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Rational Design of Naproxen–ParacetamolCocrystals for Improved Solubility, Stability, and Formulation Efficiency

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ABSTRACT

The present study focuses on the rational design and development of cocrystals composed of Naproxen (NPX) and Paracetamol (PCM) to enhance solubility, thermal stability, and formulation performance. Cocrystallization was achieved using solvent evaporation and neat grinding techniques in varying molar ratios. The resultant cocrystals were characterized by Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM). Solubility, dissolution rate, and stability studies were conducted to evaluate improvements over the pure drugs. The optimized 1:1 Naproxen–Paracetamolcocrystal exhibited a 2.3-fold increase in aqueous solubility, improved dissolution efficiency, and enhanced physical stability under accelerated conditions. The study highlights the potential of pharmaceutical cocrystallization as a green and rational approach to modulate physicochemical and biopharmaceutical properties of poorly soluble drugs.

Keywords: Naproxen–Paracetamol Cocrystals.

INTRODUCTION

Cocrystallization has emerged as one of the most versatile and sustainable solid-state modification strategies in modern pharmaceutical design. It enables the modulation of key physicochemical properties of active pharmaceutical ingredients (APIs) such as solubility, dissolution rate, stability, and mechanical behavior without altering their intrinsic pharmacological activity or chemical structure. Unlike salts, solvates, or polymorphs, pharmaceutical cocrystals are formed by the association of an API with a pharmaceutically acceptable coformer through non-covalent interactions—predominantly hydrogen bonding, π–π stacking, or van der Waals forces—resulting in a single crystalline phase with a defined stoichiometric ratio. The U.S. Food and Drug Administration (FDA) recognizes cocrystals as distinct crystalline forms, which has further encouraged their use as a formulation tool to overcome poor solubility and bioavailability challenges faced by many Biopharmaceutics Classification System (BCS) Class II drugs.

Naproxen (NPX), a propionic acid derivative and a widely used non-steroidal anti-inflammatory drug (NSAID), is indicated for the management of pain, inflammation, and fever. Despite its efficacy, its therapeutic performance is limited by poor aqueous solubility (0.015 mg/mL) and slow dissolution rate, which consequently lead to low oral bioavailability and variable absorption. Several formulation strategies such as salt formation, micronization, and solid dispersion have been employed to improve NPX solubility; however, these approaches often suffer from drawbacks such as hygroscopicity, instability, or process complexity.

Paracetamol (PCM), also known as acetaminophen, is an analgesic and antipyretic agent with moderate solubility, good chemical stability, and well-established safety profile. PCM is frequently used as a coformer in cocrystal engineering due to its ability to participate in robust hydrogen bonding via its hydroxyl and amide functionalities. Furthermore, PCM is often co-administered with NSAIDs in combined dosage forms to achieve synergistic analgesic and antipyretic effects.

However, simple physical mixtures or co-tablets containing NPX and PCM often exhibit issues related to poor dissolution uniformity, phase segregation, and inadequate compressibility during tableting. Such limitations highlight the need for a more integrated solid-state approach to combine these two molecules at the molecular level. The cocrystallization of NPX and PCM offers a rational pathway to enhance solubility, improve dissolution kinetics, and optimize mechanical properties by establishing intermolecular hydrogen bonding between the carboxylic acid group of NPX and the hydroxyl or amide groups of PCM.

Beyond solubility enhancement, cocrystallization may also contribute to improved thermal and chemical stability, reduced hygroscopicity, and enhanced manufacturability, all of which are essential for successful pharmaceutical product development. The rational design of NPX–PCM cocrystals is further supported by supramolecularsynthon theory, which predicts the formation of acid–amide and acid–hydroxyl heterosynthons as energetically favorable interactions.

Therefore, the present study aims to systematically design, prepare, and characterize cocrystals of Naproxen and Paracetamol using multiple methodologies—solvent evaporation and neat grinding—and to comprehensively evaluate their physicochemical and pharmaceutical properties. The work seeks to establish a scientific foundation for improving the solubility, dissolution behavior, and formulation efficiency of poorly soluble APIs through rational cocrystal engineering.

MATERIALS AND METHODS

Materials

Naproxen and Paracetamol were procured from Sigma-Aldrich (≥99% purity). All solvents were analytical grade and used without further purification.

Preparation of Cocrystals

Two methods were employed:

- **Solvent evaporation:** NPX and PCM were dissolved in ethanol in molar ratios (1:1, 1:2, 2:1) and stirred at 40°C until complete dissolution. The solvent was slowly evaporated under ambient conditions.
- **Neat grinding:** NPX and PCM were ground together in a mortar and pestle for 30 min at room temperature.

The resultant solids were dried, sieved, and stored in desiccators.

Characterization Techniques

Technique	Purpose
FTIR (4000–400 cm^{-1})	To identify hydrogen bonding and molecular interactions
PXRD (Cu$K\alpha$, 2θ = 5–40°)	To detect new crystalline phases
DSC (10°C/min, N_2 atmosphere)	To determine melting points and thermal behavior
SEM	To observe surface morphology
Solubility & Dissolution	To quantify enhancement in aqueous solubility

RESULTS AND DISCUSSION

FTIR Analysis

Characteristic peaks of NPX (1725 cm^{-1} for C=O) and PCM (3320 cm^{-1} for –OH, 1650 cm^{-1} for C=O amide) were shifted and broadened in

the cocrystal spectrum, indicating hydrogen bond formation between NPX carboxylic acid and PCM amide/hydroxyl groups.

Table 1: Major FTIR Peaks and Shifts

Functional Group	NPX (cm^{-1})	PCM (cm^{-1})	Cocrystal (cm^{-1})	Interaction
O–H Stretch	3320	3322	3240	H-bonding
C=O Stretch	1725	1650	1702	Carboxyl–amide interaction
C–O Stretch	1210	1230	1222	Modified environment

PXRD Analysis

Distinct new peaks appeared at 2θ = 9.6°, 16.8°, and 24.2°, absent in the parent drugs, confirming cocrystal formation. Peak intensities and patterns differed from the physical mixture, indicating a new crystalline phase.

DSC and Thermal Stability

The DSC thermogram of the NPX–PCM cocrystal showed a single endothermic peak at 148.5°C, distinct from NPX (156.4°C) and PCM (170.1°C), confirming the formation of a new crystalline entity.

Table 2: Thermal Analysis Results

Sample	Melting Point (°C)	ΔH (J/g)	Interpretation
NPX	156.4	102.3	Pure drug
PCM	170.1	98.5	Pure drug
NPX–PCM (1:1)	148.5	76.4	New cocrystal phase

Solubility Studies

Aqueous solubility was determined using shake-flask method at 37°C for 24 hours.

Table 3: Solubility Data

Sample	Solubility (mg/mL)	Fold Increase vs NPX
NPX	0.015	1.0
PCM	0.55	–
NPX–PCM (1:1)	0.034	2.3×
NPX–PCM (1:2)	0.028	1.9×
NPX–PCM (2:1)	0.025	1.7×

The 1:1 cocrystal showed maximum solubility enhancement due to optimal hydrogen bonding and lattice energy reduction.

Dissolution Studies

The dissolution behavior of the NPX–PCM cocrystals was evaluated in phosphate buffer (pH 7.4) to simulate intestinal conditions and assess potential improvements in oral bioavailability. The 1:1 molar ratio cocrystal demonstrated a significantly enhanced dissolution profile, with approximately 85% of Naproxen released within the first 30 min, compared to only 42% release from pure NPX under identical conditions. The accelerated dissolution rate can be attributed to several factors:

1. **Enhanced Wettability:** Cocrystallization with PCM improved the hydrophilicity of the crystal lattice, facilitating better contact with the dissolution medium.
2. **Reduced Lattice Energy:** Formation of a new crystalline phase reduces the lattice energy of NPX, allowing molecules to detach more readily into solution.
3. **Partial Amorphization:** The cocrystal contains microdomains with amorphous characteristics, which dissolve faster than the fully crystalline NPX.

Additionally, the dissolution efficiency was superior for the 1:1 cocrystal compared to other stoichiometric ratios (1:2 and 2:1), suggesting that this ratio provides optimal molecular interactions for solubility enhancement. Faster dissolution of the API not only improves in vitro performance but is also expected to positively impact in vivo absorption and onset of therapeutic action.

Stability Studies

The physical and chemical stability of NPX–PCM cocrystals was evaluated under accelerated conditions (40°C and 75% relative humidity) over a period of three months. PXRD and DSC analyses revealed that the cocrystals retained over 95% of their crystallinity and drug content, indicating excellent physical and chemical stability. In contrast, pure NPX displayed minor degradation under the same conditions, reflecting its susceptibility to moisture and temperature.

The high stability of the cocrystals can be explained by the strong intermolecular hydrogen bonds between NPX and PCM, which reduce the tendency of NPX to undergo polymorphic transitions or hydrolysis. This enhanced stability is critical for the development of robust pharmaceutical formulations that maintain their efficacy and safety during storage and distribution.

Formulation Efficiency

In addition to improved solubility and

stability, the NPX–PCM cocrystals exhibited superior flowability and compressibility compared to the physical mixture of NPX and PCM. These properties are essential for direct compression tablet manufacturing, enabling consistent tablet weight, uniform hardness, and reproducible disintegration.

Tableting studies revealed that tablets prepared from the 1:1 NPX–PCM cocrystals disintegrated in approximately 80 seconds, significantly faster than the 145 seconds observed for tablets prepared from the physical mixture. The improved disintegration is likely due to the enhanced wettability and altered crystal morphology of the cocrystals, which promote faster penetration of dissolution media and rapid breakdown of the tablet matrix. Overall, the cocrystals demonstrated excellent compatibility with conventional tablet manufacturing processes, highlighting their practical utility in pharmaceutical formulation development.

CONCLUSION

The rational design and preparation of Naproxen–Paracetamolcocrystals successfully generated a novel, stable crystalline form with markedly improved physicochemical and pharmaceutical properties. The optimized 1:1 cocrystal exhibited enhanced aqueous solubility, superior dissolution kinetics, and excellent stability under accelerated conditions. Furthermore, the cocrystals demonstrated improved flowability and compressibility, enabling direct compression into tablets with uniform weight, hardness, and rapid disintegration.

This study underscores the potential of pharmaceutical cocrystallization as a versatile and robust strategy to enhance the performance of poorly soluble drugs. By modulating molecular interactions and crystal lattice properties, cocrystals can overcome solubility and formulation challenges without altering the pharmacological profile of the API. Future work should focus on in vivo pharmacokinetic studies to confirm improved bioavailability and therapeutic efficacy, as well as exploration of other clinically relevant drug–coformer combinations to expand the utility of this approach in modern drug development.

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