 ASDs. However, XPS data showed that all the ASDs had some evidence of drug enrichment on the compact surface, albeit to different extents (Figure 9). In contrast to PVPVA ASDs, HPMCAS systems have been reported to be more resistant to water-induced phase separation. A study comparing PVPVA and HPMCAS ASDs showed that for the same drug, PVPVA ASDs were more susceptible to phase separation even at low DL, while phase separation was only observed with HPMCAS systems when DL was above 30%. Herein, it was observed that other enteric polymers such as HPMCP and CAP also appeared effective in minimizing AAPS during dissolution.

The role of the polymer in controlling drug release can be further illustrated by comparing the release rate of lumefantrine at 5% DL for each of the five polymers used to formulate ASDs (Figure 12). The release rate of lumefantrine from PVPVA ASD was approximately five times higher than from the HPMCP ASD. The release rate of neat PVPVA was found to be approximately five times higher than that of HPMCP, highlighting the role of the polymer in controlling drug release at low DL. While PVPVA and the enteric polymers are soluble at pH 6.8, they exhibit different extents of hydrophobicity. The water contact angles of PVPVA and HPMCAS were reported to be 30.6 and 58.6°, respectively, and the incorporation of a hydrophobic drug to formulate binary ASDs led to a further increase in the contact angle. Therefore, the much slower drug release rate from the enteric polymers could be due, at least in part, to the more hydrophobic nature of these polymers.

Given the important role of the polymer in the drug release process, it is worth considering mechanisms by which polymers dissolve, as the critical rate processes for polymer dissolution are very different from those for small molecules. Polymer dissolution is considered to be controlled by two transport processes, solvent diffusion, and chain disentanglement. Upon diffusion of solvent molecules into an initially glassy polymer, the system becomes plasticized, forming a swollen gel. In the next step, if the solvent quantity is sufficient, the polymer undergoes a transformation from an entangled gel to a disentangled solution, often described using a reptation model. For enteric polymers, ionization of carboxylic acids is also required for the polymer to become soluble enough to dissolve.

Because the dissolution of an enteric polymer requires an ionization step to occur, it is important to also consider the ionization state of the drug. Lumefantrine, with a pKₐ of 8.73, will ionize at the polymer–solvent interface, given that the bulk pH of the dissolution medium is pH 6.8. This means that, upon ionization of the polymer carboxylic acid groups, there are three potential cations that can neutralize the resultant negative charge, the sodium and potassium ions from the buffer, and the quaternary ammonium cation of the ionized lumefantrine. In addition, XPS data indicated that the ASDs of lumefantrine and enteric polymers, which were produced via solvent evaporation, exhibited evidence of some extent of salt formation between the polymer and drug, in agreement with previous studies. Thus, some level of drug–polymer ionic interactions existed in the ASD matrix prior to hydration.

Interaction of a hydrophobic species such as lumefantrine with the polymer is expected to retard polymer dissolution by reducing the rate and, if the drug–polymer interactions persist in the presence of water, the extent of hydration of the polymer chain. This, in turn, will impact the polymer disentanglement rate, and the persistent association of a lumefantrine ion with the polymer would be expected to reduce the polymer solubility (which is predicated on the hydration of ionized groups), which would also reduce the dissolution rate. These factors provide an explanation for why the dissolution rate of the enteric polymer decreased as DL increased.

Insights into the impact of an ionically interacting drug on enteric polymer-based ASD dissolution can be gained by considering mechanistic studies on ionizing polymer dissolution. Phenolic polymer dissolution has been widely studied in the context of photoresists. Two dissolution models predominate literature discussions; the percolation model and the critical ionization fraction model. Reiser and coworkers suggested that percolation theory is applicable to the dissolution of ionizable phenolic polymers and can account for the impact of additives. The essence behind percolation theory as applied to solvent diffusion is that there are empty and occupied cells, where a critical number of occupied cells must exist for the diffusant (solvent species) to be able to move.

Figure 12. Normalized lumefantrine release rate at 5% DL when formulated with different polymers.
from one site to another. The ionizable (or hydrophilic) sites on the polymer represent the occupied cells. Reiser and co-workers suggested that the following percolation equation was applicable for ionizable photoresist resins:

\[
\log \text{DR} = \text{constant} + 2\log(X_i - X_{ic})
\]

(1)

where \(\text{DR}\) is the polymer dissolution rate, \(X_i\) is the concentration of solvent-accessible ionizable groups, and \(X_{ic}\) is the critical concentration of ionizable groups required for basic solvent species to be able to diffuse through the polymer. Thus, the dissolution rate is reduced if the number of ionizable groups present in the polymer is decreased or if these groups are blocked by a hydrophobic additive. The underlying assumption of the percolation theory is that diffusion of solvent species (base and counterion) through an interfacial boundary is the rate-limiting step.

Willson and co-workers proposed an alternative model, termed the critical ionization model, where polymer dissolution is considered as a surface etching process that only occurs when each polymer chain can be solubilized by reaching a critical extent of ionization (the critical ionization fraction). For this model, the chemical reaction between the acidic (polymer) and basic groups (solvent) is the rate-limiting step and the following relationship holds:

\[
\text{DR} \propto \frac{[A^-]}{[HA]}
\]

(2)

where the dissolution rate (DR) is proportional to the fraction of the ionized sites \([A^-]\) to the nonionized sites \([HA]\) on the surface of the dissolving polymer. In turn, this ratio depends on the \(pK_a\) of the acidic groups on the polymer and the pH. Heller et al. have also related the extent of ionization to the solubilization and dissolution rate for a series of copolymers containing carboxylic acid groups.

For an enteric polymer, a critical extent of ionization is needed for dissolution to occur. It is important to consider that it is not only the ionization per se that leads to dissolution but also the accompanying hydration of the nascently formed

Figure 13. Schematic of (I) neat polymer release, (II) drug and polymer release from enteric polymer-based ASDs when the number of ionized groups is at/above the critical ionization fraction of the polymer due to minimal blocking by the drug, and (III) no release of the drug and polymer from enteric polymer-based ASDs when the number of ionized groups is below the critical ionization fraction of the polymer due to blocking by electrostatic interaction with the cationic drug.
carboxylate ion. Thus, if sufficient ionization/hydration is not achieved, either because the pH is not high enough to ionize sufficient groups, or if the ionized groups are not accessible to the solvent because they are blocked by an additive, the polymer will not dissolve; the latter concept is summarized in Figure 13. Studies have demonstrated that, in the absence of additives, the critical extent of ionization is impacted by polymer chemistry (balance of hydrophilic and hydrophobic functional groups) as well as solution pH (and hence the degree of ionization), leading to the well-known minimum dissolution pH for enteric polymers, that varies from polymer to polymer depending on the type and degree of substitution of the constituent functional groups (Figure S2). Nguyen and Fogler considered the kinetics of ionizable polymer dissolution and concluded that diffusion of protons away from the dissolving polymer interface or chain disentanglement could be rate-limiting steps.  

Unfortunately, the impact of additives on the dissolution rate of ionizable polymers is not well understood. Reiser and co-workers suggested that dissolution rate inhibitors interact with the polymer, blocking the hydrophilic diffusion channels and reducing the number of available percolation sites. He noted that inhibitor–polymer interactions can be based on hydrogen bonding or van der Waals interactions. Willson and co-workers suggested that additives capable of hydrogen bonding to the acidic group lead to an increase in the effective pH, and hence, a reduction in the ratio of the ionized to un-ionized species, which, in turn, decreases the dissolution rate. Neither mechanism readily explains our observations, where it appears that the polymer hydration sites. For this scenario, for CAP, the estimated ionization extent for HPMCP and CAP is 0.88, while for HPMCP, the effective ionization extent for HPMCP and CAP is 0.83, see Supporting Information for the calculation. Thus, dissolution still occurs, albeit at a much-reduced rate relative to the neat polymer. Thus, because CAP requires a greater fraction of −COOH groups to ionize before dissolution can commence, it is more susceptible to the consequences of an additive that interacts with the −COOH groups, which effectively reduces the number of −COOH groups available for hydration at any given pH through the formation of a hydrophobic ion pair on the polymer backbone. Consequently, as shown in Figure 11, the dissolution rate of the CAP-based ASDs decreased more rapidly compared to the HPMCP-based ASDs as a function of DL, consistent with the predictions of eqs 1 and 2, which show a nonlinear dependence between the dissolution rate and fraction of ionized polymer groups, where the critical ionization fraction for dissolution of CAP is approached more rapidly as a function of DL than for HPMCP. 

Conversely, as the release of PVPVA does not depend on polymer ionization, the rate of dissolution of this polymer shows a different dependence on DL. Notably, the polymer release remains essentially constant as a function of DL, until a critical DL is reached. This is consistent with the lack of interactions between lumefantrine and PVPVA (Figure S1) such that the additive does not interfere sufficiently with polymer hydration over a given DL range to impact polymer dissolution. Once a certain DL is reached, dilution of the blend by the hydrophobic additive likely prevents a sufficient volume of water from being absorbed to enable chain disentanglement to occur, and polymer dissolution rate is abruptly reduced.  

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50. From the XPS results, it was observed that at 25% DL, lumefantrine was 46% and 55% ionized in HPMCP- and CAP-based ASDs, respectively, and for charge balance, a stoichiometric amount of polymer −COOH groups must also be ionized. If these ionized polymer groups are blocked via ionic interaction with the lipophilic lumefantrine cation (Figure 13), this translates to a reduction in the number of available hydration sites. For this scenario, for CAP, the fraction of ionized groups that can be hydrated at pH 6.8 is effectively reduced from >0.99 to ~0.88, while for HPMCP, the change is from >0.99 to ~0.83 (calculations to derive the change in the effective ionization extent for HPMCP and CAP can be found in the Supporting Information). While CAP has a higher fraction of ionized groups available to interact with solvent in the presence of lumefantrine as compared to HPMCP due to a higher carboxylic acid content (Table 5), the 25% DL CAP-based ASD had no release. In contrast, drug and polymer release was still observed for 25% HPMCP-based ASD, even though a higher proportion of polymer −COOH groups are interacting with lumefantrine. This apparent discrepancy can be accounted for by considering that HPMCP has a lower critical ionization fraction for solubilization and dissolution relative to CAP. From Figure S3, it is apparent that CAP is approaching the critical ionization fraction at an ionized fraction of approximately 0.94 (i.e., the dissolution rate is approaching zero when the ionized fraction is ~0.94). Thus, the estimated fraction of −COO − groups in the presence of lumefantrine available for hydration (0.88) is lower than the critical ionization fraction (0.94), and dissolution does not occur. For HPMCP, the minimum pH for dissolution is ~5 based on extrapolation of the data in Figure S4, which corresponds to a critical ionization fraction of slightly less than 0.83, which is similar to the estimated ionized fraction available for hydration for the 25% DL lumefantrine–HPMCP ASD (0.83, see Supporting Information for the calculation). Thus, dissolution still occurs, albeit at a much-reduced rate relative to the neat polymer. Thus, because CAP requires a greater fraction of −COOH groups to ionize before dissolution can commence, it is more susceptible to the consequences of an additive that interacts with the −COOH groups, which effectively reduces the number of −COOH groups available for hydration at any given pH through the formation of a hydrophobic ion pair on the polymer backbone. Consequently, as shown in Figure 11, the dissolution rate of the CAP-based ASDs decreased more rapidly compared to the HPMCP-based ASDs as a function of DL, consistent with the predictions of eqs 1 and 2, which show a nonlinear dependence between the dissolution rate and fraction of ionized polymer groups, where the critical ionization fraction for dissolution of CAP is approached more rapidly as a function of DL than for HPMCP. 

Conversely, as the release of PVPVA does not depend on polymer ionization, the rate of dissolution of this polymer shows a different dependence on DL. Notably, the polymer release remains essentially constant as a function of DL, until a critical DL is reached. This is consistent with the lack of interactions between lumefantrine and PVPVA (Figure S1) such that the additive does not interfere sufficiently with polymer hydration over a given DL range to impact polymer dissolution. Once a certain DL is reached, dilution of the blend by the hydrophobic additive likely prevents a sufficient volume of water from being absorbed to enable chain disentanglement to occur, and polymer dissolution rate is abruptly reduced.
Additionally, polymer release may also be hindered by the formation of a drug-rich layer at the compact−water interface, which serves as a barrier to polymer release.

**Choice of Polymer and Its Impact on ASD Solid-State Stability.** Favorable intermolecular interactions between the drug and polymer are considered important in ASD formulations to ensure miscibility and inhibit crystallization during storage, thereby avoiding the loss of the solubility advantage associated with this formulation strategy. While one of the most frequently studied intermolecular interactions in ASDs is hydrogen bonding, other interactions between the drug and polymer, such as halogen bonding and acid−base interactions, are possible.46,47 PVPVA systems were found to be physically unstable when stored under accelerated stability conditions. This can be rationalized based on a consideration of the extent of drug−polymer interactions. In the case of PVPVA, although lumefantrine contains an −OH group, which could interact with the vinylpyrrolidone carbonyl, there was little evidence of drug−polymer hydrogen bonding from the IR spectra. This observation can be explained by considering the hydrogen bonding interactions revealed by the single-crystal structure.54,55 Lumefantrine forms an intramolecular hydrogen bond between the −OH group and the nitrogen atom, and hence if this interaction persists in the ASD, only very weak or no specific interactions will be formed with the polymer. Additionally, PVPVA is very hygroscopic, while lumefantrine is lipophilic. Together, these factors predispose lumefantrine−PVPVA ASDs to AAPS and subsequent crystallization.56 In contrast, the enteric polymers contain both hydrogen bond donor and acceptor groups as well as ionizable −COOH moieties. This means that in addition to forming intramolecular hydrogen bonds with the acceptor group of lumefantrine, they can form additional interactions with the tertiary amine of lumefantrine through acid−base interaction. Previous studies have reported different extents of acid−base interaction between basic drugs and acidic polymers.46,47 In a study with lumefantrine ASDs, no protonation was observed with HPMCAS with 20 and 40% DL, while 50−75% protonation was observed with HPMCP.47 Herein, we observe lumefantrine protonation for all enteric polymers at 25% DL. Hence, a potential explanation for the improved physical stability in ASDs with the enteric polymers is an acid−base interaction involving the tertiary amine group and the polymer carboxylic acid group. In the case of the HPMCAS ASD with 50% DL, the observed crystallization could be attributed to a low molar concentration of carboxylic acid groups (Table 5), where the molar ratio between the tertiary amine in lumefantrine and carboxylic acid moiety in HPMCAS was 1.61 (see Supporting Information for the calculation). Clearly, the extent of ionization of both the drug and polymer in the solid-state and in solution warrants more in-depth studies to better understand the role of these factors in the physical stability of the ASDs as well as their dissolution performance.

To put things in perspective, while lumefantrine dissolution from the congruently releasing PVPVA systems was rapid, its susceptibility to crystallization is disadvantageous. In contrast, while the release of lumefantrine from HPMCP and HPMCAS systems was relatively slower, these systems, especially HPMCP ASDs, were shown to be more physically stable to crystallization. Therefore, the use of enteric polymers in place of neutral polymers in the formulation of binary ASDs with basic drugs may be a worthwhile trade-off from the improved physical stability point of view.

## CONCLUSIONS

The release of lumefantrine from PVPVA-based ASDs was found to be more rapid compared to binary ASDs formulated with the enteric polymers, HPMCAS, HPMCP, CAP, and Eudragit L 100 for low DLs. A “falling-off-the-cliff” effect for drug release was observed for PVPVA-based ASDs once the DL exceeded 35%. Diminished dissolution performance in PVPVA systems at high DLs was attributed to the enrichment of lumefantrine at the compact surface during dissolution. In contrast, for the ASDs formulated with enteric polymers, the release performance decreased as a function of DL, with an impairment in dissolution observed for DLs as low as 5%. Ionic interactions between lumefantrine and the enteric polymers are postulated to be responsible for the diminished release performance as the DL increases. The formation of a lumefantrine−polymer hydrophobic ion pair is thought to reduce the hydration of the polymer carboxylate ions, reducing the tendency for the polymer to release into solution, and concurrently hindering the drug release. This study highlights the important role that drug−polymer interactions play in determining the drug release rate from ASDs.

## ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.1c00481.

Transmission infrared spectroscopy of PVPVA and PVPVA-based ASDs, pH-dependent solubility of the enteric polymers, dissolution rate of the polymers as a function of ionized fraction of carboxylic acid groups, dissolution rate of the polymers as a function of pH, calculations to determine the available fraction of −COO− groups of HPMCP-based ASD at 25% DL, calculations to determine the available fraction of −COO− groups of CAP-based ASD at 25% DL, and drug-to-polymer charge ratio between the enteric polymers and lumefantrine (PDF)

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