Influence of the pKₐ Value of Cinnamic Acid and P-Hydroxycinnamic Acid on the Solubility of a Lurasidone Hydrochloride-Based Coamorphous System

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ABSTRACT: Coamorphization of a poorly water-soluble active pharmaceutical ingredient (API) has been proven to be effective in improving its solubility. Generally, API can form multiple coamorphous systems with different coformers. However, it remains unclear how the pKₐ value of different coformers influences the solubility of the API. In this study, structurally related cinnamic acid (CA, pKₐ = 4.37) and p-hydroxycinnamic acid (pHCA, pKₐ = 4.65) were chosen as coformers for the coamorphization of lurasidone hydrochloride (LH). To investigate the influence of the pKₐ value of the coformers on the solubility of LH, LH-CA/pHCA coamorphous systems were prepared by the vacuum rotary evaporation method and characterized by powder X-ray diffraction and differential scanning calorimetry. Fourier-transform infrared spectroscopy, Raman spectroscopy, and molecular dynamics (MD) simulations were employed to investigate the intermolecular interaction of the coamorphous systems. It was found that the solubility of LH in the coamorphous LH–pHCA with a higher-pKₐ coformer was higher than that of the coamorphous LH-CA. In addition, according to the solubility product principle-based formula derivation, we established the functional relationship between the solubility of LH and the pKₐ of the coformers at different-pH buffering solution. It was found that the coformer with a larger pKₐ value would be more beneficial to improve the solubility profile of LH. Collectively, the current study offers an effective strategy to improve the poor solubility of drugs by increasing the pKₐ value of the coformer in coamorphous systems.

1. INTRODUCTION

Lurasidone hydrochloride (LH) (Figure 1A) is an antipsychotic agent used to treat schizophrenia.¹ Clinical evidence shows that compared with other commercially available antipsychotics, LH can be more effective in the treatment of schizophrenia.² However, as a Biopharmaceutics Classification System II drug, its oral bioavailability is poor because of its low solubility.³⁻⁵ Therefore, there is an urgent need to improve the solubility of LH.⁶⁻⁷ In recent years, numerous strategies have been proposed to improve the solubility of LH, including solid dispersion,⁸⁻⁹ nanotechnology,¹⁰⁻¹¹ solubilization,¹² and so forth. For example, Mahajan et al. used poloxamer P188 solid dispersion adsorption technology to prepare LH solid dispersions by a fusion method. It was found that the solubility, dissolution rate, and flow properties of LH were remarkably improved.⁷ Patel and his colleagues have developed solid lipid nanoparticles to enhance the absorption and bioavailability of LH.¹³ Despite the improved solubility being achieved, these methods have several drawbacks that limit the production, such as high cost, low drug loading, complex process, and high toxicity.

Converting crystalline LH into its amorphous form is a known strategy to improve the solubility.¹⁴⁻¹⁵ However, the pure amorphous drug is thermodynamically unstable, thus showing an inherent tendency to recrystallize.¹⁶,¹⁷ In contrast, the coamorphous system can not only improve the solubility and dissolution of drugs but also show better stability, which has increasingly become a research hotspot in the field of crystallography.¹⁸ Coamorphous system is a homogeneous amorphous single-phase system formed by the combination of two or more low-molecular-weight coformers through hydrogen bonds or other noncovalent bonds.¹⁹ Several low-molecular-weight coformers are commonly used, including lactose,²⁰ organic acids (OAs),²¹,²² bile salt,²³,²⁴ and so forth. Among them, the use of OAs as coformers in coamorphous systems was an interesting discovery because from a
thermodynamic point of view, these compounds cannot easily form an amorphous system owing to the strong interaction and adhesion between crystal layers and have a great tendency to form a stable crystalline structure. However, under some specific condition, such as rapid evaporation, it could promote kinetically favorable pathways for amorphization. At present, there is an increasing number of coamorphous systems formulated with OAs as coformers. For example, Ali’s group used solvent evaporation to prepare a clozapine–tartaric acid coamorphous system with the highest dissolution rate at a molar ratio of 1:2. Hoppe’s group found that a paracetamol–citric acid coamorphous system showed strong stability when the weight ratio was 1:1. Fung et al. investigated the molecular mobility and physical stability of a ketoconazole–OA coamorphous system. It was found that the OA possessed great potential to improve the physical stability of the amorphized API. However, in the studies of these OA-based coamorphous systems, most of the researchers have only explored their stability, and little attention has been paid to the solubility of the coamorphous system.

To improve the solubility of LH, we prepared an OA-based LH coamorphous system in our previous study. It was found that the intermolecular hydrogen-bond interaction might be the main reason for enhancing the solubility behavior of LH. Along with the intermolecular hydrogen-bond interaction, the pKₐ value of the OA is considered as one of the main factors affecting the solubility. However, it is still unknown how the pKₐ values of OAs affect the solubility of the coamorphous system.

Therefore, in this study, two OAs with varying pKₐ values [i.e., cinnamic acid (CA, pKₐ = 4.37) and p-hydroxycinnamic (pHCA, pKₐ = 4.65)] {Figure 1B,C} were chosen as coformers in the preparation of LH coamorphous systems. In brief, LH-CA and LH-pHCA coamorphous (1:1, 1:2, 2:1 molar ratio) systems were prepared. We investigated the effect of the pKₐ values of the two OAs on the solubility of the coamorphous systems and explored the possible mechanism by using the solubility product principle-based formula derivation. Moreover, the structure of the obtained coamorphous system was characterized by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). Fourier-transform infrared (FTIR) spectroscopy, Raman spectroscopy, and molecular dynamics (MD) simulations were used to explore the intermolecular interaction of the coamorphous systems.

2. RESULTS AND DISCUSSION

2.1. Powder X-Ray Diffraction. PXRD was applied to determine the formation of coamorphous LH-CA/pHCA systems. As depicted in Figure 2, crystalline LH, crystalline CA, and crystalline pHCA exhibited characteristic diffraction peaks {Figure 2a–c}. The physical mixtures of crystalline LH and CA/pHCA (1:1, 1:2, 2:1) displayed overlapping diffraction peaks of crystalline LH and CA/pHCA {Figure S1d–i}, whereas their evaporation products exhibited halo patterns {Figure 2d–i}, suggesting the formation of coamorphous LH–CA/pHCA. By contrast, each drug’s
evaporation product exhibited the same characteristic diffraction peak with the corresponding crystalline drug, indicating that the amorphous product could not be obtained under single drug evaporation (Figure S1a–c).

2.2. Differential Scanning Calorimetry. The DSC thermogram of each sample is illustrated in Figure 3. Crystalline LH showed its melting point around 260 °C, followed by a small thermal degradation peak (Figure 3a), which was the same as with our previous report.30 We found the fusion endotherms of LH and CA were 222.8 and 134.3 °C, respectively (Figure 3b,c), which were consistent with the reported results.34,35 Moreover, it was observed that the physical mixtures of LH and CA exhibited two endothermic peaks, similar to their melting points (Figure S2a–c). However, the physical mixtures of LH and pHCA showed only one melting endotherm in the temperature range of 174–177 °C (Figure S2d–f), probably suggesting that a low eutectic mixture was formed between LH and pHCA. The coamorphous system can be characterized by its glass transition temperature (Tg). As expected, only one Tg value could be observed in the LH–CA/pHCA systems (Figure 3d–i), further indicating the formation of a single-phase coamorphous system. Specifically, the coamorphous LH–CA (1:1) exhibited a glass transition event at 68.3 °C and a sharp recrystallization exothermic peak at 133.4 °C. The exothermic enthalpy was determined as −6.93 J·g−1. A larger endothermic peak at 257.7 °C was attributed to the melting or degradation of the recrystallized coamorphous system. Similarly, the coamorphous LH–pHCA (1:1) showed a glass transition event at 70.0 °C and a small exothermic peak at 154.2 °C. Its exothermic enthalpy was determined as −16.13 J·g−1. Compared with the sharp recrystallization peak of coamorphous LH–CA (1:1), the recrystallization peak of coamorphous LH–pHCA (1:1) was much smaller, indicating that the recrystallization degree of coamorphous LH–pHCA (1:1) was lower. Such phenomena were also observed in the coamorphous form of LH with saccharin36 or repaglinide.37

In addition, similar thermodynamic phenomena were observed in the coamorphous systems LH–CA/pHCA (1:1, 2:1) (Figure 3e–i).

2.3. FTIR Spectroscopy. The FTIR spectra were measured to gain insights into intermolecular interactions between coamorphous LH and CA/pHCA systems. Figure 4a shows the characteristic absorption peaks of the crystalline LH at 2258 and 1686 cm−1, which attributed to the positively charged N+–H stretching and carbonyl vibrations (C=O), respectively.30 Crystalline CA showed stretching and bending vibrations at 1686 and 594 cm−1, respectively. Moreover, we observed the stretching and bending vibrations of the −OH group at 3442 and 924 cm−1, respectively (Figure 4b). Similarly, crystalline pHCA exhibited stretching and bending vibrations of C=O at 1672 and 594 cm−1, respectively. In addition, the stretching and bending vibrations of the −OH group at 3381 and 920 cm−1 were also observed (Figure 4c). Overlapping peaks of crystalline LH and CA/pHCA could be observed in physical mixtures (Figure S3a–f). Compared with crystalline LH, the coamorphous LH–CA (1:1) exhibited a prominent hypsochromic shift for the N+–H stretch (2258 → 2570 cm−1) (Figure 4d). Similar shifting (2258 → 2597 cm−1) was also found in coamorphous LH–pHCA (1:1) (Figure 4g). In comparison to amorphous LH,36 the FTIR spectrum of the coamorphous LH–CA (1:1) showed an obvious shift for N+–H (2442 → 2570 cm−1) and the coamorphous LH–pHCA (1:1) (2442 → 2597 cm−1). The stretching vibrations of CA and pHCA in the coamorphous systems also showed apparent shifting, such as the −OH of the carboxyl group, extending from 3100 to 3600 cm−1 and 3000 to 3600 cm−1, respectively. In addition, the bending vibrations of C=O and −OH (−COOH) exhibited a significant hypsochromic effect. For example, the bending vibrations of carboxyl groups of CA showed an obvious shift for C=O (924 → 951 cm−1) and −OH (594 → 649 cm−1). Similarly, the bending vibrations of

**Figure 3.** DSC patterns of crystalline LH (a), pHCA (b), CA (c), coamorphous LH–CA (1:1) (d), coamorphous LH–CA (1:2) (e), coamorphous LH–CA (2:1) (f), coamorphous LH–pHCA (1:1) (g), coamorphous LH–pHCA (1:2) (h), and coamorphous LH–pHCA (2:1) (i).
pHCA showed an obvious shift for C=O (920 → 951 cm\(^{-1}\)) and –OH (594 → 650 cm\(^{-1}\)). These shifts strongly indicate the formation of hydrogen bonds between LH and CA/pHCA. Similarly, such shifts were observed in other coamorphous LH–CA/pHCA systems (1:1, 2:1) (Figure 4e–i).

2.4. Raman Spectroscopy. Generally, infrared spectroscopy was used to investigate the asymmetric vibration of polar groups, while Raman spectroscopy was used to investigate the symmetric vibration of nonpolar groups.\(^{38}\) As illustrated in Figure 5, we investigated the intermolecular interaction between coamorphous LH and CA/pHCA systems by Raman spectroscopy. Crystalline LH showed its stretching vibration peaks at 1757 cm\(^{-1}\) for C=O and 1025 cm\(^{-1}\) for the benzene ring (Figure 5a).\(^{39}\) Crystalline CA showed its stretching vibrations peaks at 846 cm\(^{-1}\) (–OH), 874 cm\(^{-1}\) (–COOH), 1637 cm\(^{-1}\) (C=C), and 1598 cm\(^{-1}\) (aromatic ring) (Figure 5b). Similarly, crystalline pHCA showed its stretching vibration peaks at 836 cm\(^{-1}\) (–OH), 862 cm\(^{-1}\) (–COOH), 1635 cm\(^{-1}\) (C=C), and 1603 cm\(^{-1}\) (aromatic ring) (Figure 5c). The physical mixture of crystalline LH and CA/pHCA only exhibited a simple superposition of the peaks (Figure S4a–f).

In comparison to the physical mixture LH–CA/pHCA (1:1), the strength and position of the peak of the coamorphous system LH–CA/pHCA (1:1) were changed. The Raman spectrum of LH in the LH–CA coamorphous system showed an obvious shift for benzene ring (1025 → 1027 cm\(^{-1}\)) and C=O (1758 → 1761 cm\(^{-1}\)) (Figure 5d). Meanwhile, we also found CA had some shifts for –OH (846 → 873 cm\(^{-1}\)), –COOH (874 → 883 cm\(^{-1}\)), C=C (1637 → 1642 cm\(^{-1}\)) and aromatic ring (1598 → 1601 cm\(^{-1}\)). Similarly, the Raman spectrum of LH in the LH–pHCA coamorphous system (1:1) showed an obvious shift for benzene ring (1025 → 1023 cm\(^{-1}\)) and C=O (1757 → 1761 cm\(^{-1}\)) (Figure 5g). Meanwhile, it was found that pHCA showed some shifts for –OH (836 → 840 cm\(^{-1}\)), –COOH (862 → 859 cm\(^{-1}\)), C=C (1635 → 1628 cm\(^{-1}\)), and aromatic ring (1605 → 1603 cm\(^{-1}\)). In comparison to the reported amorphous LH,\(^{39}\) it can be found that the Raman spectra of coamorphous LH–CA/pHCA (1:1) had shifted remarkably. These obvious shifts indicate that the coamorphous LH and CA/pHCA (1:1) systems might be formed via intermolecular hydrogen bonds. Similarly, such shifts were observed in the coamorphous systems LH and CA/pHCA (1:1, 2:1) (Figure 5e–i).

In summary, the results of the FTIR and Raman spectroscopy study clearly show the existence of intermolecular hydrogen bonds between LH and CA/pHCA in the coamorphous systems.

2.5. RDF Analysis under MD Simulation. MD simulation and radial distribution function (RDF) analysis
were conducted to validate the formation of intermolecular hydrogen bonds between LH and CA/pHCA in the coamorphous system. As depicted in Figure 6, the RDF profiles of the coamorphous systems between each pair of the donor and acceptor atom were illustrated. RDF describes the relationship between the distance \( r \) change between a given atom and the target atom and the atomic density \( g(r) \). Generally, when the \( g(r) \) peaks locate within 1.5−2.2 Å, it indicates that there is a hydrogen bond formed between the specified two atoms. As illustrated in Figure 6A−C, we can find that all peaks lie at 1.5−2.2 Å \([\text{O12−H (pHCA)−Cl36 (LH)}, \text{O10−H (CA)−N13−H (LH)}, \text{and O11 (CA)−Cl36 (LH)}] \), suggesting that the molecular hydrogen bond interaction of the coamorphous system might be formed through these sites.

2.6. Solubility of LH as a Function of pH and \( \text{pK}_a \). The functional relationship between pH and \( \text{pK}_a \) and the solubility of LH was investigated in this study.

2.6.1. LH Ionization. The solubility of the drug can be expressed by the balance between the solid drug LH and the solution, and the balance expression is described as follows.

\[
\text{LH}_{\text{solid}} \rightleftharpoons \text{LH}_{\text{aq}}
\] (1)
where $LH_{aq}$ represents the dissolved drug in the aqueous phase, where $LH_{solid}$ represents the undissolved drug in water. Because $LH$ is hydrochloride that can be ionized under certain aqueous conditions, the total concentration of $LH$ ($LH_T$) in an aqueous solution can be described by the sum of the nonionized and ionized substances in the solution. (This formula ignores chloride ions)

$$LH_T = B_{aq} + BH^+_{aq}$$

where $LH_T$ means the total concentration of $LH$, $BH^+$ is the protonated state of $LH$, and $B$ is the deprotonated state of $LH$. The subscripts $T$ and $aq$ represent the total solubility and the species of the drug in the aqueous phase, respectively.

Essentially, $LH$ is a salt formed by a basic compound. The following ionization equilibrium exists when a basic compound or its salt is dissolved in an aqueous solution:43

$$K_{a1} = \frac{[B]_{aq}[H_3O^+]_{aq}}{[BH^+]_{aq}}$$

According to the mass balance eq 2, the solubility of $LH$ could be expressed as follows

$$S_{diss,T} = [LH]_{aq} = [BH]_{aq} \left(1 + \frac{[H_3O^+]_{aq}}{K_{a1}}\right)$$

According to eq 5, the solubility of $LH$ could be expressed as follows

$$S_{diss,T} = [BH]_{aq} \left(1 + 10^{pK_{a1}-pH}\right)$$

### 2.6.2. Ionization of the OA-Based Coformer

The total concentration of the protic acid coformer ([OA]$_T$) in the aqueous solution could be described by the sum of the nonionized and ionized substances in the solution (mass balance)

$$OA_T = AH_{aq} + A^-_{aq}$$

where $AH$ represents the nonionized form of the coformer, and $A^-$ represents the ionized substances of the coformer.

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Figure 6. RDF analysis of the coamorphous system $LH$ and CA/pHCA (1:1, 2:1, 1:2) the distance of the hydrogen atom relative to chlorine and oxygen atoms; O12–H (pHCA)–Cl36 (LH) (A), O10–H (CA)–N13–H (LH) (B), and O11 (CA)–Cl36 (LH) (C).
When OA is dissolved in an aqueous solution, there is a balance between the unionized form and the ionized form, which can be described by the following equation.

\[ \text{AH}_{aq} + \text{H}_2\text{O} \rightleftharpoons \text{A}^-_{aq} + \text{H}_3\text{O}^+_{aq} \quad (8) \]

\( K_{a2} \) can be expressed as follows

\[ K_{a2} = \frac{[\text{A}^-]_{aq}[\text{H}_3\text{O}^+]_{aq}}{[\text{AH}]_{aq}} \quad (9) \]

According to the mass balance eq 7, the total concentration of the coformer in the solution can be described as follows

\[ \text{OA}_T = [\text{AH}]_T = [\text{BH}]_T \left(1 + \frac{[\text{H}_3\text{O}^+]_{aq}}{K_{a2}}\right) \quad (10) \]

According to eq 10, the total concentration of OA can be expressed by pH and \( pK_a \)

\[ \text{OA}_T = [\text{AH}]_T (1 + 10^{pK_{a2} - pH}) \quad (11) \]

### 2.6.3. Solubility of the Coamorphous System as a Function of pH, \( pK_a \), and \( K_{sp} \). For the coamorphous system of LH and OA formulated at a molar ratio of 1:1, the solubility \( (S_{cc}) \) of the coamorphous system under stoichiometric conditions could be described as follows

\[ S_{cc} = [\text{LH}]_T = [\text{OA}]_T \quad (12) \]

The coamorphous systems could be regarded as a single polymer instead of two individual components. The coamorphous system dissociates in solution according to the solubility product, \( K_{sp} \),

\[ \text{LH} - \text{OA}_{coamorphous} \rightleftharpoons \text{LH}_{aq} + \text{OA}_{aq} \quad (13) \]

\[ K_{sp} = [\text{LH}]_T [\text{OA}]_T \quad (14) \]

Among them, \([\text{BH}]_{aq}\) and \([\text{AH}]_{aq}\) are the nonionized species of the drug (LH) and coformer (OA). To understand the effect of the \( pK_a \) of the coformers on the solubility, the solubility product equation is presented as follows.

\[ S_{cc,T} = \sqrt{[\text{BH}]_T [\text{AH}]_T} \quad (15) \]

where \( S_{cc,T} \) is the total solubility of the coamorphous. \([\text{BH}]_T\) represents the total concentration of LH in equilibrium, and \([\text{AH}]_T\) represents the total concentration of OAs in equilibrium. Considering the mass balance of the coamorphous components (eqs 2 and 7) and substituting the corresponding balance, the coamorphous solubility can be obtained

\[ S_{cc,T} = \sqrt{K_{sp} \left(1 + \frac{[\text{H}^+]_{aq}}{K_{a1}}\right) \left(1 + \frac{[\text{H}^+]_{aq}}{K_{a2}}\right)} \quad (16) \]

Equation 16 can be rewritten in terms of pH and \( pK_a \).

Considering the equilibrium constant of the coamorphous dissociation (solubility product or \( K_{sp} \)) and its constituent ionization (\( pK_a \)), the equation describing the relationship between the coamorphous solubility with pH and \( pK_a \) is shown as follows

\[ S_{cc,T} = \sqrt{K_{sp} (1 + 10^{pK_{a1} - pH}) (1 + 10^{pK_{a2} - pH})} \quad (17) \]

where \( pK_{a1} \) represents the ionization constant of the base drug (LH) in the coamorphous system, and \( pK_{a2} \) represents the ionization constant of the OAs in the coamorphous system.

### 2.7. Equilibrium Solubility Studies. The equilibrium solubility of different forms of LH in varying buffering solutions (i.e., pH 1.0–6.8) are shown in Figure 7. Our previous study showed that the crystalline LH exhibited a maximum solubility of 0.426 mg/mL at pH 3.8,\textsuperscript{30} which was attributed to its pH\textsubscript{max} effect.\textsuperscript{44} In addition, we also found the following phenomena: (1) compared with crystalline LH, the pH\textsubscript{max} of LH in both the physical mixture and the coamorphous system decreased from pH 3.8–2.0; (2) compared with the physical mixtures, the solubility of the coamorphous systems was remarkably improved; (3) the solubility of the LH–pHCA coamorphous system was greater than that of the LH–CA coamorphous system. Such phenomena can be explained by the following equations.\textsuperscript{43} When the total solubility of the base \( (S_{T,base}) \) at a given pH is saturated, it could be expressed by the following equation

\[ S_{T,base} = \sqrt{K_{sp} (1 + 10^{pK_{a1} - pH}) (1 + 10^{pK_{a2} - pH})} \quad (17) \]
When the salt is saturated, the equilibrium solubility \( S_{T,salt} \) at a particular pH may be expressed as follows

\[
S_{T,salt}(pH > pH_{max}) = [B]_s + [BH^+] = [B]_s \left( 1 + \frac{10^{\text{pK}_a}}{10^{\text{pH}}} \right) \tag{18}
\]

where \( S \) represents the saturated condition.

When the salt is saturated, the equilibrium solubility \( S_{T,salt} \) at a particular pH may be expressed as follows

\[
S_{T,salt}(pH < pH_{max}) = [BH^+]_s + [B] = [BH^+]_s \left( 1 + \frac{10^{\text{pH}}}{10^{\text{pK}_a}} \right) \tag{19}
\]

When the pH is equal to \( pH_{max} \) then \( S_{T,base} = S_{T,salt} \cdot pH_{max} \) can be expressed as follows

\[
pH_{max} = \text{pK}_a - \log \left( \frac{[BH^+]_s}{[B]_s} \right) \tag{20}
\]

where \([BH^+]_s\) and \([B]_s\) are the solubility of the ionized and unionized species, respectively. According to eq 18, when the pH value is much higher than \( \text{pK}_a \), the undissociated part of the solution can be ignored, and the experimentally measured solubility under this condition corresponds to \([B]_s\). In contrast, according to eq 19, when the pH is lower than \( \text{pK}_a \), the dissociated part of the solution is negligible, and the experimentally measured solubility under this condition corresponds to \([BH^+]_s\).

In this study, \([BH^+]_s\) and \([B]_s\) of crystalline LH were experimentally determined to be \( 5.2 \times 10^{-2} \) and \( 3.0 \times 10^{-6} \) mg mL\(^{-1}\) at pH 1.0 (\( S_{T,salt} \approx [BH^+]_s \)) and pH 10 (\( S_{T,base} \approx [B]_s \)), respectively. The \( \text{pK}_a \) of LH declared by the FDA is 7.6. According to eq 20, the calculated \( pH_{max} \) of LH was 3.84, which was basically consistent with the experimental pH value.
of 3.8 (Figure 7A,B). In comparison to crystalline LH, we found that the pH_{max} of the physical mixtures of LH−CA/pHCA (1:1, 1:2, 2:1) decreased to pH 2.0. For example, in the physical mixture of LH−CA and LH−pHCA (1:1), the solubility of LH at pH 3.8 was 0.474 and 0.514 mg·mL\(^{-1}\), respectively, while the solubility at pH 2.0 increased to 0.501 and 0.574 mg·mL\(^{-1}\), respectively. This phenomenon could be explained by the following theory. According to eq 8, it is predicted that the concentration of H\(_3\)O\(^+\) increases with the dissolution of AH. In other words, the pH of the solution would be decreased, accompanied by the dissolution of AH. In this context, the concentration of BH\(^+\) would be increased based on eq 3.

According to eq 20, we found that when the concentration of BH\(^+\) increases, the pH_{max} would decrease. Such a phenomenon was consistent with our experimental results, indicating that OAs can change the pH_{max} of crystalline LH.

As depicted in Figure 7, the solubility of the LH−CA/pHCA coamorphous systems at pH 1.0−6.8 buffers was greatly improved, and pH-dependent behavior still exists in this range, which was consistent with our previous report.\(^{30}\) In comparison to the physical mixtures of LH−CA, the solubility of the LH−CA coamorphous systems formulated with different ratios in the pH range of 1−6.8 increased by at least 1.2 times. For instance, the solubility of the LH−CA coamorphous systems showed the most improvements with pH 2.0 buffer, achieving 1.39-, 1.46-, and 1.34-fold increment for the 1:1, 1:2, and 2:1 molar ratios, respectively. Similarly, in comparison to the physical mixture of LH−pHCA, the solubility of coamorphous LH−pHCA also has a similar increase in the range of pH 1.0−6.8. Under the condition of pH 2.0, the solubility of the coamorphous LH−pHCA (1:1, 1:2, 2:1) increased by 1.92-, 1.82-, and 4.25-fold, respectively. The dissolving of the drug in the solvent was the result of the interaction between the drug and the solvent molecule. If the interaction between drug molecules is greater than the interaction between the drug molecules and solvent, the solubility is small; otherwise the solubility is large.\(^{45}\) Therefore, the improved solubility of the coamorphous system might be attributed to the hydrogen bond between LH and CA/pHCA. In addition, compared with the coamorphous LH−CA (1:1), we found that the coamorphous LH−pHCA formulated with a molar ratio of 1:1 increased in the pH range of 1−6.8. Similarly, this phenomenon was also observed in LH−CA/pHCA coamorphous systems (1:2, 2:1) (Figure 7). Such a phenomenon could be explained by the following theory. Based on eq 17, it can be predicted that the greater the pK\(_a\) value is, the greater the solubility of the coamorphous system would be, achieved under at same pH. As expected, Figure 7 shows that the solubility of the LH−pHCA coamorphous system at pH 1−6.8 buffers was remarkably higher than that of the LH−CA coamorphous system. This was probably because of the higher pK\(_a\) value of pHCA. Therefore, according to the solubility product principle-based formula derivation, we concluded that the higher pK\(_a\) value of the coformer in the coamorphous system might contribute to the enhanced solubility of the API.

2.8. Intrinsic Dissolution Study. The dissolution curves of crystalline LH, coamorphous LH−CA/pHCA (1:1, 1:2, and 2:1) are shown in Figure 8. The intrinsic dissolution rate (IDR) of crystalline LH was basically the same with our previous studies.\(^{30}\) Figure 8A,C shows that the crystalline LH in pH 2.0 buffering solution had a good linear dissolution curve (R\(^2\) = 0.9995), and the IDR was 0.0512 mg·cm\(^{-2}\)·min\(^{-1}\). Similarly, we also found that the coamorphous LH−CA (1:1, 1:2, and 2:1) and LH−pHCA (1:1 and 1:2) systems exhibited good linear release curves. In comparison to crystalline LH, the IDR of the above five coamorphous systems significantly improved, which were 1.20-, 2.33-, 1.33-, 1.92-, and 2.19-fold higher than that of the crystalline LH, respectively. However, the LH−pHCA (2:1) coamorphous systems underwent a rapid dissolution behavior in the first 60 min with an IDR of 0.0765 mg·cm\(^{-2}\)·min\(^{-1}\), followed by a slow dissolution with an IDR of 0.00368 mg·cm\(^{-2}\)·min\(^{-1}\). The initial rapid dissolution of LH in coamorphous could be attributed to its long-term disordered and short-term ordered arrangement, as well as higher free energy than crystalline drugs.\(^{86−48}\) Moreover, the profound reduction in IDR after the dissolution was probably due to solvent-assisted recrystallization.

Figure 8B,D shows that the crystalline LH had a good linear dissolution curve (R\(^2\) = 0.9921) in pH 3.8 acetate buffer, and the IDR was 0.0139 mg·cm\(^{-2}\)·min\(^{-1}\). Similarly, we also found that the coamorphous LH−CA/pHCA (1:2) systems exhibited good linear release curves. In comparison to crystalline LH, the IDR of the above two coamorphous systems were profoundly improved, which were 1.27- and 4.87-fold higher than that of the crystalline LH, respectively. However, in the initial period of intrinsic dissolution, the dissolution rates of the LH−CA/pHCA (1:1) tablet were 0.0426 and 0.0569 mg·cm\(^{-2}\)·min\(^{-1}\), followed by a slow dissolution after 20 min with IDRs of 0.00111 and 0.0153 mg·cm\(^{-2}\)·min\(^{-1}\), respectively. Similarly, the dissolution of the coamorphous LH−CA/pHCA (2:1) also possessed the same dissolution behavior. At the end of the dissolution, the tablet under the dissolution condition was collected and lightly touched with a tissue paper to remove moisture from the surface of the tablet.\(^{37}\) The powder was scraped from the surface of the tablet and observed under a polarizing microscope and scanning electron microscope, respectively.\(^{49}\) Figure S5 shows that the LH−CA/pHCA (1:2, 2:1) powders have almost no birefringence under a polarizing microscope, indicating that no significant recrystallization occurred during the dissolution of the coamorphous LH−CA/pHCA (1:2) (Figure S5b,c,e,f). However, the LH−CA/pHCA (1:1) powder exhibited obvious birefringence under the polarizing microscope, indicating that the coamorphous LH−CA/pHCA (1:1) exhibited obvious recrystallization during the dissolution process (Figure S5a,d). This phenomenon indicates that the decrease in the dissolution rate of coamorphous LH−CA/pHCA (1:1) might be due to the recrystallization of coamorphous LH−CA/pHCA (1:1) during the dissolution process. Figure S6 shows that LH−CA/pHCA (2:1) powders are tightly bound with a large number of small spherical particles observed under SEM, indicating that the coamorphous LH−CA/pHCA (2:1) was remarkably gelatinized during the dissolution process (Figure S6c,f). However, LH−CA/pHCA (1:1, 2:1) powders were dispersed in spherical particles, as observed by SEM, indicating that there was no obvious gelation during the dissolution of coamorphous LH−CA/pHCA (1:1, 1:2) (Figure S6a,b,d,e). This phenomenon indicates that the decrease of the dissolution rate of coamorphous LH−CA/pHCA (2:1) might be caused by the gelation of coamorphous LH−CA/pHCA (2:1) during the dissolution process. In summary, the gelatinization behavior of the amorphous form does not affect the amorphous recrystallization, which was consistent with the reports of amorphous ribavirin\(^{30}\) and amorphous capcetibantin.\(^{53}\) In
addition, this phenomenon also shows that both the degree of crystallization and the gelation can affect the dissolution rate of the coamorphous system.

2.9. Supersaturated Dissolution Study. Because the amorphous system is thermodynamically unstable and solvent-mediated recrystallization is prone to occur, the LH−CA/pHCA amorphous system may undergo recrystallization before the maximum solubility is reached. Therefore, the solubility and stability profiles of the coamorphous LH−CA/pHCA system were evaluated by the dissolution curve under supersaturation conditions. The supersaturated dissolution curves of crystalline LH and coamorphous LH−pHCA (1:1, 1:2, and 2:1) are shown in Figure 9. The dissolution profile of crystalline LH was basically the same as our previously published. As shown in Figure 9A,C, the solubility of the water-insoluble crystalline LH in the pH 2.0 buffer is very low. After 10 h of dissolution, the supersaturated solubility of LH was 0.39 mg/mL. The coamorphous system of LH−pHCA (2:1) exhibited a distinctive supersaturated dissolution curve, reaching its peak dissolution rate in the first 1h. However, the dissolution was slowly decreased close to that of crystalline LH. This phenomenon may be due to the poor stability of the coamorphous system in the pH 2.0 buffer. However, in comparison with crystalline LH and LH−pHCA (2:1), the supersaturation dissolution curves of coamorphous LH−CA (1:1, 1:2, and 2:1) and LH−pHCA (1:1 and 1:2) systems were significantly improved. Its supersaturated solubility is 1.75-, 1.79-, 1.65-, 1.59-, and 1.92-fold higher than that of LH, respectively. Such a phenomenon indicates that these formulations might not be recrystallized in the dissolution. The significant enhancement of supersaturated dissolution indicates that these five coamorphous systems hold great potential to enhance the absorption of water-insoluble LH \textit{in vivo}. Under the supersaturated condition of LH, the solubility of LH in solution is relatively large, and more LH in free state can be absorbed in solution. Therefore, this may be beneficial to the improvement of oral bioavailability of drugs.

Similarly, Figure 9B,D shows that the solubility of the water-insoluble crystalline LH in the pH 3.8 buffer is very low. The coamorphous system of LH−CA (2:1) exhibited a distinctive supersaturated dissolution curve, reaching its peak dissolution rate before 2 h and then slowly descending to the dissolution

![Figure 9. Supersaturated dissolution curves of crystalline LH, coamorphous LH−CA (1:1, 1:2, and 2:1) at pH 2 (A) and pH 3.8 buffer solution (B). The intrinsic dissolution curves of crystalline LH and coamorphous LH−pHCA (1:1, 1:2, and 2:1) at pH 2 (C) and pH 3.8 buffer solution (D) (n = 6).](image-url)
Each sample was gently placed in an aluminum holder, in di-
to the coamorphous LH indicating that the OAs could change the dissolution behavior
K decreased from pH 3.8
deamorphous system would be an e-
Biological (Shanghai, China). All other chemical reagents were
CA and LH
that the pHmax of the LH
intermolecular hydrogen bonds
employed to investigate the intermolecular hydrogen bonds between coamorphous systems. Solubility studies have shown that the pHmax of the LH−CA/pHCA coamorphous systems decreased from pH 3.8−2.0 compared to crystalline LH, indicating that the OAs could change the dissolution behavior of crystalline LH. In addition, the solubility of the coamorphous LH−pHCA was remarkably improved compared to the coamorphous LH−CA, which was attributed to the higher pKa value of pHCA than that of CA according to the solubility product principle-based formula derivation. It is expected that increasing the pKa value of the coformer in coamorphous system would be an effective strategy to improve the solubility of drugs. Moreover, the pKa value of the coformers would become a direct criterion for estimating the solubility behavior of the coamorphous system.

3. CONCLUSIONS
In conclusion, we prepared the LH−CA/pHCA (1:1, 1:2, and 2:1) coamorphous system by the vacuum rotary evaporation method and characterized it by PXRD and DSC. FTIR spectroscopy, Raman spectroscopy, and MD simulations were employed to investigate the intermolecular hydrogen bonds between coamorphous systems. Solubility studies have shown that the pHmax of the LH−CA/pHCA coamorphous systems decreased from pH 3.8−2.0 compared to crystalline LH, indicating that the OAs could change the dissolution behavior of crystalline LH. In addition, the solubility of the coamorphous LH−pHCA was remarkably improved compared to the coamorphous LH−CA, which was attributed to the higher pKa value of pHCA than that of CA according to the solubility product principle-based formula derivation. It is expected that increasing the pKa value of the coformer in coamorphous system would be an effective strategy to improve the solubility of drugs. Moreover, the pKa value of the coformers would become a direct criterion for estimating the solubility behavior of the coamorphous system.

4. EXPERIMENTAL SECTION

4.1. Materials. The model drug LH was gifted by Wuhan Humanwell Pharmaceutical Co., Ltd. (Hubei, China). Cinnamic acid (CA) and pHCA were purchased from Leaf Biological (Shanghai, China). All other chemical reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

4.2. Preparation of the Coamorphous System. Solvent evaporation method was used to prepare coamorphous LH−CA and LH−pHCA samples. Specifically, LH and CA or pHCA formulated with molar ratios of 1:1, 1:2, and 2:1 were dissolved in 40 mL of methanol and then dried in a round-bottom flask under vacuum at 45 °C for 45 min, respectively. A white sample was obtained and dried in a vacuum at a temperature of 32 °C for 20 h to remove the remaining methanol solvent. The dried sample was sieved with 120 mesh (125 μm) screen and stored in a desiccator with silica gel at 4 °C for further studies.

4.3. Powder X-Ray Diffraction. A Bruker D8 ADVANCE diffractometer (Bruker GmbH-Karlsruhe, Germany) with Cu Ka X-radiation (λ = 1.5406 Å) was used to collect diffractograms of different samples at ambient temperature. Each sample was gently placed in an aluminum holder, in which 40 kV of the tube voltage and 30 mA of the current were set. The PXRD pattern was recorded at a step size of 0.03 from 5 to 60° (2θ) with a scanning speed of 10°/min.

4.4. Differential Scanning Calorimetry. DSC of solid phases was carried by using a TA-DSC2500 calorimeter (TA-Instruments-Waters LLC, New Castle, DE, USA). Indium was used to calibrate the temperature and enthalpy of the instrument before the test. All experiments were carried out in open aluminum pans at a heating rate of 10 °C/min from 25 to 300 °C. Data were collected and analyzed using TA-Universal Analysis 2000 software (version 4.7A).

4.5. Fourier Transform Infrared Spectroscopy. The FTIR spectra of the samples were scanned with a Nicolet Impact 410 FT-IR spectrophotometer (Thermo Fisher Scientific Inc., MA, USA). In short, the samples were mixed with KBr and compressed into tablets. The measurement was performed under the condition of a scanning range of 4000−400 cm−1 (resolution 4 cm−1).

4.6. Raman Spectroscopy. The Raman spectrum was obtained by using a BWS Raman spectrometer (B&W Tek, Inc., USA) with a 1064 nm excitation laser. The spectrum of each sample was recorded over a range of 600−1800 cm−1 with a resolution of 9.5 cm−1.

4.7. MD Simulation. Through the analysis of the RDF under MD simulation, the specific atomic groups involving intermolecular hydrogen bonds were investigated. All calculations were performed by Materials Studio 2017 (Accelrys Software Inc., US). The amorphous cell module was used to construct the common amorphous structure, and the Forcite module was used to optimize the structure and perform the calculation of RDF.54,55 Specifically, the coamorphous LH−CA/pHCA (1:1, 1:2, and 2:1) were simulated under 45/45, 45/30, 60/60, and 60/30 number rations, respectively. All coamorphous systems were built in amorphous boxes and geometrically optimized. After that, the NPT ensemble was used to dynamically operate the cell, using Andersen54 and Berend-sen57 methods to control temperature and pressure for the adjustment of density. The NVT simulation was then performed by the Andersen thermostat. The time step of the NPT and NVT simulation was 1 fs, and the period was 1000 ps. We set the simulation of RDF analysis to 700−1000 ps, where the simulation showed a stable behavior during this interval.50

4.8. High-Performance Liquid Chromatography. Shimadzu LC-20A HPLC with a UV−vis detector was used to determine the concentration of LH. The mobile phase consisted of 91% (v/v) of acetonitrile and 9% (v/v) of buffer solution (0.05% of triethylamine and 0.05% of acetic acid). The separation was achieved using a DIKMA C18 (250 × 4.6 mm, 5 μm) column with a flow rate of 1.0 mL/min. The wavelength used for LH was set at 230 nm. The acquired calibration curve was linear in the range of 0.1−100 μg/mL (R2 = 0.9999) (Figure S7), and the retention time was 8.8 min for LH.

4.9. Solubility Experiments. The solubility study was performed under different buffering solutions with varying pH values (i.e., pH = 1.0, 2.0, 3.8, 4.5, 5.5, and 6.8). Excess solid sample was added to a 10 mL buffer solution and stirred at 25 °C for 24 h. After that, the sample was filtered through a 0.45 μm membrane (Millipore, Bedford, MA) and analyzed according to the previously described HPLC method.

4.10. Dissolution Tests. 4.10.1. IDR Experiments. The IDRs of coamorphous LH−CA/pHCA (1:1, 2:1, and 1:2)
were determined by using a ZRS-8G (Tianda Tianfá Technology Co., Ltd., China) dissolution tester. Prior to the test, different samples were compressed with a hydraulic press. The dissolution test within 120 min was conducted with a paddle rotation speed of 50 rpm/min and 900 mL of hydrochloric acid solution (pH 2.0) or acetate buffer (pH 3.8) as the medium at 37 °C. The sample (3 mL) was removed and immediately replaced with the same volume of buffer. Each sample was analyzed by HPLC, as described above.

4.10.2. Supersaturated Dissolution. As previously reported, supersaturated dissolution of cosolvent morphous LH–CA/pHCA (1:1, 2:1, and 1:2) test were determined by using a ZRS-8G (Tianda Tianfá Technology Co., Ltd., China). In brief, the supersaturated dissolution test was conducted with a paddle rotation speed of 50 rpm/min in 200 mL of hydrochloric acid solution (pH 2.0) or acetate buffering solution (pH 3.8) for 36 h. The sample (3 mL) was removed and immediately replaced with the same volume of buffer. Each sample was analyzed by HPLC, as described above.

4.11. Data Analysis. One-way ANOVA was used for all statistical data analysis. The difference was considered significant at p < 0.05.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05510.

PXRD for the evaporation product and physical mixture, DSC for physical mixtures, Fourier transform infrared spectroscopy (FTIR) for physical mixtures, Raman spectroscopy for physical mixtures, powder polarizing microscope, powder scanning electron microscope, standard curve (PDF)

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Notes
The authors declare no competing financial interest.

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