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Enhancing Norfloxacin's Solubility and Antibacterial Activity through Pharmaceutical Salt Formation with Fluorobenzoic Acids

Shuhui Wang, Jiashu He, Chenyu Ruan, Panyue Cao, Ziyi Zhang, Chengjun Jiang*

School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou, China
Email: *jcj312@zust.edu.cn

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Abstract

Norfloxacin (NOR), a broad-spectrum fluoroquinolone antibiotic, is widely used to treat bacterial infections. However, its clinical application is hindered by poor aqueous solubility and low oral bioavailability. To address these limitations, this study developed two novel pharmaceutical salts of NOR using 4-fluorobenzoic acid (4-FA) and 2-fluorobenzoic acid (2-FA) as counterions. The salts were synthesized via slow evaporation crystallization, and their structures were characterized by single-crystal X-ray diffraction (SCXRD). Comprehensive solid-state analyses, including powder X-ray diffraction (PXRD), Fourier-transform infrared (FT-IR) spectroscopy, and differential scanning calorimetry (DSC), confirmed the successful formation of the salts. Notably, the salt formation significantly improved NOR's solubility and dissolution behavior. Furthermore, these modifications enhanced NOR's antibacterial efficacy, as evidenced by stronger bacterial inhibition and reduced minimum inhibitory concentration (MIC) values. This study demonstrates a promising strategy for optimizing the biopharmaceutical performance of NOR through salt formation.

Subject Areas

Pharmaceutical Engineering

Keywords

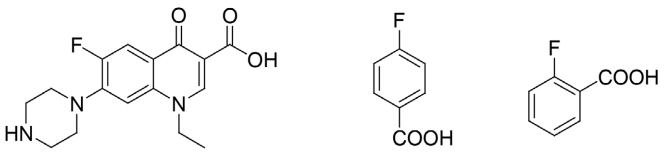
Norfloxacin, Crystal Structure, Solubility, Bioavailability, Antimicrobial Activity

1. Introduction

Pharmaceutical salt formation is one of the most effective and widely employed

strategies to optimize the physicochemical properties of active pharmaceutical ingredients (APIs), including solubility, bioavailability, stability, and processability. Salts are crystalline materials composed of ionized drug molecules and counterions within the same crystal lattice, stabilized primarily by ionic interactions [1]. While salt formation requires the API to possess ionizable functional groups, the resulting products often exhibit enhanced stability compared to their free forms. However, the formation of hydrates-a common phenomenon in pharmaceutical salts—may introduce challenges in stability and downstream processing [2]. Despite these considerations, salt formation remains a cornerstone of pharmaceutical development, enabling the rational design of drug formulations with tailored properties [3]-[5].

Norfloxacin (NOR, **Figure 1**), a broad-spectrum fluoroquinolone antibiotic, is widely used to treat bacterial infections. However, its therapeutic potential is limited by poor aqueous solubility and low bioavailability. To address these limitations, various salt and cocrystal forms of NOR have been explored, including those with adipic acid, malonic acid, hydroxybenzoic acids, sulfonic acids, and non-steroidal anti-inflammatory drugs (NSAIDs) [6]-[12]. Additionally, cocrystals with flavonoids such as naringenin and hesperetin have been reported to improve NOR's physicochemical properties [13]-[15]. The increasing incorporation of fluorine into bioactive molecules is attributable to the profound effects this substitution has on their activity and disposition. Building upon these advancements in supramolecular crystal engineering, this study aims to develop novel pharmaceutical salts of NOR using 4-fluorobenzoic acid (4-FA) and 2-fluorobenzoic acid (2-FA) as counterions. These pharmaceutically acceptable phenolic acids were selected to modulate NOR's solubility and antibacterial activity. Through systematic solid-form screening and characterization, we demonstrate how salt formation can serve as a viable strategy to enhance NOR's biopharmaceutical performance.



(a) (b) (c)

Figure 1. Chemical structure of (a) Norfloxacin (NOR), (b) 4-Fluorobenzoic acid (4-FA), (c) 2-Fluorobenzoic acid (2-FA).

2. Results and Discussion

2.1. Single-Crystal X-Ray Diffraction (SCXRD) Analysis

Colorless single crystals of **NOR-2-FA hydrate (Salt 1)** and **NOR-4-FA hydrate (Salt 2)** were successfully obtained via solvent evaporation using ethanol/water and methanol/water, respectively. Structural analysis confirmed the formation of ionic salts rather than cocrystals. The salt formation was first assessed using the **ΔpKa rule**, where ΔpKa (pKa(base) – pKa(acid)) values for the piperazinyl NH

group of NOR (pKa = 8.67) and the carboxylic acid groups of 2-FA (pKa = 3.27) and 4-FA (pKa = 3.98) were greater than 3, indicating complete proton transfer from the carboxylic acids to NOR's piperazine nitrogen. This ionic interaction was further supported by **SCXRD data**, revealing nearly identical C=O and C-O bond lengths in the carboxylate groups: **Salt 1 (NOR-2-FA):** C23-O4 (1.259 Å), **Salt 2 (NOR-4-FA):** C23-O4 (1.256 Å). The comparable bond lengths confirm delocalization of the negative charge across the carboxylate oxygens, consistent with salt formation.The three-dimensional (3D) packing motifs and intermolecular interactions were elucidated from SCXRD analysis. Both salts exhibit extensive hydrogen-bonding networks, with detailed crystallographic parameters and hydrogen-bond geometries summarized in Table 1.

Table 1. Crystallographic parameters of NOR-2-FA and NOR-4-FA.

	NOR-2-FA	NOR-4-FA
Empirical formula	$C_{23}H_{25}F_2N_3O_6$	$C_{23}H_{27}F_2N_3O_7$
Formula weight	477.46	495.47
Temperature/K	170.00	170.00
Crystal system	triclinic	triclinic
Space group	P-1	P-1
a/Å	7.3162 (3)	7.1250 (4)
b/Å	10.4107 (5)	11.2451 (7)
c/Å	15.4537 (7)	14.7193 (8)
α/°	84.3830 (10)	88.852 (2)
β/°	82.7090 (10)	76.514 (2)
γ/°	70.1110 (10)	86.292 (2)
Volume/Å3	1096.01 (9)	1144.40 (11)
Z	2	2
ρcalcg/cm^3	1.447	1.438
μ/mm^{-1}	0.653	0.661
F(000)	500.0	520.0
Crystal size/mm^3	0.28 × 0.1 × 0.06	0.23 × 0.06 × 0.04
Radiation	GaKα (λ = 1.34139)	GaKα (λ = 1.34139)
2Θ range for data collection/°	7.87 to 121.426	6.854 to 108.036
Index ranges	−9 ≤ h ≤ 9, −13 ≤ k ≤ 13, −20 ≤ l ≤ 20	−8 ≤ h ≤ 8, −13 ≤ k ≤ 13, −17 ≤ l ≤ 17
Reflections collected	23440	16710
Independent reflections	4977 [R_{int} = 0.0343, R_{sigma} = 0.0380]	4183 [R_{int} = 0.0330, R_{sigma} = 0.0345]

Continued

Data/restraints/parameters	4977/0/312	4183/1/324
Goodness-of-fit on F2	1.021	1.091
Final R indexes [I>=2σ (I)]	R_1 = 0.0376, wR_2 = 0.1083	R_1 = 0.0381, wR_2 = 0.1019
Final R indexes [all data]	R_1 = 0.0390, wR_2 = 0.1097	R_1 = 0.0433, wR_2 = 0.1061
Largest diff. peak/hole / e Å-3	0.28/−0.27	0.17/−0.27

2.1.1. NOR-2-FA Hydrate (Salt 1)

NOR-2-FA hydrate crystallizes in the monoclinic system with space group P-1. The asymmetric unit contains one NOR molecule, one 2-FA molecule, and one water molecule in a 1:1:1 stoichiometric ratio. Structural analysis confirms complete proton transfer from the carboxylic group of 2-FA to the piperazine N1 atom of NOR. The crystal structure features an intricate hydrogen bonding network: The water molecule serves as a bridge between NOR and 2-FA through two strong hydrogen bonds:N3-H3B···O4 (1.779 Å, 166.30˚), resulting in the formation of an extended one-dimensional (1D) chain structure along the crystallographic axis (**Figure 2**). This well-defined hydrogen bonding network contributes to the stability of the crystal lattice and may influence the compound's physicochemical properties.

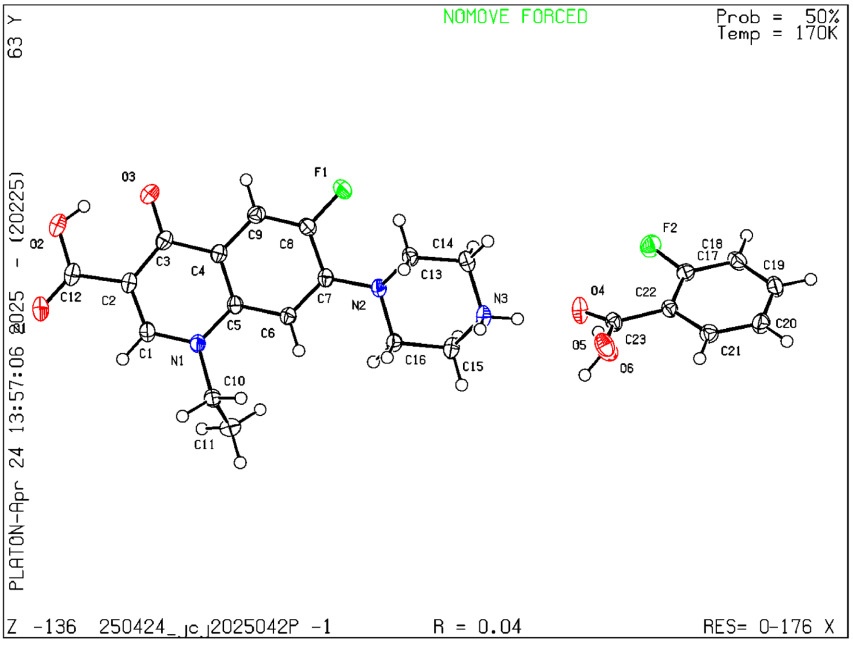


Figure 2. Asymmetric unit of salt 1.

2.1.2. NOR-4-FA Hydrate (Salt 2)

NOR-4-FA hydrate crystallizes in the monoclinic P-1 space group, with each asymmetric unit containing one NOR molecule, one 4-FA molecule, and two water molecules in a 1:1:2 stoichiometric ratio. The structure exhibits complete pro-

ton transfer from 4-FA to the piperazine N3 atom of NOR, forming a charge-assisted hydrogen bond network. Proton transfer creates strong N-H···O hydrogen bonds: N3-H3A···O5 (2.829 Å, 161.84˚), N3-H3A···O4 (2.993 Å, 133.71˚). The presence of two water molecules in the crystal lattice creates an extensive hydrogen bonding network that significantly influences the overall packing arrangement (**Figure 3**). This hydration pattern, combined with the charge-assisted interactions, contributes to the structural stability of the salt form. The 1D chain formation through water-mediated hydrogen bonds suggests potential implications for the compound's dissolution behavior and solid-state stability.

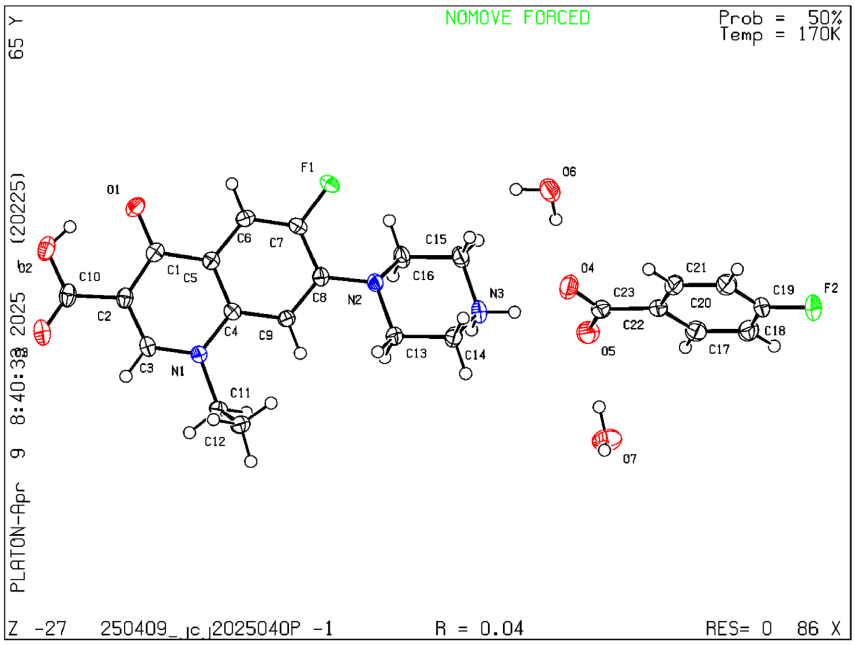
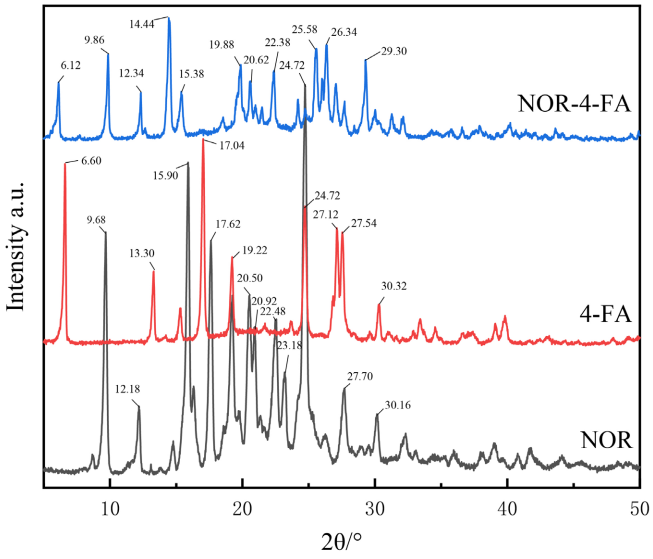


Figure 3. Asymmetric unit of salt 2.

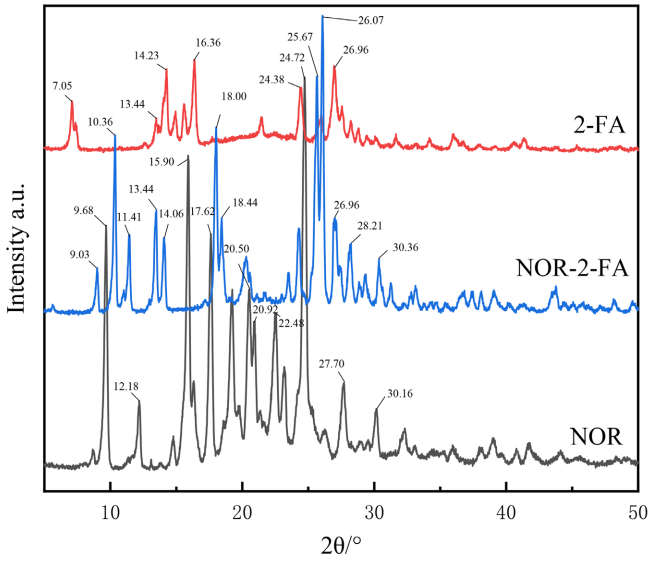
2.2. Powder X-Ray Diffraction (PXRD) Analysis

Powder X-ray diffraction serves as a primary analytical technique for assessing the purity and phase homogeneity of active pharmaceutical ingredients (APIs) and their crystalline forms. This method enables direct comparison of diffraction patterns between starting materials and resulting multicomponent products, providing a rapid and reliable means of crystalline phase identification. NOR-2-FA Salt Formation: Distinct new diffraction peaks emerged at 10.36˚, 18.00˚, and 26.07˚ (2θ), The characteristic 2-FA peak at 16.36˚ disappeared completely. These changes confirm successful salt formation (**Figure 4(a)**). NOR-4-FA Salt Formation: sharp new reflections appeared at 6.60˚, 17.04˚, and 24.72˚ (2θ). Notable attenuation of 4-FA peaks at 13.30˚ and 19.22˚ was observed. The pattern evolution verifies new phase formation (**Figure 4(b)**). Both salt forms exhibited completely distinct PXRD profiles compared to their individual components. The disappearance of coformer peaks coupled with emergence of new reflections confirms successful crystalline phase transformation. The sharpness and intensity of new peaks indi-

cate high crystallinity of the resulting salts. The above changes in diffraction patterns indicate that a new crystal phase has formed in two salts.



(a)



(b)

Figure 4. PXRD pattern of NOR (a) NOR-4-FA and (b) NOR-2-FA.

2.3. Thermal Analysis

The thermal behavior of NOR and salts was analyzed by DSC. The DSC curves for the NOR experiments with new solid phases are shown in **Figure 5**. It shows that the two salts exhibited a distinct endothermic peak with a pronounced profile, and their peak temperatures were different from those of NOR or the counterions. This change meant that new phases were formed. For salt **1**, its peak temperature (213.8˚C) was between those of NOR (224.2˚C) and 2-FA (142˚C). However, the

peak temperature (214.6˚C) of salt **2** was between those of NOR (224.2˚C) and 4-FA (184˚C). This shows that the melting point of the salt has little relationship with the API and counterions. Furthermore, endotherm peaks prior to melting were observed for the two salts, indicating that the two salts were of hydrous nature, which was also supported by their single-crystal structures. The release of water over a wide temperature range suggests a variety of hydrogen-bonding interactions and energies involved in the bonding of water to the salts.

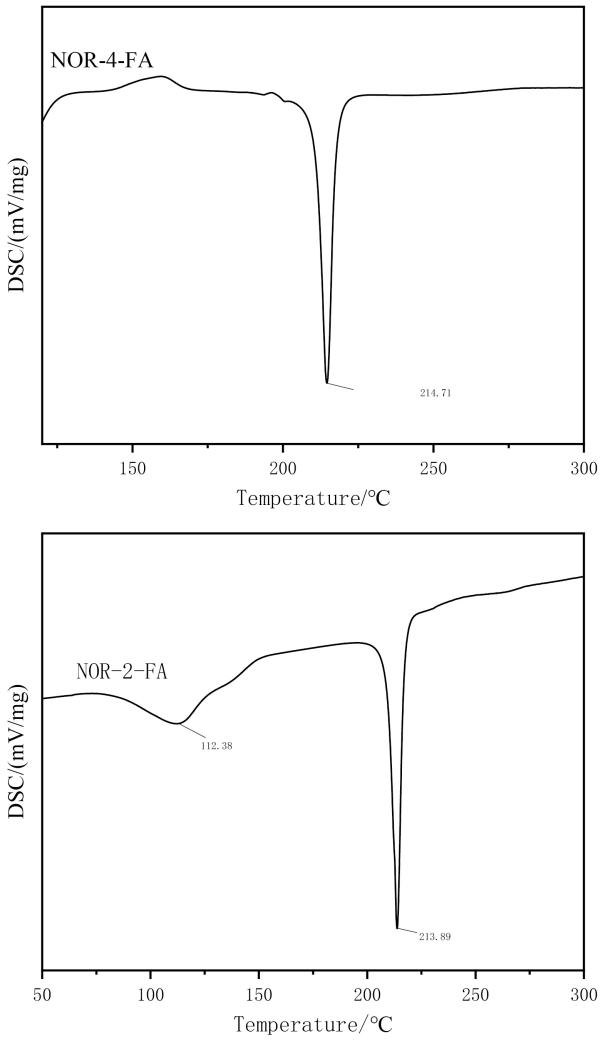
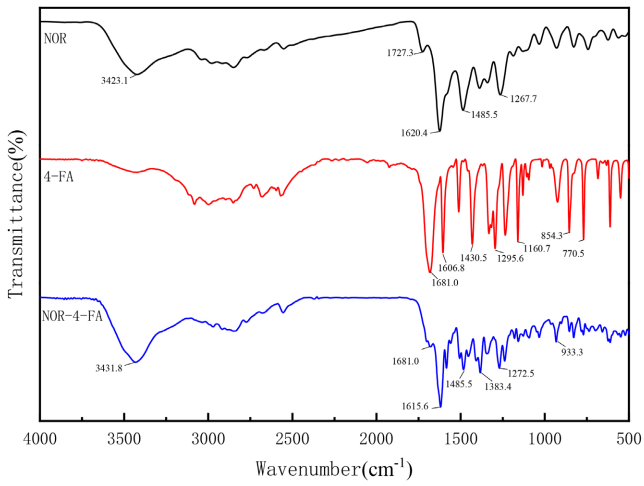


Figure 5. DSC curves of NOR Salt 1 and Salt2.

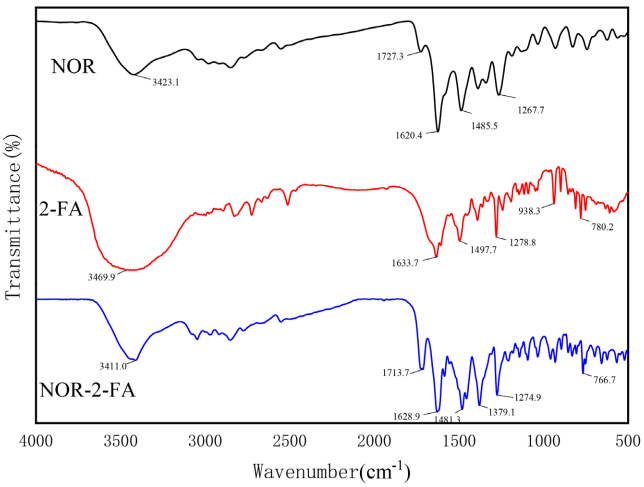
2.4. FT-IR Analysis

FT-IR spectra are useful for identifying changes in hydrogen bonding during salts forming by analyzing the frequency shifts in the relevant vibrational bands. IR spectroscopy was used to analyze the two novel salts, along with pure NOR, 2-FA, and 4-FA, and the obtained spectra are presented in **Figure 6**. The characteristic peaks of NOR at 1622 and 1729 cm^{-1} were attributed to the C=O stretching of pyridinone and the C=O stretching of carboxylic acids, respectively, aligning with

the findings reported in the existing literature. Both salt **1** and salt **2** exhibited characteristic peaks for pyridinone C=O at 1625 cm^{-1} that were essentially consistent with NOR. Furthermore, in the spectra of salt **1** and salt **2**, the absorption peaks for the C=O stretching vibration of carboxylic acids shifted from 1727 to 1713 cm^{-1} and 1681 cm^{-1}, respectively. These significant wavenumber changes may have resulted from intramolecular interactions (hydrogen bonding), consistent with the results obtained by SCXRD. This suggested that the ketone and carboxylic acid group of NOR remained stable without forming zwitterions. Additionally, the broad IR absorption frequencies between 2480 and 2520 cm^{-1} for the two salts indicate the protonation of the N atom (NH_2^+) in the piperazinyl ring, with the proton clearly transferring from the carboxylic acid. This observation further implies an interaction between NOR and phenolic acid via the piperazine ring. These changes were corroborated by the crystal structure analysis.



(a)



(b)

Figure 6. FT-IR pattern of NOR (a) NOR-2-FA and (b) NOR-4-FA.

2.5. Equilibrium Solubility Study

Solubility is a critical parameter for enhancing the bioavailability and effectiveness of a drug product. The forming salt is utilized to increase the solubility of insoluble drugs and is considered one of the effective methods for increasing their aqueous solubility. To assess whether the salt technique improved the solubility of NOR, we conducted tests of the solubility of NOR and the two salts in dilute hydrochloric acid solution (pH = 1.2), phosphate buffer (pH = 6.8), and pure water, separately. A slight excess of the appropriate NOR and the two salts' solid form was dissolved in each medium and stirred at 100 rpm at 37 ± 0.5˚C for 24 h. The solution was filtered, and the NOR concentration of the filtrate after filtration was determined by high performance liquid chromatography, with the results shown in Figure 7.

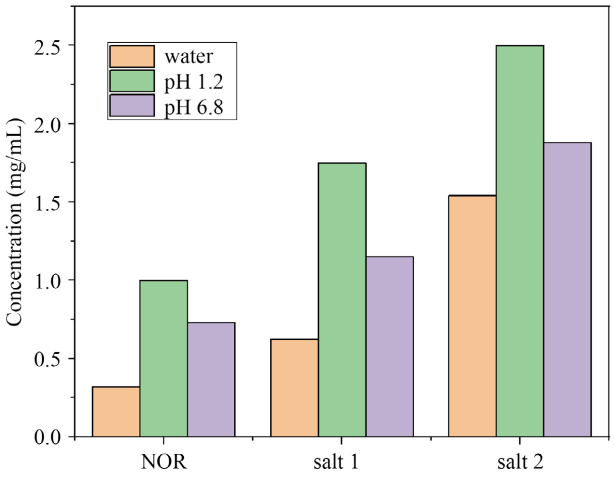


Figure 7. Equilibrium solubility of NOR and its salts.

As depicted in Figure 7, it was observed that the solubilities of both salts consistent with the trend in the solubility changes for NOR. Although both the pure NOR and the two salts displayed similar solubility, it was consistently found that NOR in the salt exhibited a higher solubility than pure NOR when placed into the corresponding buffer solutions, following the orders: salt **2** > salt **1** > NOR. Consequently, it can be concluded that the concentrations of NOR from these two solid forms in media with pH 1.2, pH 6.8, and pure water are 2-5 times higher than those of pure NOR, indicating an advantage provided by utilizing a salt strategy to establish superior solubility. Noteworthily, the pH 6.8 environment chosen for this study accurately reflects the physiological conditions of the human small intestine. Consequently, the enhanced solubility contributes to facilitating better absorption, which lays a foundation for further improving the bioavailability of NOR.

2.7. Antibacterial Activity Study

To obtain quantitative and precise data on the biological activity of the current

salts, minimum inhibitory concentration (MIC) tests were conducted against bacterial strains such as *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Bacillus subtilis* (*B. subtilis*), and *Staphylococcus aureus* (*S. aureus*).

The results are summarized in Table 2, which clearly indicates that the MIC values for both salts are significantly lower than those for NOR, showing enhanced antimicrobial susceptibility. The salts demonstrated moderate to relatively high effectiveness against all tested pathogens, with MIC values ranging from 0.12 to 0.5 μg/mL. Prior research has also suggested that dissolution performance is a crucial factor in determining antibacterial activity, with samples that dissolve more rapidly exhibiting stronger antibacterial effects. Therefore, both salts may have enhanced antibacterial activity owing to their increased solubility.

Table 2. Minimum inhibitory concentration values for NOR, salt1 and salt2.

MIC (μg/mL)	*E. coli*	*P. aeruginosa*	*B. subtilis*	*S. aureus*
NOR	0.51	0.55	0.53	0.51
Salt 1	0.22	0.13	0.15	0.18
Salt 2	0.25	0.23	0.24	0.10

3. Materials and Methods

3.1. Materials and methods

Materials NOR (≥99%, Zhejiang Lepu Pharmaceutical Co., Ltd., China), 4-Fluorobenzoic acid, (≥99.0%, Energy Chemical, China), 2-Fluorobenzoic acid (≥99.0%, Energy Chemical, China), were purchased and used exactly as prescribed.Analytical grade solvents were used for the crystallization experiments. All purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd.

3.2. Synthesis of Salts

3.2.1. Preparation and Crystal Cultivation of NOR-2-FA Salt

NOR (319 mg, 1 mmol) and 2-FA (140 mg, 1 mmol) were stirred in a solvent of ethanol: water = 1:1 in a constant temperature magnetic stirrer and heated in a water bath at 60˚C - 65˚C for 30 minutes. The solid powder in the glass bottle was basically dissolved. Filter while hot, place the filtrate in a 5 ml glass bottle, slowly evaporate in a fume hood to obtain needle shaped crystals, and characterize them by SC-XRD.

3.2.2. Preparation and Crystal Cultivation of NOR-4-FA Salt

NOR (319 mg, 1 mmol) and 4-FA (140 mg, 1 mmol) were stirred in a solvent of methanol: water = 1:1 in a constant temperature magnetic stirrer and heated in a water bath at 60 - 65˚C for 30 minutes. The solid powder in the glass bottle was basically dissolved. Filter while hot, place the filtrate in a 5 ml glass bottle, slowly evaporate in a fume hood to obtain needle shaped crystals, and characterize them by SC-XRD.

3.3. Single Crystal X-Ray Diffraction

Single-crystal XRD data were collected on a Bruker SMART APEX II single-crystal X-ray CCD difiractometer with graphite-monochromatized (Mo Kα, λ = 0.71073 Å) radiation at room temperature (293 - 296 K). The X-ray generator operated at 50 kV and 30 mA. We performed data reduction using APEX-II Software, corrected intensities for absorption using SADABS, and solved and refined the structure using SHELX2018. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were fixed geometrically at calculated positions and refined using the riding model. A solvent mask was applied in crystal structure refinement because the partial stoichiometry/nonstoichiometric water molecules present in the channels could not be located properly. So, crystal structures are described without water molecule occupancy, and the same crystallographic files have been deposited.

3.4. Powder X-Ray Diffraction

PXRD data were acquired utilizing a Rigaku Ultima IV X-ray Diffractometer (Rigaku, Tokyo, Japan) operating at 40 kV and 30 mA employing Cu-Kα radiation having wavelength of 1.5406 Å.

3.5. Vibrational Spectroscopy

The study utilized Fourier transform IR (FTIR) spectroscopy to analyze NOR, salt1 and salt2 on a Bruker Alpha FT-IR spectrometer), with potassium bromide (KBr) as the background material. The samples' IR spectra were recorded in a spectral range of 400 to 4000 cm^{-1}. To correct for background effects and improve visualization, the spectra were normalized using Omnic software.

3.6. Solubility and Dissolution Rate Studies

Determination of Equilibrium Solubility. The equilibrium solubility of NOR, salt1 and salt2 were determined in three dissolution media (hydrochloric acid solution with pH = 1.2, phosphate buffer with pH = 6.8, and pure water) using the shake flask method as specified in the Chinese Pharmacopoeia at 310 K. Saturated solutions of the above-mentioned compounds were first prepared in triplicate by pouring an excess of sample into 5 mL of each of the three different media and stirred with continuous oscillation at 200 rpm for 48 h. After equilibration, the samples were allowed to stand for a few hours, and the supernatant was filtered through a 0.22 μm microporous membrane. The resultant filtrate was diluted with respective dissolution media to a suitable magnification and then determined by HPLC, with each set of samples in parallel three times. The remained solid after the experiment was collected, and the stability was tested by PXRD.

3.7. Antibacterial Activity Measurement

Pseudomonas aeruginosa (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Esch-*

erichia coli (*E. coli*), and *Bacillus subtilis* (*B. subtilis*) were chosen as experimental strains to comparatively investigate the antibacterial effects of the salt and NOR. The minimal inhibitory concentration (MIC) was determined using the dilution method. In aseptic conditions, all test samples were diluted to gradient concentrations with medium and inoculated with approximately 1×10^8 cfu/mL of actively dividing bacterial cells. After incubation at 37˚C for 24 h, bacterial growth was assessed visually and spectrophotometrically. The MIC was defined as the lowest concentration that inhibited bacterial growth. All the experiments were conducted in triplicate.

4. Summary

In this study, salts of the antibacterial agent NOR with 4-Fluorobenzoic acid and 2-Fluorobenzoic acid were meticulously designed and successfully self-assembled based on established optimization tactics and synergistic enhancement efficacy. The obtained salts were structurally characterized, and their *in vitro* biopharmaceutical peculiarities were systematically investigated both theoretically and experimentally. The solubility experiments indicated that the salts could enhance the solubility of NOR. However, the formation of hydrates in NOR salts may introduce challenges in stability and downstream processing.

Furthermore, the antimicrobial activity tests proved that salts exhibit a satisfactory increase in antimicrobial effect, pointing to a novel direction for optimizing the efficacy of NOR. Clearly, *in vivo* confirmations are required to exploit their applications in the field of pharmacy.

Acknowledgements

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Supporting Information

CCDC (2446703, 2442402) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Contributions

All authors contributed to the study's conception. The whole experimental design was guided by Chengjun Jiang. Data analysis and writing were performed by Shu hui Wang. Solubility experiment and sample characterization were performed by Jiashu He. The acute toxicity test was performed by Ziyi Zhang. All authors read and approved the final manuscript.

Conflict of Interests

All the authors declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in/or the review of this manuscript.

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