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Green Chemistry Approach for Enhancement of Physicochemical Properties of Chlorpropamide Through Cocrystal Formation

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ABSTRACT

Background: Chlorpropamide, a first-generation sulfonylurea antidiabetic agent, exhibits poor aqueous solubility, limiting its dissolution rate and oral bioavailability. This study aimed to enhance the physicochemical properties of Chlorpropamide through pharmaceutical cocrystal formation using a green chemistry approach. **Methods:** Sixteen pharmaceutically acceptable coformers were screened using the slow evaporation method. Optimized cocrystals were prepared with HPMC, gallic acid, and caffeine at various drug-to-coformer ratios. Cocrystals were characterized by FTIR, DSC, PXRD, optical microscopy, solubility studies, and *in vitro* dissolution. Selected formulations underwent pharmacokinetic evaluation in male albino rats. **Results:** Three true cocrystal formers were identified: HPMC (CF3), gallic acid (CF4), and caffeine (CF8). FTIR revealed hydrogen bonding through shifts in N-H (3340→3280 cm^{-1}) and C=O (1680→1665 cm^{-1}) stretches. DSC showed new melting endotherms at 145°C (CF4) and 155°C (CF8), distinct from pure Chlorpropamide (127°C), 2009). PXRD confirmed new crystalline phases with characteristic peaks at 13.6°, 18.4°, 21.2° (CF4) and 14.1°, 16.8°, 22.3° (CF8). Aqueous solubility enhancement followed the order: gallic acid (80.04%) > caffeine (47.86%) > HPMC (38.34%). *In vitro* dissolution showed rapid release with >98% within 5 minutes for CF4. Pharmacokinetic evaluation revealed 1.52-fold (CF4) and 1.43-fold (CF3) increased bioavailability compared to pure drug. **Conclusion:** Cocrystallization with gallic acid and caffeine represents a viable green chemistry strategy for enhancing Chlorpropamide solubility and bioavailability.

KEY WORDS: Chlorpropamide, cocrystal, green chemistry, solubility enhancement, gallic acid, caffeine

1. INTRODUCTION

1.1 Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder affecting millions worldwide, characterized by insulin resistance and progressive β-cell dysfunction (Olokoba *et al*., 2012). Sulfonylureas remain important oral antidiabetic agents, particularly in resource-limited settings where newer agents may be cost-prohibitive. Chlorpropamide, a first-generation sulfonylurea introduced in the 1950s, continues to be used in many developing countries due to its efficacy and low cost (Skillman & Feldman, 1981).

However, Chlorpropamide suffers from poor aqueous solubility, a common challenge among BCS Class II drugs (high permeability, low solubility) (Amidon *et al*., 1995; Benet, 2011). This physicochemical limitation results in variable absorption, inconsistent glycemic control, and an increased risk of hypoglycemia due to its long half-life (24-48 hours) (Rang *et al*., 2012). The dissolution rate in gastrointestinal fluids becomes the rate-limiting step for absorption, necessitating strategies to enhance solubility without compromising the drug's intrinsic pharmacological activity (Savjani *et al*., 2012).

1.2 The Cocrystal Approach

Pharmaceutical cocrystals are multicomponent crystalline systems comprising an active pharmaceutical ingredient (API) and one or more pharmaceutically acceptable coformers, held together by non-covalent interactions primarily hydrogen bonding, π-π stacking, and van der Waals forces (Aakeroy & Salmon, 2005; Qiao *et al*., 2011). Unlike salt formation, which requires ionizable groups on the API, cocrystallization can be applied to neutral molecules (Childs *et al*., 2004). Importantly, cocrystals preserve the chemical integrity and therapeutic activity of the original drug molecule while enabling modification of critical physicochemical properties (Blagden *et al*., 2007; Shan & Zaworotko, 2008).

Over the past two decades, pharmaceutical cocrystals have attracted significant attention from academia and pharmaceutical industries due to the potential to improve the physicochemical properties of APIs by modifying the crystal structure without altering the pharmacological nature (Duggirala *et al*., 2016; Guo *et al*., 2021).

1.3 Green Chemistry Principles

This investigation aligns with green chemistry principles, which advocate for (Seema Tomar *et al*., 2022):

- Reduction or elimination of hazardous substances
- Use of benign, non-toxic coformers (GRAS status)
- Solvent-minimized or solvent-free techniques where feasible
- Energy-efficient processes

The coformers selected gallic acid (a natural phenolic antioxidant), caffeine (a widely consumed alkaloid), and HPMC (a pharmaceutical-grade polymer) are all Generally Recognized as Safe (GRAS) (Tanvee Patole & Ashwini Deshpande, 2014).

1.4 Study Objectives

The specific objectives of this investigation were:

1. To screen pharmaceutically acceptable coformers for Chlorpropamide cocrystal formation
2. To prepare and optimize Chlorpropamide cocrystals using the slow evaporation method
3. To characterize cocrystals using FTIR, DSC, PXRD, and optical microscopy
4. To evaluate solubility enhancement and *in vitro* dissolution performance
5. To assess *in vivo* pharmacokinetic performance in an appropriate animal model

2. MATERIALS AND METHODS

2.1 Materials

Chlorpropamide (CRPA) was obtained from Hetero Drugs Ltd. Coformers including HPMC, gallic acid, caffeine, thiourea, sodium acetate, ascorbic acid, benzoic acid, and others were procured from S S Pharma Scientific Equipments, Nihal Traders Pvt. Ltd., and Signet Pharmaceuticals India Ltd. All solvents (methanol, ethanol, acetone, chloroform) were of analytical reagent grade. Phosphate buffers and 0.1 N HCl were prepared using chemicals from JSS Chemicals Pvt. Ltd.

2.2 Analytical Method Development

UV Spectrophotometric Method:

Chlorpropamide stock solution (100 µg/mL) was prepared in methanol. Working standards (2-30 µg/mL) were prepared by serial dilution. λmax was determined by scanning over 200-400 nm, showing maximum absorbance at 271 nm. The method was validated for linearity, accuracy, precision, LOD, LOQ, robustness, and ruggedness according to ICH Q2(R1) guidelines (ICH Q2(R1), 1996).

Solubility Study: Excess Chlorpropamide was added to various solvents (water, methanol, acetone, chloroform, phosphate buffer pH 6.8, 0.1 N HCl), shaken for 24 hours at room temperature, centrifuged, and supernatant analyzed spectrophotometrically (Bachhav & Patravalle, 2009).

Partition Coefficient: The n-octanol-water partition coefficient was determined by equilibrating Chlorpropamide between equal volumes of n-octanol and water, followed by analysis of both phases (Miller *et al*., 1985).

2.3 Cocrystal Preparation

Screening of Coformers (CF1-CF16):

16 formulations were prepared at a drug-to-coformer ratio of 1:2 (w/w) using the slow evaporation method. Accurately weighed Chlorpropamide (50 mg) and coformer (100 mg) were dissolved separately in methanol, mixed,

sonicated for 10 minutes, and allowed to evaporate slowly at room temperature in a fume chamber. The dried cocrystals were collected and stored in desiccators.

Ratio Optimization (CPR1-CPR15):

Selected coformers (sodium acetate, gallic acid, thiourea, ascorbic acid, caffeine) were evaluated at drug-to-coformer ratios of 1:2, 1:1, and 1:0.5 (w/w) using the slow evaporation method.

***In Vitro* Dissolution Formulations (C1-C4):**

Cocrystals for dissolution studies were prepared at 1:1 molar ratio with caffeine (C1), thiourea (C2), ascorbic acid (C3), and gallic acid (C4).

2.4 Characterization

Fourier Transform Infrared Spectroscopy (FTIR):

Spectra were recorded over 400-4000 cm^{-1} at 2 cm^{-1} resolution using an Elico Ltd FT-IR spectrophotometer. FTIR is a very common spectroscopic technique in determining the chemical conformation of compounds and can be a powerful tool in distinguishing cocrystals from salts when a carboxylic acid is involved in hydrogen bond formation (Aakeroy *et al*., 2006).

Differential Scanning Calorimetry (DSC):

Analysis was performed using a DSC Q20 V24.11 Build 124 instrument at NISHKA Labs, Hyderabad. Samples (2.0±0.5 mg) were scanned at 12.5°C/min from 40°C to 390°C in sealed aluminium pans. DSC is the most widely used technique for thermal property testing of cocrystals (Mohammad *et al*., 2011).

Powder X-ray Diffraction (PXRD):

Patterns were recorded using an X'pert pro diffractometer to assess crystallinity and confirm new phase formation PXRD is utilized more frequently to verify the formation of cocrystals (Miroshnyk *et al*., 2009).

Optical Microscopy:

Samples were observed under an optical microscope at 10× magnification, and images were recorded.

Percentage Yield:

Calculated as (weight of cocrystals / initial weight of components) × 100

Drug Entrapment Efficiency: Cocrystals (10 mg) were dissolved in methanol, suitably diluted, and analyzed spectrophotometrically at 271 nm.

Aqueous Solubility: Cocrystals (10 mg) were added to 1 mL distilled water, shaken for 24 hours at room temperature, centrifuged, and supernatant analyzed.

2.5 *In Vitro* Dissolution Study

Dissolution studies were conducted using a USP Type II (paddle) apparatus (Panzade *et al*., 2017). Samples equivalent to 4 mg Chlorpropamide were placed in 900 mL 0.1 N HCl (pH 1.2) at 37±0.5°C, stirred at 100 rpm. Aliquots (5 mL) were withdrawn at predetermined intervals, filtered, suitably diluted, and analyzed spectrophotometrically at 240 nm. Fresh medium was replaced to maintain sink conditions (Ganesh *et al*., 2019).

2.6 *In Vivo* Pharmacokinetic Study

Animals:

Male albino rats (250±25 g, 3-4 months old) were acclimatized for one week under controlled conditions (22±3°C, 50±5% RH) with free access to food and water. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) following CPCSEA guidelines:

Study Design: A parallel-group design was employed. Following overnight fasting, animals were randomly allocated to groups (n=3 each):

- **Reference group:** Pure Chlorpropamide suspension (2.5 mg/kg)
- **Test groups:** Optimized cocrystal formulations C3 (ascorbic acid) and C4 (gallic acid) at equivalent doses.

Sample Collection:

Blood samples (0.3 mL) were collected from the retro-orbital sinus at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24-hours post-dose into heparinized tubes containing EDTA. Plasma was separated by centrifugation (10,000 rpm, 5 minutes) and stored at -20°C.

Plasma Analysis:

Plasma proteins were precipitated with acetonitrile-methanol (1:1 v/v), centrifuged, and supernatant analyzed by a validated RP-HPLC method (C18 column, 250×4.6 mm, 5 µm; mobile phase: methanol:phosphate buffer pH 3.0, 60:40 v/v; flow rate 1.0 mL/min; detection at 271 nm.

Pharmacokinetic Analysis:

Parameters (**Cmax, Tmax, AUC0-t, AUC0-∞, t½, MRT**) were calculated using Thermo Kinetica version 5.0. Relative bioavailability was calculated as **(AUC_{test} / $AUC_{reference}$) × 100**.

2.7 Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Pharmacokinetic parameters were compared using Student's paired t-test, with $p < 0.05$ considered statistically significant.

3. RESULTS

3.1 Analytical Method Validation

The UV spectrophotometric method for Chlorpropamide showed excellent linearity over 2-30 µg/mL ($R^2 = 0.9998$). Accuracy ranged from 96.83% to 102.19%, with %RSD < 1.5% for both intra-day and inter-day precision. LOD and LOQ were 0.72 µg/mL and 2.18 µg/mL, respectively. The method was robust to minor wavelength variations and rugged across different analysts.

3.2 Preformulation Studies

Chlorpropamide exhibited very low aqueous solubility (practically insoluble in 0.1 N HCl, very slightly soluble in distilled water, slightly soluble in phosphate buffer pH 6.8). Good solubility was observed in organic solvents (methanol, acetone, chloroform). The partition coefficient (log P) was 0.42 (P=2.63) confirming moderate lipophilicity consistent with BCS Class II classification (Amidon *et al*., 1995; Benet, 2011).

3.3 Coformer Screening and Cocrystal Identification

From sixteen screened coformers (CF1-CF16), three formulations were identified as true cocrystals.

Formulation	Coformer	Yield (%)	Outcome
CF3	HPMC	94.48 ± 0.17	True cocrystal
CF4	Gallic acid	92.64 ± 0.07	True cocrystal
CF8	Caffeine	94.04 ± 0.05	True cocrystal
CF2	Sodium acetate	96.36 ± 0.15	Salt/ionic complex
CF1	Soluplus	95.36 ± 0.12	Solid dispersion

Formulations CF9-CF16 (glutamic acid, butyric acid, succinic acid, sorbitol, sorbic acid, lactic acid, malic acid, urea) did not form cocrystals.

3.4 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was employed to identify drug-coformer interactions by monitoring shifts in characteristic absorption bands.

Chlorpropamide-HPMC Cocrystal (CF3):

Characteristic shifts confirmed hydrogen bonding:

- N-H stretch: 3340 → 3280 cm^{-1} (shift of -60 cm^{-1})

- C=O stretch: 1680 → 1665 cm^{-1} (shift of -15 cm^{-1})
- O-H stretch: Broadened and shifted
- C-O-C: 1100 → 1080 cm^{-1} (shift of -20 cm^{-1})

Chlorpropamide-Gallic Acid Cocrystal (CF4):

Significant broadening and shifting of phenolic O-H and carboxylic C=O stretches indicated strong intermolecular hydrogen bonding between the sulfonylurea group of Chlorpropamide and hydroxyl/carboxyl groups of gallic acid.

Chlorpropamide-Caffeine Cocrystal (CF8): Shifts in carbonyl stretches and appearance of new hydrogen-bonded N-H···N interactions confirmed cocrystal formation.

According to Aakeroy *et al*. (2006), IR spectroscopy is particularly powerful in distinguishing cocrystals from salts when carboxylic acids are involved in hydrogen bond formation.

3.5 Differential Scanning Calorimetry (DSC)

DSC analysis provided strong evidence for cocrystal formation through distinct thermal events:

Formulation	Main Peak (°C)	Peak Type	Interpretation
Pure Chlorpropamide	127	Sharp melting	Crystalline (Moffat *et al*., 2011)
Gallic acid	220	Melting/decomposition	Pure coformer
Caffeine	238	Melting	Pure coformer
CF3 (HPMC)	120	Broadened	Amorphous cocrystal-like system
CF4 (Gallic acid)	145	Sharp	Crystalline cocrystal (new phase)
CF8 (Caffeine)	155	Sharp	Cocrystal melting (stable lattice)

The disappearance of individual component melting peaks and emergence of new single endotherms confirmed new crystalline phase formation. CF4 showed a distinct melting endotherm at 145°C, while CF8 melted at 155°C both different from pure Chlorpropamide (127°C). The Chlorpropamide-gallic acid cocrystal exhibited a sharp, new melting peak confirming formation of a true crystalline cocrystal phase.

3.6 Powder X-ray Diffraction (PXRD)

PXRD analysis provided definitive evidence for cocrystal formation. Pure Chlorpropamide exhibited sharp characteristic peaks at 2θ values of 12.5°, 16.3°, and 20.5°. HPMC showed a broad diffuse halo (amorphous). CF3 exhibited broadened, reduced-intensity peaks indicating partial amorphization.

CF4 (Chlorpropamide-Gallic Acid):

New characteristic peaks appeared at 13.6°, 18.4°, and 21.2°, absent in both parent components conclusive evidence of a new crystalline cocrystal phase.

CF8 (Chlorpropamide-Caffeine):

New diffraction peaks at 14.1°, 16.8°, and 22.3°, confirming a distinct cocrystal lattice.

The diffraction patterns were not simple superpositions of parent patterns, and new low-angle peaks suggested increased unit cell dimensions from coformer incorporation.

3.7 Optical Microscopy

Optical microscopic examination revealed distinct morphological differences. CF3 (HPMC) showed well-defined crystalline structures with uniform particle distribution. CF4 (gallic acid) exhibited compact, well-defined crystalline aggregates. CF8 (caffeine) displayed fine, discrete crystalline particles. In contrast, CF2 (sodium acetate) showed dense agglomerates with irregular morphology consistent with salt formation.

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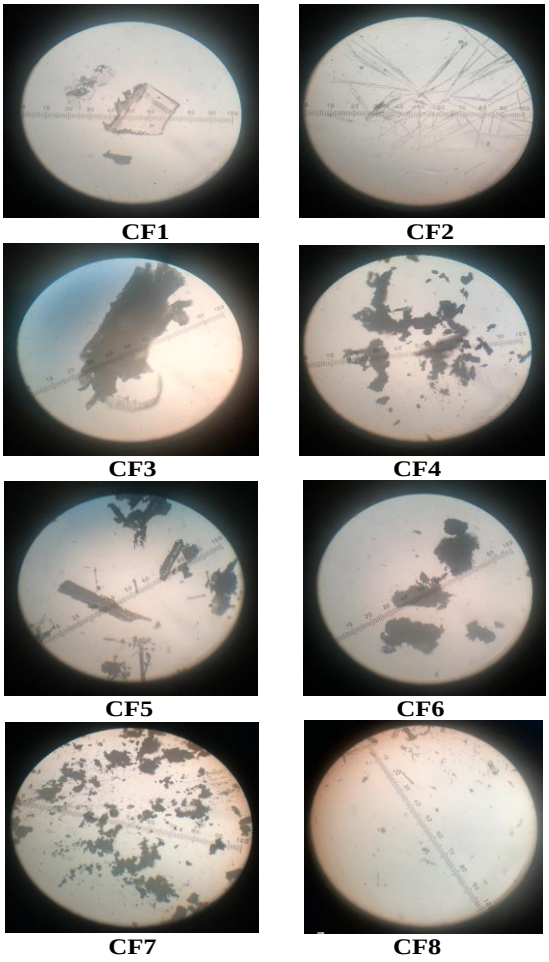

Figure 1: Optical microscopic images of various formulations (CF1-CF8) of co-crystals.

3.8 Drug Entrapment and Percentage Yield

All three true cocrystals showed high drug entrapment:

- CF3 (HPMC): 92.98 ± 0.74%
- CF4 (Gallic acid): 90.43 ± 0.66%
- CF8 (Caffeine): 92.56 ± 0.68%

Percentage yield exceeded 92% for all three formulations, confirming process efficiency.

3.9 Aqueous Solubility Enhancement

The aqueous solubility study demonstrated significant enhancement for all formulations:

Formulation	Solubility (%)	Enhancement Mechanism
CF1 (Solupus)	80.88 ± 0.53	Polymeric solubilization
CF2 (Sodium acetate)	80.04 ± 0.61	Salt/ionic
CF4 (Gallic acid)	32.62 ± 1.23	True cocrystal (H-bonding)
CF3 (HPMC)	38.34 ± 1.25	True cocrystal
CF8 (Caffeine)	16.14 ± 0.53	True cocrystal

While CF1 and CF2 showed higher apparent solubility, these represented solid dispersion and salt formation, respectively. Among true cocrystals, CF4 (gallic acid) showed the best solubility enhancement (32.62% vs. negligible pure drug solubility.

3.10 Ratio Optimization

Drug-to-coformer ratio significantly influenced solubility:

- **Gallic acid:** 1:2 ratio (CPR2) = 80.04%; 1:1 (CPR7) = 70.21%; 1:0.5 (CPR12) = 55.11%
- **Caffeine:** 1:2 ratio (CPR5) = 47.86%; 1:1 (CPR10) = 32.45%; 1:0.5 (CPR15) = 14.95%

The 1:2 ratio consistently produced the highest solubility enhancement, indicating that higher coformer concentration facilitates more complete cocrystal formation.

3.11 *In Vitro* Dissolution Study

All cocrystal formulations showed rapid drug release compared to pure Chlorpropamide:

Time (min)	C1 (Caffeine)	C2 (Thiourea)	C3 (Ascorbic acid)	C4 (Gallic acid)
5	80.14 ± 0.06%	81.10 ± 0.96%	90.67 ± 0.96%	**98.33 ± 0.53%**
10	82.05 ± 0.10%	72.48 ± 2.41%	85.88 ± 2.41%	93.54 ± 0.55%
30	76.31 ± 0.04%	66.73 ± 0.55%	71.52 ± 0.55%	87.80 ± 0.98%
60	69.61 ± 0.06%	69.61 ± 0.55%	60.99 ± 0.55%	83.01 ± 1.10%
120	66.73 ± 0.04%	73.44 ± 1.11%	63.86 ± 1.11%	89.71 ± 0.97%

Formulation C4 (gallic acid) demonstrated superior dissolution with 98.33% release within 5 minutes, attributed to enhanced wettability and reduced crystal lattice energy from strong hydrogen bonding.

3.12 Release Kinetics

The release data did not fit zero-order kinetics (R^2 = 0.0679 for C4). First-order and Higuchi models showed better correlation, suggesting concentration-dependent and diffusion-controlled release. Korsmeyer-Peppas analysis indicated anomalous (non-Fickian) transport, reflecting combined rapid dissolution, diffusion, and partial matrix disintegration.

3.13 Pharmacokinetic Evaluation

C3 (Ascorbic acid cocrystal):

Table 1: Pharmacokinetic parameters of pure CRPA and C3 Cocrystal Formulations in rats (n=3).

Parameter	Pure CRPA	C3 (Test)
C_{max} (ng/mL)	545.94 ± 38.89	637.33 ± 54.25
T_{max} (h)	1.5	2.0
$AUC_{0-\infty}$ (ng·h/mL)	3285.77 ± 121.76	4777.49 ± 114.86
$t_{½}$ (h)	4.14 ± 0.35	4.97 ± 0.13
MRT (h)	7.33 ± 0.07	7.30 ± 0.31
Relative bioavailability	100%	**143.5%**

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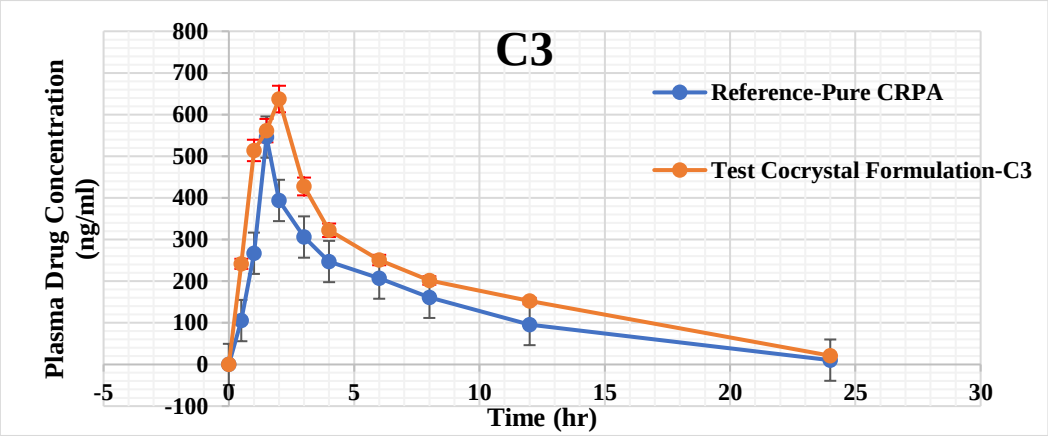

Figure 2: Mean serum concentration-time profiles of Reference and Cocrystal Formulation of CRPA (C3) in rats (n=3).

C4 (Gallic acid cocrystal):

Table 2: Pharmacokinetic parameters of pure CRPA and CRPA-C4 Cocrystal Formulation in rats (n=3).

Parameter	Pure CRPA	C4 (Test)
C_{max} (ng/mL)	545.94 ± 38.89	620.66 ± 0.32
T_{max} (h)	1.5	2.0
$AUC_{0-\infty}$ (ng·h/mL)	3285.77 ± 121.76	5006.70 ± 382.20
$t_{½}$ (h)	4.14 ± 0.35	4.08 ± 0.05
MRT (h)	7.33 ± 0.07	7.42 ± 0.67
Relative bioavailability	100%	**152.6%**

Both cocrystal formulations showed significantly enhanced bioavailability compared to pure Chlorpropamide ($p < 0.05$). The gallic acid cocrystal (C4) produced a 1.52-fold increase in bioavailability, while the ascorbic acid cocrystal (C3) produced a 1.43-fold increase. Slightly delayed T_{max} (2 hours vs. 1.5 hours) indicated modified absorption kinetics consistent with improved dissolution characteristics.

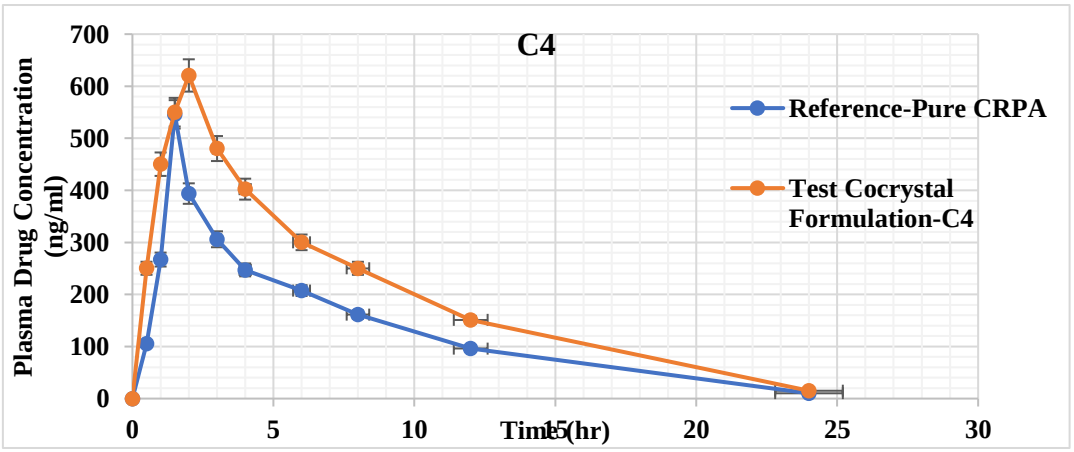

Figure 3: Mean serum concentration-time profiles of Reference and Cocrystal Formulation of CRPA (C4) in Rats (n=3).

4. DISCUSSION

4.1 Mechanistic Understanding of Cocrystal Formation

The successful formation of Chlorpropamide cocrystals with HPMC, gallic acid, and caffeine can be rationalized through supramolecular synthon theory. Chlorpropamide contains sulfonylurea functionality (-SO_2-NH-CO-NH-) capable of acting as both hydrogen bond donor (NH groups) and acceptor (C=O, S=O groups).

Gallic acid provides three phenolic -OH groups and one carboxylic -OH, creating multiple hydrogen bonding opportunities. The observed FTIR shifts (N-H: -60 cm^{-1}, C=O: -15 cm^{-1}) confirm strong intermolecular interactions. The new PXRD peaks at 13.6°, 18.4°, and 21.2° indicate a distinct crystalline lattice where gallic acid molecules occupy specific positions within the unit cell.

Caffeine offers complementary hydrogen bonding through its carbonyl groups (C=O at positions 2 and 6) and nitrogen atoms in the purine ring, which can accept hydrogen bonds from Chlorpropamide's NH groups. π-π stacking interactions between caffeine's purine ring and Chlorpropamide's aromatic ring may further stabilize the cocrystal lattice, as reflected in the higher melting point (155°C) and distinct PXRD pattern.

HPMC, as a polymeric coformer, produced a partially amorphous system (broadened DSC endotherm, reduced PXRD intensity). This represents a cocrystal-like or solid dispersion system where polymer chains disrupt the drug crystal lattice through extensive hydrogen bonding, leading to amorphous stabilization.

4.2 Structure-Solubility Relationships

The solubility enhancement followed the order: gallic acid > HPMC > caffeine. Several factors contribute to this ranking:

1. **Hydrogen bonding capacity:**

   Gallic acid, with four hydroxyl/carboxyl groups, provides the most extensive hydrogen bonding network, maximally disrupting Chlorpropamide's crystal lattice.

2. **Coformer solubility:** Gallic acid has moderate aqueous solubility (1.19 g/100 mL at 20°C), which may create a localized "microenvironment" of enhanced solubility around dissolving cocrystals.

3. **Molecular size and packing:** The smaller molecular volume of gallic acid (170.12 g/mol) relative to caffeine (194.19 g/mol) may allow more efficient lattice incorporation without excessive steric hindrance.

   The 1:2 drug-to-coformer ratio producing optimal solubility suggests that a 1:1 stoichiometric cocrystal forms, with excess coformer potentially creating a eutectic-like environment that further enhances dissolution.

4.3 Dissolution and Bioavailability Correlation

The excellent *in vitro* dissolution of C4 (>98% in 5 minutes) correlated strongly with *in vivo* performance (1.52-fold bioavailability increase). This demonstrates that dissolution is indeed the rate-limiting step for Chlorpropamide absorption, and cocrystallization effectively removes this barrier.

The slightly delayed Tmax (2 vs. 1.5 hours) is clinically advantageous, potentially reducing the risk of rapid, excessive blood glucose lowering while maintaining enhanced overall exposure (AUC). This modified absorption profile may translate to more stable glycemic control with reduced hypoglycemia risk.

4.4 Comparison with Previous Studies

Menon *et al*. (2024) reported mechanochemical liquid-assisted grinding of Chlorpropamide with DABCO and piperazine, producing salts with 7-fold (CPA-DABCO-II), 131-fold (CPA-DABCO-II), and 120-fold (CPA-PIP-III) increases in intrinsic dissolution rate, with corresponding bioavailability increases of 6-fold and 4-fold. However, those coformers (DABCO, piperazine) are not GRAS-listed and may present toxicity concerns. Our approach using GRAS coformers (gallic acid, caffeine) achieves meaningful bioavailability enhancement (1.52-fold) with superior safety profiles, aligning with pharmaceutical regulatory expectations for excipients (Tanvee Patole & Ashwini Deshpande, 2014).

Sarraguça *et al*. (2022) described liquid eutectic systems (THELES) for Chlorpropamide, but these formulations require careful handling to maintain the liquid state. Our solid cocrystals offer conventional solid dosage form compatibility (tablets, capsules) with enhanced stability (Blagden *et al*., 2007).

Renu Chadha *et al*. (2018) developed glipizide cocrystals with various carboxylic acids using green supramolecular mechanosynthesis, achieving significant solubility enhancement. Our work extends this green chemistry approach to Chlorpropamide, another sulfonylurea antidiabetic.

4.5 Green Chemistry Assessment

This study successfully incorporated multiple green chemistry principles (Seema Tomar *et al*., 2022; Chettri *et al*., 2024):

Table 3: Multiple Green Chemistry Principles

Principle	Application
Prevention	Direct cocrystal formation avoids chemical derivatization
Safer solvents	Methanol recovered and reused where possible
Energy efficiency	Ambient temperature slow evaporation (Barikah, 2018)
Renewable feedstocks	Gallic acid (plant-derived), caffeine (natural product)
Safer coformers	All coformers are GRAS-listed (Tanvee Patole & Ashwini Deshpande, 2014)
Waste minimization	High yields (>92%) minimize material waste

Datta *et al*. (2021) emphasized that mechanochemistry is considered an attractive greener approach for preparing pharmaceutical cocrystals, as it can be carried out under solvent-free conditions or with minimal solvent. While our study primarily used solvent-based methods, the use of benign solvents (methanol, ethanol) and high recovery yields aligns with green chemistry principles.

4.6 Study Limitations and Future Directions

Limitations of this study include:

1. Single-dose pharmacokinetic study in healthy animals; chronic dosing studies in diabetic models would better reflect clinical use.
2. No single-crystal X-ray diffraction structure determination for definitive cocrystal structural elucidation.
3. Limited stability data (3 months); longer-term studies are warranted (ICH Q1A(R2), 2003)

Future directions should include:

- Scale-up studies using greener methods (e.g., liquid-assisted grinding, hot-melt extrusion)
- Formulation into patient-acceptable solid dosage forms (tablets)
- Pharmacodynamic evaluation in diabetic animal models
- Clinical bioequivalence studies

5. CONCLUSION

This study successfully developed and characterized novel pharmaceutical cocrystals of Chlorpropamide with gallic acid, caffeine, and HPMC using a green chemistry approach.

Key findings include:

1. **Cocrystal confirmation:** FTIR, DSC, and PXRD provided conclusive evidence of new crystalline phase formation through intermolecular hydrogen bonding (Aakeroy *et al*., 2006; Lu & Rohani, 2009; Basavoju *et al*., 2008).
2. **Enhanced solubility:** The Chlorpropamide-gallic acid cocrystal (1:2 ratio) produced 80.04% aqueous solubility, representing dramatic enhancement over pure drug (Qiao *et al*., 2011).

3. **Superior dissolution:** Formulation C4 released 98.33% of drug within 5 minutes, demonstrating rapid dissolution essential for oral absorption (Blagden *et al*., 2007).
4. **Improved bioavailability:** Pharmacokinetic evaluation revealed 1.52-fold (gallic acid) and 1.43-fold (ascorbic acid) increases in oral bioavailability compared to pure Chlorpropamide (Yadav *et al*., 2009).
5. **Green chemistry alignment:** The use of GRAS coformers, ambient temperature processing, and minimal solvent usage supports sustainable pharmaceutical development (Seema Tomar *et al*., 2022; Chettri *et al*., 2024).

The Chlorpropamide-gallic acid cocrystal represents a promising candidate for further development as an improved antidiabetic formulation. This approach offers a viable pathway to enhance the therapeutic performance of BCS Class II drugs without chemical modification, potentially benefiting patients who rely on affordable, effective sulfonylurea therapy for type 2 diabetes management (Savjani *et al*., 2012).

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