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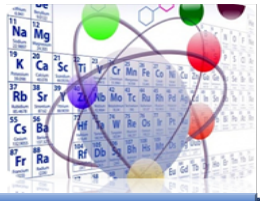

Influence of Citric, Acetic, and Ascorbic Acids on the Solubility of Paracetamol

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ABSTRACT

This study examined the influence of citric, acetic, and ascorbic acids on the solubility of paracetamol, an analgesic with inherently low aqueous solubility. Paracetamol tablets were dissolved in different concentrations of organic acid solutions, and dissolution times were visually monitored. The most rapid dissolution occurred in 30% acetic acid solution (190 seconds), followed by the citric–acetic acid mixture. Increasing paracetamol mass extended dissolution time, with saturation reached at 3.5 g. Enhanced solubility was attributed to hydrogen bonding interactions between organic acids and paracetamol molecules. Compared with complex techniques such as solid dispersions or co-amorphous systems, this acid-assisted approach is simple, low-cost, and requires no specialized equipment. These findings highlight the role of weak organic acids as practical solubility enhancers and suggest a promising strategy to improve paracetamol bioavailability and therapeutic effectiveness.

Keywords: Acetic acid, Ascorbic acid, Citric acid, Paracetamol, Solubility

1. INTRODUCTION

Oral drug performance is often governed by dissolution behavior and the physicochemical microenvironment around a solid dose. A widely used strategy to accelerate dissolution is microenvironmental pH (pH_m) modification, wherein weak organic acids or bases are embedded in or co-administered with the dosage form to locally adjust pH, disrupt crystal packing, and facilitate solvation. This approach has been shown to enhance dissolution and, in many cases, absorption for drugs whose solubility is pH dependent. [1–4]

Paracetamol (acetaminophen) remains a first-line antipyretic–analgesic worldwide. Although its aqueous solubility at 20 °C is ~12.8 mg mL^{-1}, dissolution from compressed tablets can still be rate-limiting under certain conditions, motivating formulation tactics that promote faster disintegration and molecular dispersion.[5–7]

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Paracetamol's crystal lattice is stabilized by a dense hydrogen-bond network (phenolic –OH and amide –NH/C=O), and its solute–solvent interactions including specific H-bonding strongly influence spectroscopic signatures and dissolution behavior features that can be exploited by hydrogen-bond-donating co-formers and pH_m modifiers.[8, 9]

Beyond polymeric solid dispersions, co-amorphous systems (CAMs) and co-crystals have emerged as agile platforms to disrupt crystallinity and improve apparent solubility. Contemporary reviews highlight the value of low-molecular-weight organic acids as efficient co-formers, with citric acid frequently cited due to its trifunctional carboxylate scaffold and strong hydrogen-bonding propensity.[3, 10] Robust evidence also supports pH-modifier selection as a design variable to optimize dissolution rate and extent across acidic/basic drugs and dosage architectures.[2, 11, 12]

Building on these principles, the present work evaluates citric, acetic, and ascorbic acids as practical, low-cost enhancers for paracetamol dissolution using a simple, equipment-light protocol. We hypothesize that (i) localized pH_m shifts and (ii) transient hydrogen-bonding interactions between organic acids and paracetamol synergistically accelerate dissolution; we further benchmark concentration and mass-loading effects to identify operational windows relevant to introductory formulation practice.[1, 3, 10, 13]

2. EXPERIMENTAL

2.1. Chemicals, Equipment and Instrumentation

Paracetamol tablets (OTC, labeled 500 mg per tablet) were used as the model drug. Organic acids included citric acid ($C_6H_8O_7$), acetic acid (CH_3COOH), and ascorbic acid ($C_6H_8O_6$) of reagent grade. Deionized water was used as the solvent for all preparations. Where applicable, food-grade sources (e.g., vinegar and citrus juice) were evaluated only after clarification by filtration to remove suspended solids. All chemicals were used as received unless otherwise specified.

The apparatus comprised Class-A glassware (borosilicate beakers), an analytical balance (±0.001 g), a stopwatch for dissolution timing, and filter paper for residue separation; auxiliary tools (spatula, beaker tongs) were used as needed. Experiments were performed at ambient laboratory temperature (25 ± 2 °C). No specialized equipment was required beyond standard teaching-laboratory items.

2.2. Research Procedure

2.2.1. Preparation of acid media

Stock solutions of citric, acetic, and ascorbic acids were prepared in deionized water. Working media were made by volumetric dilution of the corresponding stocks to prescribed test volumes of 10, 30, 50, or 100 mL, depending on the experiment. For mixture experiments, binary acid media (citric–acetic) were prepared by combining equal volumes of the respective single-acid working solutions to maintain the same total acid content as in single-acid runs. When food-grade vinegar or clarified citrus juice were used for comparison, they were first paper-filtered before use.

2.2.2. Dissolution time measurements

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Dissolution tests were conducted in quiescent conditions. A whole paracetamol tablet was gently introduced into the test medium (t = 0 at first contact). The vessel was left unstirred; brief manual swirling (≤5 s) every 30–60 s was used only to prevent surface caking without imparting bulk agitation. Dissolution time was defined as the time from t = 0 to complete disappearance of visible solids, followed by a 60-s hold with no re-precipitation. Timing was recorded with a stopwatch. Each condition was tested in triplicate, and results are reported as mean ± SD.

2.2.3. Effect of medium type and volume

To assess the effect of acid identity, tablets were dissolved separately in citric, acetic, or ascorbic acid media at the selected volumes (10, 30, 50, or 100 mL). Dissolution time was recorded as in § 2.2.2. For binary mixtures (citric–acetic, acetic–ascorbic, citric–ascorbic), the same procedure was applied using the 1:1 (v/v) mixed media described in 2.2.1.

2.2.4. Effect of paracetamol mass

To evaluate mass-loading effects, paracetamol was tested at nominal masses of 0.5, 1.5, 2.5, and 3.5 g using the designated acid media and volumes. Dissolution time was determined as in 2.2.2. The operational saturation was inferred from persistent undissolved residue after prolonged observation.

2.2.5. Saturation point in acetic acid

A targeted saturation assessment was performed in 30% (w/w) acetic acid. Incremental paracetamol loading was increased up to 3.5 g; the point at which a visible solid phase persisted despite extended observation was taken as the saturation point under these conditions.

3. RESULTS AND DISCUSSION

3.1. Effect of acid concentration on paracetamol dissolution

Across all media, higher acid concentration shortened the visual dissolution time of the whole paracetamol tablet. The fastest dissolution was observed in 30% (w/w) acetic acid with a time of ~190 s (Figure 1), as also reflected in the summary statement of the manuscript. This trend is consistent with microenvironmental pH (pH_m) modification principles: co-administered organic acids can locally depress pH at the solid–liquid interface, improving wetting, disintegration of the compact, and molecular dispersion, even when the drug itself is weakly acidic.[1, 2] In particular, paracetamol (pK_a ≈ 9.5) is largely unionized in acidic media; thus the improvement here is unlikely due to classical ionization, but more plausibly from matrix/disintegrant erosion, wettability changes, and specific hydrogen-bonding interactions that facilitate crystal-lattice disruption at the interface.[2, 3, 14]

Moreover, recent formulation studies have demonstrated that the presence of low-molecular-weight organic acids can not only alter microenvironmental pH but also promote non-covalent interactions such as hydrogen bonding and ion–dipole associations, thereby facilitating drug dispersion in aqueous environments.[5,7] For instance, citric acid has been widely recognized as a multifunctional excipient capable of disrupting crystalline packing and stabilizing drug molecules in a transiently amorphous state, which directly enhances dissolution kinetics.[6,7] Similarly, acetic acid has been reported to act as a practical processing aid, improving solvation and wettability of poorly soluble drugs during dispersion and dissolution.[9] These findings are

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consistent with the observed acceleration of paracetamol dissolution in concentrated acetic and citric acid media, underscoring the role of weak organic acids as simple yet effective solubility enhancers in drug delivery.

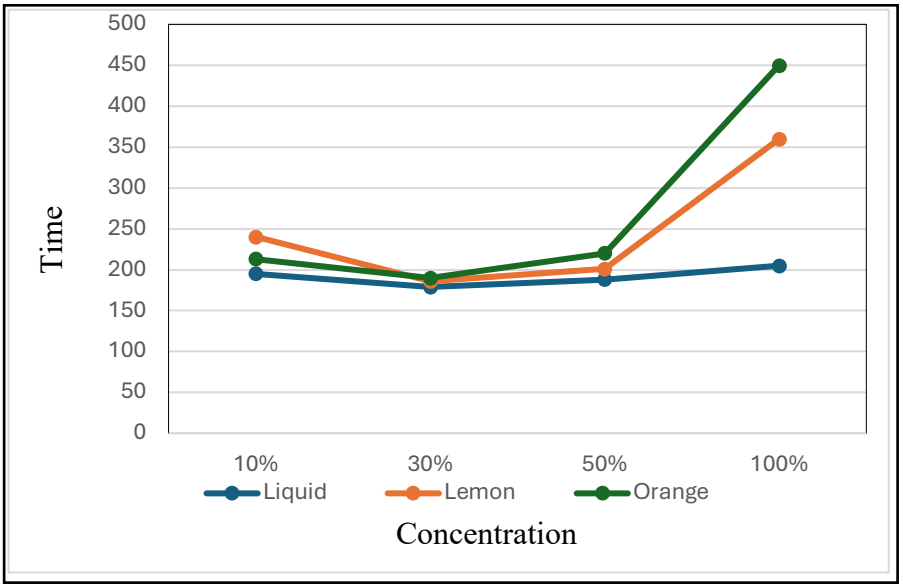

Figure 1. Effect of acid concentration (citric, acetic, and ascorbic acids) on the dissolution time of paracetamol tablets.

3.2. Effect of acid identity and binary mixtures

When comparing single-acid media, acetic and citric acids outperformed ascorbic acid in reducing dissolution time. For binary mixtures, the citric–acetic system provided among the fastest profiles (≈190 s), followed by orange (citric surrogate)–acetic (~252 s) and lemon (citric surrogate)–orange (~250 s), aligning with the concentration findings (Figure 2).

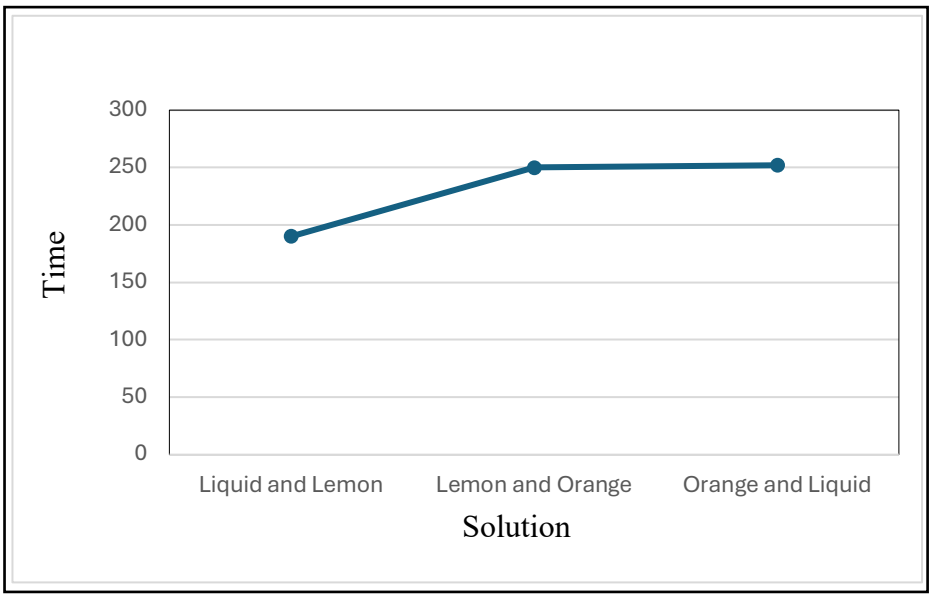

Figure 2. Effect of different acid media (citric, acetic, ascorbic, and their binary mixtures) on the dissolution time of paracetamol tablets.

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Mechanistically, multifunctional carboxylic acids such as citric acid can form strong, directional hydrogen bonds with paracetamol's phenolic and amide sites, weakening its crystal lattice at the dissolving front. Evidence for paracetamol–citric acid co-crystal formation with explicit mapping of H-bond donors/acceptors has been reported and supports this interaction-based rationale.[5, 9] Moreover, organic acids can alter pH_m and the solid-state form of co-formulated actives, thereby modulating release kinetics; such effects have been documented across weakly ionizable drugs. [15]

Although ascorbic acid is a competent H-bond donor and has been co-crystallized with paracetamol in model systems, its performance in simple aqueous media can be less pronounced, potentially due to different solution chemistry and redox sensitivity relative to tricarboxylic acids.[7]

The particularly strong performance of acetic acid alone or with citric acid may also reflect its solvent/processing-aid behavior that enhances drug–excipient wetting and matrix erosion, thereby expediting tablet disintegration. Related work highlights acetic acid as a valuable processing aid that improves solubility handling and bioavailability-enabling manufacture for diverse APIs, reinforcing its utility as a practical enhancer.[8]

3.3. Effect of paracetamol mass loading and saturation behavior

Increasing the mass loading (0.5 → 3.5 g) proportionally extended dissolution time at fixed medium volumes, consistent with a solvent-capacity and boundary-layer limitation (Figure 3). The study identified an operational saturation in 30% acetic acid at 3.5 g, where visible residue persisted despite extended observation indicating exhaustion of the medium's ability to fully solvate the added solid.

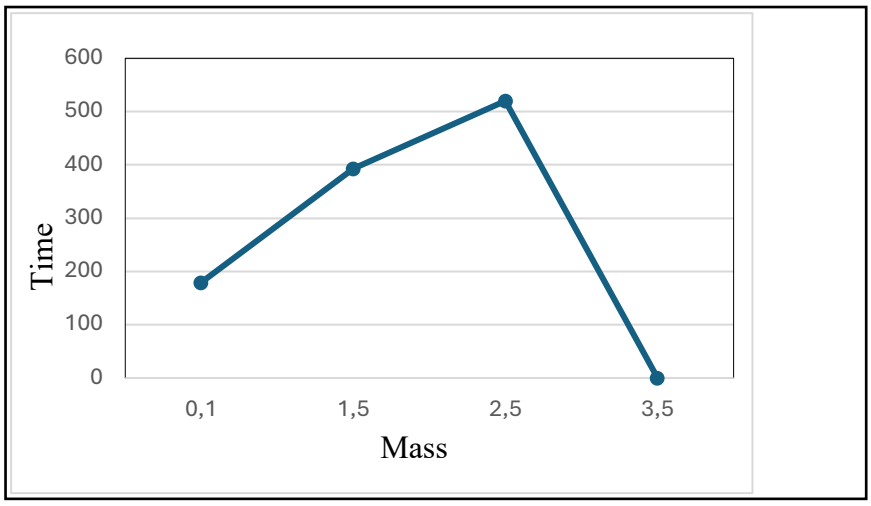

Figure 3. Relationship between paracetamol mass (0.5–3.5 g) and dissolution time in 30% acetic acid solution.

This observation is qualitatively compatible with known solubility constraints for paracetamol (≈23.7 mg mL^{-1} at 37 °C in water), wherein finite volumes impose an upper bound on dissolved mass; while the present system uses acidic aqueous media, the same dose/solubility ratio logic applies.[2,9]

The data demonstrate that simple acid-assisted media can markedly accelerate the visual dissolution of paracetamol tablets without specialized equipment, concordant with broader literature on pH_m modifiers

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and small-molecule co-formers that disrupt crystallinity and improve apparent solubility. In contrast to co-amorphous or polymeric solid-dispersion technologies which are powerful but equipment-intensive this acid-assisted approach is low-cost and instructional, suitable for early-stage formulation screening or teaching laboratories.[16]

4. CONCLUSION

This study demonstrated that the fastest dissolution of paracetamol occurred in 30% acetic acid solution, with complete solubilization within approximately 190 seconds. The enhanced solubility is attributed to hydrogen-bonding interactions between acetic acid and the functional groups of paracetamol, which facilitate crystal-lattice disruption and molecular dispersion. The saturation limit was identified at 3.5 g of paracetamol in 30% acetic acid, beyond which undissolved residue remained, indicating solvent capacity constraints under constant temperature and volume. These findings confirm that simple acid-assisted approaches can improve paracetamol dissolution without requiring specialized equipment, offering a practical strategy for preliminary formulation studies.

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