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# Preparation and Quantitative Analysis of a Ciprofloxacin-Mefenamate Multicomponent Salt Using Solvent-Drop Grinding and UV-Derivative Spectrophotometry

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**ABSTRACT**

A drug-drug multicomponent system (MS) is an effective strategy to improve the physicochemical properties of both participating drugs. Recent studies have reported the formation of ciprofloxacin-mefenamate using automated liquid-assisted grinding, solvent evaporation, and single-crystal X-ray diffraction. While HPLC studies confirmed a twofold increase in ciprofloxacin solubility, data on mefenamic acid solubility remain unavailable. Moreover, studies often used expensive and less accessible instrumentation. To address this limitation, this study developed affordable, reliable green methods to prepare the ciprofloxacin–mefenamate salt. The MS was prepared by solvent-drop grinding (SDG) using 98% ethanol with a mortar and stamper. It was analyzed using PXRD, an electrothermal, an FTIR, and an NMR analysis. Next, a UV spectrophotometry derivative was developed using water to determine the drug's concentration. Results confirmed that green preparation and analysis yielded products with comparable characteristics, including PXRD patterns, thermal profiles, and FTIR spectra. These were confirmed using NMR. The UV derivative methods were also valid and suitable for simultaneously determining the ciprofloxacin and mefenamic acid levels. Ciprofloxacin solubility increased 2.7-fold, while mefenamic acid solubility rose 7.6-fold compared to its pure form. Electrothermal analysis, FTIR, and NMR confirmed ionic interactions in the salt. Derivative spectrophotometry enabled simultaneous drug quantification, offering a green alternative to HPLC. Mefenamic acid solubility increased 7.6-fold by the salt reaction with ciprofloxacin, remained stable in solution, and has the potential for further development. These findings support the potential application of the CF-MA salt in developing solid oral pharmaceutical formulations, especially in resource-limited settings.

**Keywords:** Multicomponent salt, Solubility, UV-Vis Spectrophotometer derivative, Green analytical chemistry, Simultaneous drug quantification.

## INTRODUCTION

The pharmaceutical industry continues to face a significant challenge in drug formulation. Two of the most common problems found in several antibiotics are low solubility and instability. In fact, the drugs must dissolve quickly to gain good bioavailability. Scholars argue that two important aspects must be considered in drug development: determining the ideal dose and creating high solubility (Guo et al., 2014; Champeau et al., 2015). Failure to achieve one of these may lead to suboptimal drug levels in the bloodstream, thereby negatively affecting its therapeutic efficacy (Piper et al., 2020). To address poor solubility, several researchers have proposed potential methods to increase drug solubility in the body, including the creation of multicomponent systems (Khodov et al., 2023). A multicomponent system is a solid phase formed by the interaction of two or more substance molecules or components within a certain stoichiometric ratio (Najih et al., 2023). This method has become a powerful strategy to improve the physicochemical characteristics of a drug, particularly by increasing its solubility and, eventually, its bioavailability (Yu et al., 2023; Nugrahani et al., 2020). One of the antibiotics that has a low level of solubility and instability is ciprofloxacin (CF). This fluoroquinolone-class


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antibiotic possesses broad-spectrum activity and is effective against both Gram-positive and Gram-negative bacteria. Thus, CF is widely used to treat bacterial infections (Thai et al., 2023). Despite its clinical efficacy, according to the Biopharmaceutical Classification System (BCS), CF is categorized into the class IV compound category, which has poor solubility and permeability (Hansmann et al., 2018; Olivera et al., 2011). Therefore, the characteristics of this antibiotic need to be modified to improve its solubility and permeability so that it works effectively. Nowadays, CF is widely marketed in solid dosage forms, especially tablets, where its low solubility poses formulation challenges. To address this issue, the formation of a multicomponent system with some organic compound has become a promising approach to improve its physicochemical characteristics (Cavanagh et al., 2018; Nugrahani et al., 2022; Abdullah et al., 2022).

A recent study by Acebedo-Martínez et al. (2023) investigated the ciprofloxacin – mefenamate multicomponent salt (CF-MA MS). They reported an enhancement in ciprofloxacin (CF) solubility. However, their study did not address the solubility of mefenamic acid (MA). The crystal structure of the CF–MA multicomponent salt was determined using single-crystal X-ray diffraction, a method that is still rarely accessible in developing countries, such as Indonesia. Moreover, the solubility of CF in its salt form was previously assessed using HPLC, a high-cost method as it requires high-grade organic solvents and specialized columns, as well as contributing to hazardous chemical waste. Due to this limited accessibility and costly method, it is important to explore simpler preparation techniques and widely available instruments for analyzing the drug-drug multicomponent system. Therefore, this study reintroduces the use of water as a solvent to encourage greener technology development. For example, the mathematically manipulated method, such as the spectrophotometer UV derivative, can be used to replace HPLC. Unlike HPLC, which needs organic solvents and is more costly, this UV-based method is more time-efficient. In this study, mefenamic acid (the neutral form) was used as the starting material, while mefenamate (the anionic salt form) is its derivative that could be considered for further applications.

The molecular structure of CF and MA (Figure 1). FC indicates the amphoteric form due to the carboxylic and amine moieties, while the acidic form of MA shows its carboxylic site. The ionic bond occurs when the carboxylic acid group releases $H^+$ and protonates the piperazinyl group on CF from the COOH group on MA (Acebedo-Martínez et al., 2023). The right counterion can reduce the intrinsic melting point and solubility (Izutsu et al., 2016). Based on this understanding and supported by prior studies on a promising approach to enhance drug solubility (Khodov et al., 2023), this study hypothesizes that the solubility of mefenamic acid will significantly increase in its salt form due to ionic interaction with ciprofloxacin.

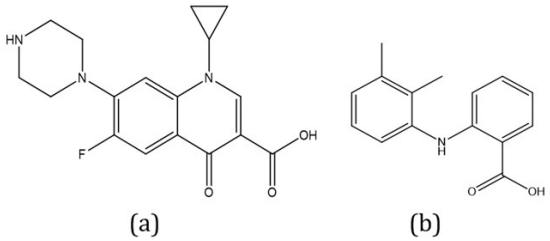



Figure 1. (a) Ciprofloxacin (CF) and (b) Mefenamic Acid (MA) (NCBI ., 2025).

Notably, combining ciprofloxacin and mefenamic acid in a multicomponent salt offers dual therapeutic potential, antibacterial and anti-inflammatory, in a single dosage form. This combination may be beneficial for treating infections associated with inflammation, such as dental abscesses, gastrointestinal infections, and post-surgical wounds (Liu et al., 2022). However, previous studies have not reported the solubility improvement of MA in the salt form, which remains a crucial aspect of dual-drug formulation efficacy.

This study introduces some novelties that contribute to both scientific advancement and sustainable pharmaceutical practices. Notably, this is the first study to investigate MA solubility enhancement in its salt form. The findings are expected to address limitations related to solubility and analytical costs, while also contributing to sustainable pharmaceutical development aligned with green chemistry principles (Asif, 2021).

Based on this background, this research has several key aims. First, it attempts to prepare the CF-MA multicomponent salt (CF-MA MS) using a conventional technique. It also characterizes the solid-state form of the salt using electrothermal analysis, PXRD, and FTIR. After that, the strength of intermolecular interactions in solution is evaluated using *nuclear magnetic resonance* (NMR). Then, a derivative UV-spectrophotometric method is developed in an aqueous medium for the simultaneous quantification of CF and MA. Finally,

the study aims to assess the solubility enhancement of MA in its salt form.

## MATERIALS AND METHODS

### Instrumentation

This study utilized a range of instruments for sample preparation and analysis. For general lab equipment, tools like an analytical balance (Fujitsu FSR-A220, Japan), spatula, Pyrex® glass beaker, dropper pipette, stir bar, measuring cup Pyrex®, vial, Petri dish, watch glass, mortar, pestle/stamper, and ultrasonic cleaner (WiseClean WUC-D06H, in Gangwon-do, South Korea) were used. Meanwhile, analytical instruments included electrothermal IA 9000 (Stanford, UK), FTIR spectrometer type A FT/IR-4200 instrument from Jasco (Tokyo, Japan), NMR (*Nuclear Magnetic Resonance*) Nanalysis 60 MHz (Santa Clara, USA), UV-Vis spectrophotometer Diode Array Hewlett-Packard 8453 (Santa Clara, USA), and PXRD (*powder X-ray diffractometry*) Rigaku Miniflex (Tokyo, Japan).

### Materials

Like the instruments, the study also involved various materials from different sources. Ciprofloxacin (98%) and mefenamic acid (98%) in this study were obtained from TCI (Tokyo, Japan), while ethanol (98%) and potassium bromide (KBr, for FTIR use) were provided by Merck®. Deuterated chloroform ($CDCl_3$, 99%) was supplied by Sigma-Aldrich (Jakarta, Indonesia), and distilled water was prepared in-house at the Bandung Institute of Technology (Bandung, Indonesia).

### Preparation of CF-MA MS

The CF-MA multicomponent was prepared by mixing ciprofloxacin (331.34 g/mol) and mefenamic acid (241.29 g/mol). A total of 1g of an equimolar powder was weighed and transferred to a mortar, while 0.5 mL of 98% ethanol was added gradually to aid homogenization. The mixture was manually ground for 30 minutes at room temperature to facilitate solid-state interaction and salt formation. The 98% ethanol was then selected for its moderate polarity and classification as a green solvent with low toxicity and minimal environmental impact. The reaction was confirmed using electrothermal analysis and powder X-ray diffraction (PXRD).

### Characterization

#### Powder X-ray diffractometer analysis

The sample was placed evenly in the holder and leveled well to avoid changes in particle orientation during the analysis process. The diffractometric scan was conducted across a 2θ range of 3° to 40°, with a scanning rate set to 5° per minute. Data were acquired under Cu-Kα radiation (wavelength: 1.5418 Å), operated at 40 kilovolts and 35 milliamperes.

#### FTIR spectrophotometer analysis

To prepare for FTIR analysis, the sample was finely blended with potassium bromide (KBr) at a 1:100 ratio and compressed into a transparent pellet. Infrared absorbance data were collected across the 4000–400 $cm^{-1}$ region, using a spectral resolution of 16 $cm^{-1}$.

#### Nuclear Magnetic Resonance Analysis

This analysis was conducted by elucidating the two-dimensional structure of the CF-MA multicomponent salt through $^1$H-NMR analysis. The resulting spectra were examined to identify the functional groups present. CF-MA MS and its individual components were dissolved in $CDCl_3$, with each solution containing tetramethylsilane (TMS) added as the internal standard. Data acquisition was performed at a resolution of 0.179 Hz per point, with a relaxation delay set to 1.929335 seconds. NMR signals were acquired and interpreted using *NMReady software version 2.0.7* (Nanalysis, Calgary, Canada).

### Solubility test

#### Spectrophotometry derivative method development

To quantify ciprofloxacin (CF), mefenamic acid (MA), and their multicomponent system (CF–MA MS) in aqueous media, a derivative UV-Vis spectrophotometric method was developed. Firstly, each component and the multicomponent system (MS) were dissolved in distilled water. Subsequently, their UV spectra and maximum absorption wavelengths (λ-max) were scanned and compared. Due to the overlapping spectra, derivative spectrophotometric methods were applied to identify well-separated absorbance curves for each compound. The absorption maxima of CF and MA in the mixture were identified using the first- and second-derivative spectra.

Next, a series of concentrations was prepared and filtered using Whatman No. 2 paper. The optimum derivative absorbance was measured and plotted against the concentration. A calibration curve was composed, which should have good linearity, accuracy, and precision, with $r > 0.98$ (European Medicines Agency, 1995). The method validation was carried out in accordance with ICH Q2(R2) guidelines, evaluating parameters such as linearity, accuracy, and precision. Using the resulting calibration curve, the

solubility sample concentration was subsequently quantified.

**Solubility test procedure**

The CF-MA MS was subsequently tested to assess the concentration of the combined compound. A total of 500 mg each of CF-MA MS, CF, and MA was weighed and added into 25 mL of purified water in individual vials. The mixtures were agitated using ultrasonic treatment, and sample portions were incrementally added until saturation was visually observed. The concentration of each solution was quantified using a validated UV-Vis spectrophotometric method based on derivative analysis. The outcomes were later compared to those of the individual components.

**Statistical Analysis**

The spectral data obtained from FTIR, NMR, PXRD, and UV-Vis analyses were processed and plotted using Microsoft Excel 2016 (Microsoft Corporation, USA). Meanwhile, molecular structures were drawn and visualized using ChemDraw Professional 19.0 (Perkin Elmer Informatics, USA). Solubility results were statistically evaluated through one-way ANOVA using Minitab® version 17.0.

## RESULTS AND DISCUSSION

CF-MA MS obtained from the SDG technique was a bright white powder. Next, this product was characterized using electrothermal analysis and PXRD (Powder X-ray diffractometer), comparing it with the starting material and referring to the previous report by Acebedo-Martínez et al. (2023).

Table I. Melting point data of the ciprofloxacin-mefenamate system.

| Sample (n=3) | Melting Point (˚C) |
|---|---|
| CF (ciprofloxacin) | 264-266 |
| MA (mefenamic acid) | 230-231 |
| CF-MA PM 1:1 | 240-246 |
| CF-MA MS 1:1 | 244-245 |

CF = ciprofloxacin; MA = mefenamic acid; PM = physical mixture; MS = multicomponent salt

Lists of the melting point of CF-MA MS compared to the single components and an equal mixture without grinding, named a physical mixture (Table I). The CF-MA MS's melting point differed from that of PM and its constituent components (Table I). The CF melted at 264-266 °C, and MA melted at 230-231°C. The CF-MA PM displayed a melting point of 240-246°C, while the CF-MA MS showed a sharper and slightly higher point at 245-246°C. These data were observed from 3 times measurements and matched with the differential scanning calorimetry data reported in previous studies (e.g. Acebedo-Martínez et al., 2023).

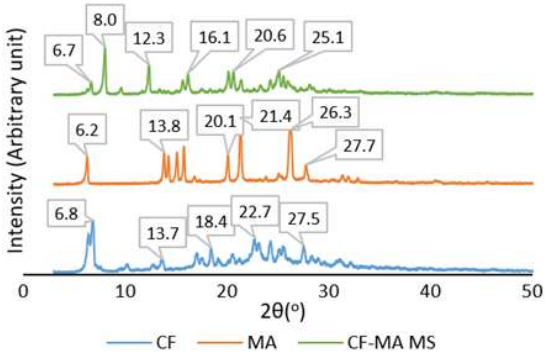



Figure 2. Diffractogram of CF-MA MS compared to the constituent compounds (CF and MA)

The CF-MA MS diffraction has new distinctive peaks at 2θ = 6.7, 8.0, 12.3, 16.1, 20.6, and 25.1° (Figure 2). These findings confirmed the formation of a novel crystalline phase, consistent with the reported PXRD profile of the multicomponent salt.

Furthermore, the FTIR and NMR data were checked for the CF-MA interaction.

**Fourier transform infrared spectrophotometer analysis**

FTIR analysis is commonly applied to identify intermolecular interactions within newly formed structures (Nugrahani et al., 2020). In the physical mixture (CF-MA PM), the IR spectrum exhibited characteristic absorption from the carboxylic group (–COOH) with a strong carbonyl absorbance, represented by the C=O stretch at wavenumbers 1619 $cm^{-1}$ and 1658 $cm^{-1}$, respectively (Figure 3). Meanwhile, the peak shifted to a wavenumber of 1724 $cm^{-1}$ in CF-MA MS. This shift indicates an interaction with the carboxylic acid group on CF and MA (Nugrahani et al., 2020). In addition, the piperazinyl group of CF underwent protonation, as indicated by the narrowing of the spectral band and a shift in the wavenumber from 3363 $cm^{-1}$ in CF to 3475 $cm^{-1}$ in the CF–MA salt. Next, the O–H stretching vibration of the –COOH group from MA at 3309 $cm^{-1}$ was not detected in the CF–MA MS. Meanwhile, the carbonyl stretching vibration of CF at 1658 $cm^{-1}$ shifted to

1724 $cm^{-1}$ in the CF–MA MS. This shift is attributed to the interaction associated with the formation of the multicomponent salt.

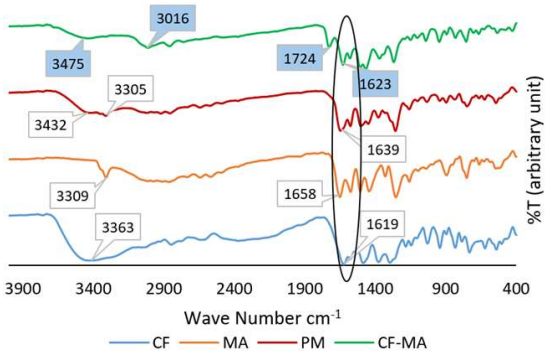



Figure 3. FTIR spectra of CF-MA MS compared to CF, MA, and its PM (physical mixture)

However, no new covalent reaction signs were detected. These significant changes are consistent with the formation of a multicomponent salt through ionic interaction between CF and AM (Alatas et al., 2020). FTIR observations can support the prediction of CF-MA MS formation. Next, a more adequate but still commonly available NMR was used to identify the interaction between CF-MA.

**Nuclear magnetic resonance analysis**

The PXRD pattern of CF-MA (Figure 2) presence of new peaks that are not found in the individual components, indicating the formation of a new phase. This finding is consistent with the pattern reported by Acebedo-Martínez et al. (2023), strengthening the successful formation of a multicomponent salt. To further confirm the structural interaction, $^{1}$H-NMR was used to determine the 2D structure by characterizing the hydrogen nuclei in the CF-MA MS.

The $^{1}$H-NMR spectrum of CF, MA, and CF-MA MS confirmed the formation of the salt, as indicated by the disappearance of the MA peak at 9.119 ppm and shifts observed in several other peaks (Figure 4a). The overlay image shows that the proton NMR spectrum of CF-MA MS contains no MA hydroxy protons because the MA hydrogen was released, allowing the formation of an ionic bond between CF and MA and the formation of a salt. These NMR spectra confirmed the SCXRD data, proving that the drug-drug combination's ionic interaction still occurred in the solution phase. The NMR results not only confirm salt formation in the solid state but, more importantly, demonstrate that the ionic interaction remained intact in solution. This is particularly relevant for liquid dosage forms, as it indicates that the salt is stable upon dissolution and does not revert to its parent compounds. Such stability enhances the predictability of solubility, bioavailability, and shelf life in aqueous pharmaceutical formulations.

This information strengthened the solubility increase as the phenomenon of a salt, which may be different from a neutral/cocrystal formation, commonly showed a “spring and parachute” profile (increase first but decrease after a peak of concentration) due to a very weak hydrogen or van der Waals interaction (Shi & Li, 2023).

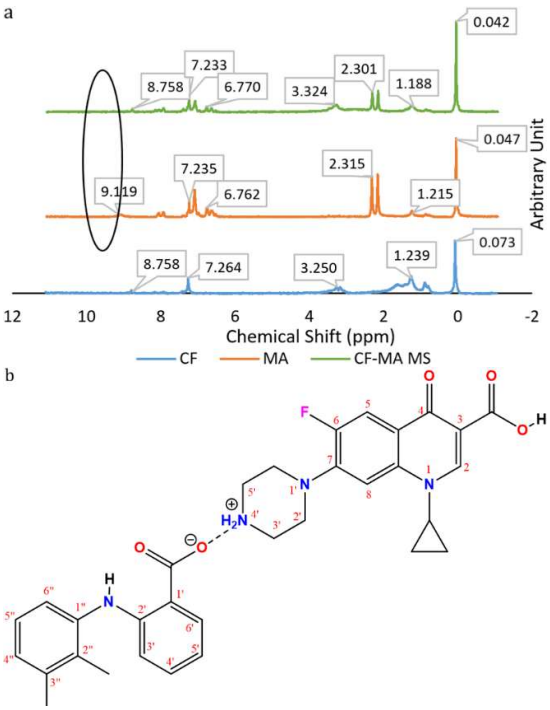



Figure 4. (a) $^{1}$H-NMR spectra of the CF-MA multicomponent salt compared with those of the individual compounds (ciprofloxacin and mefenamic acid); (b) Structure of ciprofloxacin – mefenamic acid from solvent-drop grinding, identified by FTIR and NMR.

**Development and Validation of a UV-Spectrophotometric Method for Simultaneous Determination of Drug Content and Solubility**

To evaluate the solubility of CF-MA MS, a derivative UV-Vis spectrophotometric method was developed and validated. Because the maximum wavelengths between CF and MA overlapped,

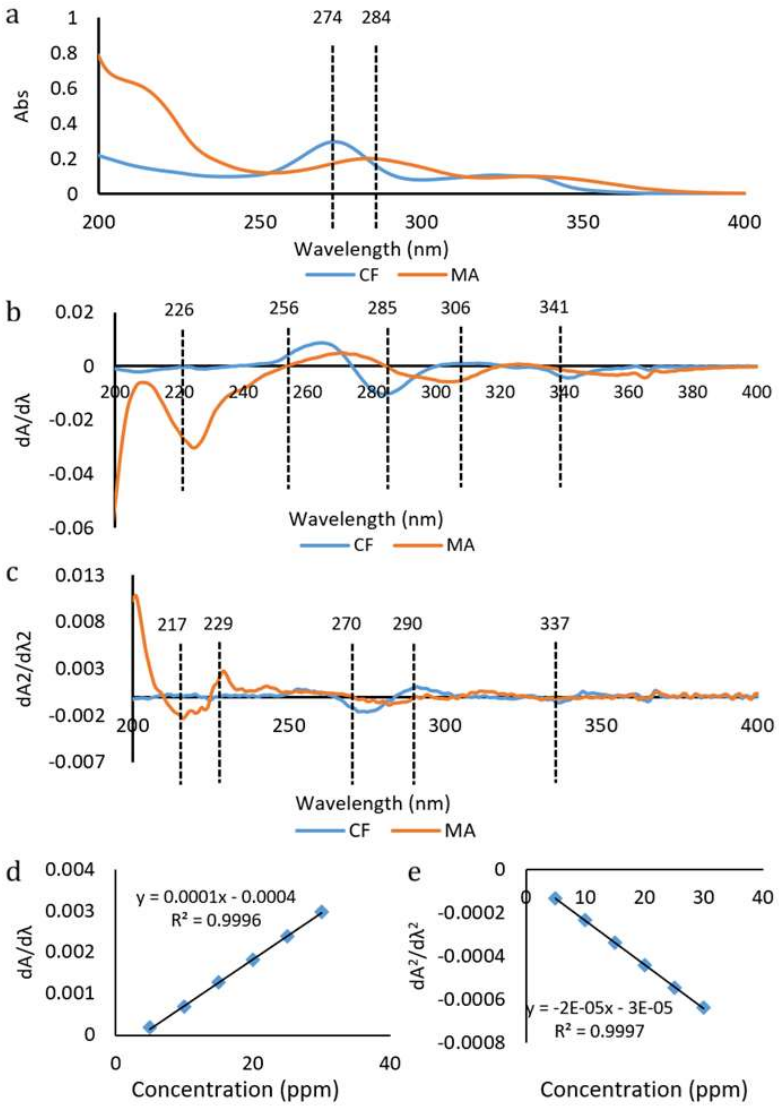



Figure 5. (a) Zero, (b) First, and (c) Second Derivative of CF-MA MS – UV spectra; Calibration curves of (d) ciprofloxacin and (e) mefenamic acids

it was necessary to carry out derivatization to measure CF and MA simultaneously without the need for physical separation (Wahyuni et al., 2022).

**UV-derivative spectrophotometry development**

The wavelengths of ciprofloxacin and mefenamic acid in the zero-order spectrum (Figure 5a) indicate that both compounds exhibit overlapping spectra at those wavelengths. Thus, derivatization is necessary to analyze both compounds in a mixture without prior separation (Wahyuni et al., 2022). In this study, the measurement wavelengths were determined using a spectral derivatization method with a zero-crossing approach. The approach utilized the zero-crossing point in the first derivative (D1) and second derivative (D2) spectra, where the absorbance of a compound was zero at a specific wavelength. This condition enables the selected wavelength to quantify the other compound in the mixture without interference or absorption from the first compound, as it does not absorb at that point (Figure 5b-c). Based on this analysis, CF exhibited a maximum wavelength at 256 nm (first

derivative) (Figure 5b). Meanwhile, MA showed a maximum wavelength at 217 nm (second derivative) (Figure 5c). This finding indicates that the UV-based method provided a reliable, simple, and cost-effective approach to simultaneously determine the solubility and content of both CF and MA in the CF-MA MS system.

The calibration curve showed a linear relationship with r =0.9998 and 0.9998 for CF and MA, respectively. Hence, this value confirms the suitability of the UV-based method in measuring solubility (Figures 5d-e). The method showed good precision and accuracy with a standard deviation of less than 2%. Additionally, the yield was between 98-100% (Committee for Medicinal Products for Human Use, 2022). In addition, this method was more sustainable because only water was used as the solvent, and it was calculated mathematically without any empirical extraction and separation.

The solubility of CF in the CF-MA MS form increased compared to the solubility of the single compound (CF) (Figure 6). CF alone had a solubility of 1.357 µg/mL, while the multicomponent system (MS) form was 3.694 µg/mL. This means that the solubility of CF in its salt form increases by 2.7-fold and is significantly higher ($p < 0.05$) than that of the single compound. The increase in solubility of CF in the CF-MA MS occurred because changes influence the thermodynamics of the solid phase (Sartinah et al., 2024). The previous report also explained that the CF's solubility in the salt form increased twofold (Acebedo-Martínez et al., 2023). Hence, it is still consistent with the results of the present experiment.

CF is difficult to dissolve in water because of its lipophilic structure, inhibiting its solubility in polar solvents. Therefore, the formation of the multicomponent system was an effective way to increase the intrinsic solubility of CF because ionization, in general, increases the solubility in polar solvents, such as water (Bandaru et al., 2021).

Similarly, MA in the predicted salt form (CF-MA MS) exhibited a 7.6-fold increase in solubility and was significantly higher ($P < 0.05$) compared to single mefenamic acid. Single MA has a 91 µg/mL solubility in water, while the CF-MA salt became 698 µg/mL (Figure 6). The greater solubility enhancement of mefenamic acid (MA) compared to ciprofloxacin (CF) may be primarily attributed to the salt structure formed, which facilitates stronger interactions with water molecules and enhances the dissolution process (Nugrahani et al., 2021). MA is a weakly acidic compound with a relatively rigid and hydrophobic crystal structure, and salt formation disrupts this lattice significantly. Upon proton transfer to the piperazinyl group of CF, a mefenamate anion is produced, increasing ion–dipole interactions and reducing lattice energy, which further contributes to its higher solubility in aqueous media.

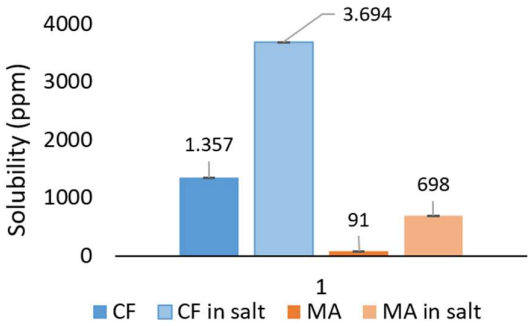



Figure 6. Solubility of ciprofloxacin (CF) and mefenamic acid (MA) in the multicomponent system in a single form; (n = 3); RSD ≤ 2; $P < 0.05$.

Modifying the characteristics of CF with an appropriate coformer can change the compound's physicochemical properties, such as pH and polarity, which can increase solubility. In this case, the acidic nature of MA can change the ionization of CF, thereby increasing its solubility in solution (Serajuddin, 2007), and vice versa. These results show that forming a system between CF and MA in the MS increased the solubility of the two compounds compared to their single forms.

Beyond enhancing physicochemical characteristics, the methodology used in this study also demonstrates alignment with green chemistry principles, contributing to sustainable pharmaceutical development. The overall methodology developed in this study aligns with several key principles of green chemistry. The use of ethanol 98%, classified as a green solvent due to its low toxicity and biodegradability, replaces more hazardous solvents like methanol. Furthermore, the quantification method employed water as a solvent and utilized derivative UV spectrophotometry. These methods eliminated the need for organic solvents required in HPLC and reduced chemical waste. The synthesis method SDG is energy efficient and avoids bulk heating or high-pressure conditions. Together, these features support environmentally friendly, safe, and resource-efficient pharmaceutical practices.

While SDG offers advantages in terms of simplicity, low cost, and eco-friendly

characteristics, its applicability in large-scale pharmaceutical manufacturing remains limited. Manual grinding processes rely heavily on operators. Additionally, they are difficult to control and may result in batch-to-batch variability. Therefore, to meet commercial production standards, the SDG process should be adapted into more sustainable and automated techniques to ensure reproducibility, product uniformity, and regulatory compliance.

## CONCLUSION

The preparation of CF-MA was confirmed using the solvent-drop grinding (SDG) method with the addition of a small amount of solvent. Its formation was analyzed using electrothermal analysis and FTIR. Further confirmation was obtained using NMR analysis, highlighting the stability of the salt structure in solution. This indicates the successful formation of ionic interactions. In addition, the water-based derivative UV-Vis spectrophotometric method developed in this study was validated and proven suitable for the simultaneous analysis of both compounds without the need for prior separation.

The method discussed in this study offers several advantages, as it is more economical, simpler, and environmentally friendly. It avoids the use of costly instruments such as SCXRD and HPLC that require harmful organic solvents. Therefore, this method provides a valuable alternative for developing solid dosage formulations of ciprofloxacin–mefenamate, particularly in developing countries with limited access to advanced laboratory facilities.

Despite the promising takeaways, this study did not evaluate the solid-state stability of the salt under storage conditions such as high temperature and humidity, which is one of the limitations of this study. Further research should address this issue to obtain a more comprehensive understanding. Additionally, studies on toxicity testing, anti-inflammatory activity evaluation, and final dosage form development are still necessary to advance this multicomponent salt candidate toward pharmaceutical development.

Overall, this approach reflects the application of green chemistry principles, particularly in solvent selection, waste minimization, and analytical simplicity.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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