UPSCALE PREPARATION AND PRECLINICAL EVALUATION OF A POTENTIAL ANTIBIOTIC–NSAID MULTICOMPONENT SYSTEM: CIPROFLOXACIN MEFENAMATE

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Abstract

Ciprofloxacin mefenamate (CIPMEF) combines an antibacterial fluoroquinolone with an anti-inflammatory fenamate in a 1:1 ionic solid. This study evaluated ethanol grade during 1 g solvent-drop grinding and related the resulting phases to stability, antibacterial activity, anti-inflammatory performance, and acute in vivo safety. Ethanol–water composition produced a previously unreported sesquihydrate, mixed hydrates, monohydrate, and anhydrous CIPMEF. The selected product remained stable, inhibited Gram-negative, Gram-positive, and methicillin-resistant bacteria at lower ciprofloxacin-equivalent concentrations, produced the lowest paw-inflammation profile, and showed a more favorable histopathological pattern than the physical mixture.

Keywords: ciprofloxacin mefenamate; pseudopolymorphism; solvent-drop grinding; antibacterial potency; anti-inflammatory activity; toxicity.

Introduction

Solid-state phase identity strongly affects pharmaceutical stability and performance. Ciprofloxacin (Fig. 1a) and Mefenamic acid (Figure 2b) produced a multicomponent salt, named CIPMEF (Fig. 1c), which was found in anhydrous (Fig. 1d) and monohydrate (Fig. 1e) forms [1]. CIPMEF was designed as an antibiotic–NSAID salt in which proton transfer from MEF to the piperazinyl nitrogen of CIP reorganized the crystal lattice. The study examined whether solvent-controlled phase formation could provide a reproducible product with improved biological performance. Recently, we have reported the SDG product of CIPMEF using ethanol grade 98% [2], but have not yet investigated the ethanol level for pseudopolymorphism as well as the biological performance and toxicity.

The present research aimed to optimize scaling up using solvent-drop grinding using a series of ethanol grades (30-98%), and evaluate the solubility, stability, antibiotic, in vivo anti-inflammatory performance, and safety in vivo, followed by histopathology.

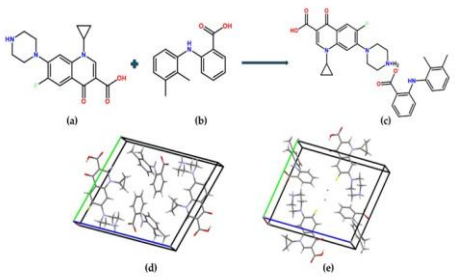


Figure 1. Chemical structures of (a) CIP, (b) MEF, and (c) the 2D structure of CIPMEF; (d) the 3D structure of anhydrous (form I) CIPMEF from slow evaporation using acetone [1], and (e) CIPMEF monohydrate from slow evaporation using acetonitrile–methanol [1].

Research Method

The study linked solvent composition, solid-state phase formation, stability, and preclinical performance through the following experimental pathway.

1 Raw materials
CIP + MEF at a 1:1 molar ratio

2 Solvent-drop grinding
1.0 mg batch; 500 µL ethanol–water (0–98% v/v); drying for 12 h

3 Solid-state characterization
Electrothermal analysis, DSC, PXRD, TG/DTA, FTIR, and derivative UV

4 Phase selection and stability
Hydration-state identification; 4 weeks at 25 ± 3 °C and 75 ± 5% RH

5 Antibacterial potency
Broth microdilution MIC/MBC against E. coli, S. Typhi, S. aureus, and MRSA

6 In vivo evaluation
Carrageenan paw edema in rats and 14-day acute toxicity in BALB/c mice

Decision point: ethanol grade determined the hydrate states and the homogeneous phase selected for biological testing.

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Discussion & Result

Ethanol grade directed CIPMEF pseudopolymorphism. ≤70% ethanol produced a new sesquihydrate; 80–90% produced mixed sesquihydrate/monohydrate; 95% produced monohydrate; and 98% yielded an anhydrous form. The anhydrous material converted to monohydrate under ambient conditions, while both hydrates remained stable for four weeks.

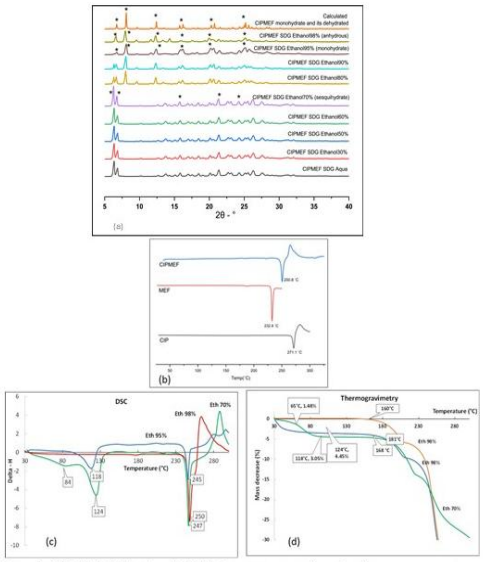


Figure 2: PXRD (a), DSC (b,c), and TG (d) of starting materials and multicomponent system



Figure 3. Mouse observation during the 14-day acute-toxicity study.

CIPMEF lowered CIP-equivalent MIC values across all tested organisms and reduced MBC values for three strains. It also produced the lowest paw-inflammation profile. In the acute study, body weight and organ findings remained broadly comparable, while gastric histology more closely resembled the control than the physical mixture.

Conclusion

Solvent composition provided practical control over CIPMEF hydration state and phase purity during scale-up. The newly identified sesquihydrate, monohydrate, and anhydrous forms linked process conditions with storage behavior. CIPMEF combined stronger antibacterial inhibition with improved anti-inflammatory performance and a favorable preliminary safety profile. These findings support pharmacokinetic, formulation, dose-optimization, and longer-term stability studies.

References

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