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Review Article

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Cocrystals of Two Co-Occurring Plant Metabolites: Purification with Synergistic Potentiation and Bioavailability- A Tale of Two Case Studies

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Abstract

This study reviews advances in the design and application of co-crystals derived from plant metabolites as enhanced antimalarial agents. Co-crystallization, involving the combination of a bioactive plant-derived compound (e.g., quinoline derivatives, artemisinin) with a suitable co-former such as hydroxy aromatic acids or other bioactive molecules, has been shown to improve solubility, stability, bioavailability, and therapeutic potency without altering the active pharmaceutical ingredient's chemical identity. Examples include aminoquinoline–hydroxybenzoic acid co-crystals, which display lower IC50 values against chloroquine-resistant Plasmodium falciparum, and artemisinin-based co-crystals that achieve 21–26-fold increases in solubility and enhanced in vivo efficacy. Synergistic formulations, such as artemisinin with flavonoid-rich extracts, exploit complementary mechanisms of action to increase parasite inhibition and potentially delay resistance. Novel systems, including 11-aza-artemisinin co-crystals, show improved solubility and preclinical promise. Additionally, alkaloid–anthraquinone co-crystals, exemplified by the rhein–matrine system, demonstrate up to 50-fold improved dissolution and higher oral bioavailability through hydrogen bonding and supramolecular organization. These multi-mechanistic hybrids enhance pharmacokinetic profiles, tablet ability, and stability, broadening the pharmaceutical potential of plant-derived compounds. Collectively, plant metabolite-based co-crystals represent a valuable strategy for overcoming solubility-limited bioactivity, improving antimalarial efficacy, and addressing drug resistance challenges.

1. Introduction

Co-crystals derived from plant metabolites represent a promising approach in the hunt for improved therapies. These co-crystals involve the combination of a plant-derived active compound, such as a quinoline derivative or artemisinin, with another co-former (often an acid or another bioactive molecule), which enhances the therapeutic efficacy or bioavailability compared to the individual components alone [1-3].

2. Key Examples and Research

Co-crystals of aminoquinolines (a plant metabolite class) with hydroxy aromatic acids have demonstrated increased antimalarial activity in vitro when compared to the parent compounds. For example, co-crystals formed from 8-aminoquinoline and hydroxybenzoic acids displayed lower IC50 values (indicating higher potency) against chloroquine-resistant strains of Plasmodium falciparum than individual compounds [1,2].

Recent advances have focused on artemisinin, a natural sesquiterpene lactone from Artemisia annual, where formulation with certain co-formers or hydrotropes increased extraction yields and antimalarial efficacy. These enhanced extracts exploit synergistic effects between artemisinin and co-extracted plant metabolites (like flavonoids), resulting in stronger inhibition of malaria parasites than artemisinin alone [4,5].

A novel co-crystal based on the synthetic derivative 11-aza-artemisinin has shown promise in preclinical testing, with improved solubility and potentially greater clinical utility than conventional formulations [3].

2.1. Mechanisms and Benefits

- Co-crystallization can enhance the solubility, stability, and bioavailability of plant metabolites, overcoming some major limitations associated with plant-derived drugs.
- These hybrid materials may combine different mechanisms of action, such as iron chelation or inhibition of hemozoin formation, increasing efficacy and potentially delaying resistance development [1,2].
- Safety profiles of these co-crystals are generally favorable, and certain combinations can even retain or enhance selectivity for the malaria parasite over host cells [1,2].

2.2. Notable Plant Metabolites Used

- Quinoline derivatives (from plants or semi-synthetic sources) with hydroxy aromatic coformers [1,2].
- Artemisinin and flavonoid-rich extracts from Artemisia annual, co-crystallized or co-extracted with natural or synthetic acids and conformers [4,5].
- Other secondary metabolites, such as xanthones and related compounds, are actively being explored for co-crystallization strategies to potentiate their antimalarial activity [6].

Overall, the development and use of antimalarial co-crystals using plant metabolites is an area of active research, with the potential to yield new, more effective treatments as resistance to traditional therapies grows [1-5].

Co-crystallization can significantly enhance both the potency and solubility of antimalarial compounds, offering a promising strategy for improving drug efficacy and addressing challenges like poor bioavailability and drug resistance. Effects on Potency-crystallization can lead to increased antimalarial potency by stabilizing the active pharmaceutical ingredient (API) in a form that exhibits greater biological activity, sometimes by promoting more favorable interactions with the target pathogen or enhancing uptake by cells. For example, artesunate-nicotinamide co-crystals showed improved antimalarial activity in vivo compared to pure artesunate or its physical mixture with nicotinamide. The formation of co-crystals can also enable new mechanisms of action or synergistic effects that are not present in the individual components or their physical mixtures.

2.3. Effects on Solubility and Bioavailability

One of the main benefits of co-crystallization is the significant improvement of solubility and dissolution rate for poorly soluble antimalarial drugs. Artemisinin cocrystals, for instance, demonstrated a 21- to 26-fold increase in solubility compared to pure artemisinin, leading to much higher bioavailability and faster drug action. Enhanced solubility translates directly to better absorption and, therefore, increased effectiveness upon oral administration. Improved solubility via co-crystals can result in drugs reaching therapeutic concentrations in the bloodstream more rapidly and consistently.

2.4. Additional Advantages

Co-crystals can also improve other pharmaceutical properties such as stability, hygroscopicity, and tablet ability, making them more desirable for pharmaceutical development. Importantly, co-crystallization achieves these improvements without altering the chemical identity of the active molecule, maintaining its pharmacological properties while optimizing its physical form. In summary, co-crystallization effectively boosts both the antimalarial potency and solubility of plant-derived and synthetic compounds, making it a valuable tool in modern antimalarial drug development.

2.5. Cocrystals of an Alkaloid with an Anthraquinone

Cocrystals combining alkaloids with anthraquinones are an innovative approach in pharmaceutical science to enhance the solubility and bioavailability of active compounds, as said earlier. A notable example is the cocrystal formed between rhein, an anthraquinone derivative, and matrine, an alkaloid. This cocrystal demonstrates significantly improved dissolution properties and oral bioavailability compared to pure rhein, as shown by a 50-fold increase in dissolution and improved pharmacokinetic parameters. This improvement arises from the molecular interactions in the cocrystal, typically mediated by hydrogen bonding and other noncovalent forces, which enable better release and absorption in biological systems [15]. For example:
Rhein-Matrine Cocrystal

- Rhein (anthraquinone derivative) and matrine (alkaloid) cocrystal
- Characterized using single crystal X-ray diffraction and other physico-chemical methods
- Results include improved in vitro dissolution and increased in vivo absorption [15].

3. Significance and Applications

- Cocrystals can address poor aqueous solubility—one of the major limitations for many bioactive natural compounds [16].
- Designing cocrystals involving alkaloids and anthraquinones may lead to novel drug formulations with enhanced therapeutic efficacy and better pharmacokinetics [15-25].

This approach broadens the pharmaceutical use of plant-based compounds found in traditional and modern medicines [15,16].

3.1. Mechanisms and Formation

- Cocrystal formation between an alkaloid and an anthraquinone typically leverages supramolecular synthons (i.e., specific patterns of molecular recognition such as hydrogen bonding between complementary functional groups) [25,26].
- Analytical methods such as X-ray diffraction, thermal analysis, and molecular modeling are used to characterize and understand these cocrystals [15].

Cocrystals of alkaloids with anthraquinones thus provide a promising strategy to enhance the performance and potential of natural product-based drugs in the pharmaceutical industry [27-29].

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