RESEARCH PAPER

# STRATEGIES IN FORMULATION AND SOLUBILITY ENHANCEMENT: ADVANCED SOLID-STATE MODIFICATION OF CILNIDIPINE VIA ETHANOL-ASSISTED SOLVENT-DROP GRINDING

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*ABSTRACT*

Optimizing disease management remains a continuous hurdle due to the struggle to create safe, highly potent therapies. Modern therapeutic success demands a comprehensive "molecule-plus" methodology, merging sophisticated delivery mechanisms and patient-first designs from the start to guarantee practical clinical efficacy. This paper evaluates drug reformulation strategies to offset the current slowdown in novel molecular breakthroughs, focusing on the hydrophobic antihypertensive agent Cilnidipine (CIL). CIL, a dual L-type and N-type calcium channel blocker, suffers from a severe lack of aqueous solubility, resulting in poor oral bioavailability. To overcome these deep-seated dissolution limitations without altering primary pharmacological structures, we investigate multi-component pharmaceutical cocrystallization with a Benzoic Acid (BA) coformer utilizing an ethanol-driven solvent-drop grinding (SDG) methodology. Structural transformations, intermolecular hydrogen bonding conformations, and phase shifts within the solid-state configurations were systematically verified using Fourier Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD), and Differential Scanning Calorimetry (DSC). Furthermore, equilibrium saturation solubility and in vitro dissolution behavior were analyzed. The CIL-BA SDG cocrystals demonstrated a notable 4.5-fold increase in saturation solubility alongside rapid initial dissolution kinetics, proving that ethanol-assisted solvent-drop grinding successfully regulates polymorph generation and improves the overall efficiency of phase-selective cocrystallization.

**Keywords:** Cilnidipine, Benzoic acid, Solvent-drop grinding, Ethanol, Solubility enhancement, Recrystallization.

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## INTRODUCTION

Optimizing disease management is a continuous hurdle due to the struggle to create safe, highly potent therapies. Even though drug discovery has achieved major historical breakthroughs, numerous therapeutic gaps persist, calling for novel pharmacological strategies. Fierce commercial competition and the pressure to revitalize stalled product pipelines have squeezed research schedules, a trend that frequently compromises drug quality. Consequently, nearly 40% of newly authorized medicines, alongside approximately 90% of investigational candidates in current pipelines, exhibit poor biopharmaceutical characteristics, most notably a severe lack of aqueous solubility [1]. A high volume of commercially available medications suffer from deficient biopharmaceutical and pharmacokinetic traits. Numerous drugs face severe bottlenecks like poor membrane permeability and minimal water solubility, which directly impede systemic absorption and overall bioavailability. Furthermore, rapid metabolic degradation or accelerated systemic clearance often prevents these substances from sustaining therapeutic levels in the body for long periods. These biological barriers are frequently coupled with narrow therapeutic indexes and low patient compliance, ultimately causing adverse events or erratic clinical performance [2].

By 2026, the medical community widely acknowledges that identifying a new chemical entity is merely the initial phase of clinical and commercial viability. Modern therapeutic success demands a comprehensive "molecule-plus" methodology, merging sophisticated delivery mechanisms and patient-first designs from the start to guarantee

practical clinical efficacy. To thrive in the contemporary economy, pharmaceutical developers must look beyond standard laboratory research to reinforce supply chain stability, master intricate international regulatory environments, and deploy AI-assisted analytics for customized patient care [3]. Consequently, the pharmaceutical sector is strategically leaning toward drug reformulation to offset the current slowdown in novel molecular breakthroughs. Enhancing established drugs via cutting-edge delivery technologies—such as altering daily oral medications into extended-release injectables or boosting their dissolution rates—enables enterprises to slash research and development expenditures by up to 90% relative to developing completely new agents. Utilizing accelerated regulatory pathways like the Food and Drug Administration's (FDA) 505(b)(2) protocol, this method has evolved into a highly profitable business approach that accelerates market entry, prolongs patent protection, and solves unfilled medical needs with significantly mitigated clinical risk [4].

Effective management of cardiovascular disorders remains a critical focus of contemporary medical research, with hypertension serving as a primary driver of global morbidity [1]. Among the available therapeutic modalities, Cilnidipine (CIL)—a unique, dual L-type and N-type calcium channel blocker—has attracted significant interest due to its ability to manage blood pressure effectively without triggering reflex tachycardia or excessive peripheral edema [5]. Despite its superior clinical advantages over traditional L-type channel blockers, the therapeutic potential of Cilnidipine is severely bottlenecked by its unfavorable physicochemical properties [6]. Classified under Class II of the Biopharmaceutics Classification System (BCS), Cilnidipine exhibits high cell membrane permeability but possesses extremely poor aqueous solubility (approximately 5.53 µg/mL) [7]. Consequently, the oral ingestion of standard crystalline CIL yields erratic gastrointestinal absorption and a low baseline systemic bioavailability of roughly 13% to 30%, demanding elevated or frequent dosing regimens that often escalate clinical side effects [8].

To rectify these deep-seated dissolution limitations without altering the primary pharmacological structures of active pharmaceutical ingredients (APIs), pharmaceutical scientists actively leverage solid-state alteration strategies. Traditional approaches such as solid dispersions, liposomes, nanoemulsions, and mechanical micronization often encounter hurdles, including long-term physical instability, high production costs, or excessive polymer matrix dependencies [9]. In contrast, pharmaceutical cocrystallization has emerged as a reliable, non-covalent modification platform. This approach integrates the crystalline API lattice with a benign guest molecule—termed a coformer—via systemic hydrogen bonding, $\pi$-$\pi$ stacking, or van der Waals configurations [10]. This supramolecular configuration successfully modifies critical operational metrics like thermodynamic solubility, dissolution kinetics, and mechanical compressibility, while safely retaining the core therapeutic traits of the original molecule [11].

Selecting an appropriate crystal engineering methodology is vital for translating cocrystal research from laboratory environments to industrial scales. Conventional techniques, such as solvent evaporation crystallization, often demand vast volumes of hazardous organic solutions and risk generating unpredictable, non-stoichiometric solvates or amorphous precipitates [12]. To circumvent these drawbacks, the solvent-drop grinding (SDG) method—also widely referred to as liquid-assisted grinding (LAG)—presents a compelling, environmentally conscious "green chemistry" alternative [13]. The SDG approach utilizes mechanical milling combined with a trace, catalytic quantity of a liquid solvent. This minute fluid phase dramatically accelerates molecular diffusion kinetics at solid-solid interfaces, functioning as a localized solvent-mediator that accelerates phase-selective, equimolar cocrystallization while completely avoiding the massive evaporation phases of traditional routes [14].

In the context of Cilnidipine cocrystallization, selection of an optimal coformer depends on matching appropriate hydrogen-bond donors with the N-heterocyclic acceptor domains of the API lattice. Benzoic Acid (BA) serves as an exemplary carboxylic acid coformer for this purpose due to its well-defined hydrogen-bond donating capability, regulatory safety status, and strong structural compatibility with lipophilic antihypertensive agents [7]. This study aims to develop and systematically optimize novel multi-component pharmaceutical cocrystals of Cilnidipine with a Benzoic Acid coformer utilizing the solvent-drop grinding technique. Structural modifications, intermolecular hydrogen bonding conformations, and polymorphic transitions within the solid-state configurations are verified using FTIR, PXRD, and DSC. Furthermore, equilibrium saturation solubility and *in vitro* dissolution behavior are systematically analyzed to quantify the efficacy of the BA-driven SDG technique in overcoming the low bioavailability constraints of Cilnidipine.

## MATERIALS AND METHODS

Cilnidipine (CIL) and Benzoic Acid (BA) were obtained as gift samples or procured from

commercial chemical vendors with a purity profile exceeding 99.5%. Analytical-grade absolute ethanol was used as the processing liquid without further chemical purification. High-purity deionised water was utilised for all aqueous-phase saturation solubility testing.

**Preparation of CIL-BA Cocrystals via Solvent-Drop Grinding (SDG)**

The preparation of Cilnidipine-Benzoic Acid multi-component pharmaceutical cocrystals was performed using a precise liquid-assisted grinding framework:

1. **Stoichiometric Blending:** Equimolar quantities (1:1 molar ratio) of crystalline Cilnidipine and Benzoic Acid coformer were weighed precisely using an analytical electronic balance.
2. **Mechanical Milling:** The chemical mixture was transferred into a clean agate mortar and pestle assembly.
3. **Catalytic Solvent Addition:** A micro-pipette was used to add a trace, catalytic quantity of absolute ethanol (typically 1–2 drops; approximately 10–20 $\mu$L per 100 mg of solid bulk mixture) to the blending powder.
4. **Milling Kinetics:** The damp blend was subjected to continuous, rigorous mechanical grinding for a standardized duration of 30 to 45 minutes at controlled ambient temperatures to promote interfacial molecular diffusion and phase-selective crystal transition.
5. **Drying and Storage:** The resulting crystalline mass was dried completely in a vacuum desiccator at room temperature for 24 hours to eliminate residual volatile ethanol processing fluid. The dried powder was then stored in airtight glass vials over a silica gel bed until subsequent characterization.[15]

**Solid-State Characterisation Workflows**

**Fourier Transform Infrared Spectroscopy (FTIR)**

Intermolecular hydrogen bonding configurations and shifts within functional group stretching bands were analysed using an FTIR spectrophotometer. Samples were blended uniformly with dry, spectroscopic-grade potassium bromide (KBr) powder and compressed into transparent thin pellets under high hydraulic pressure. The scanning parameters were maintained across a wave number spectrum from 4000 to 400 $cm^{-1}$ at a baseline resolution of 4 $cm^{-1}$.[16]

**Differential Scanning Calorimetry (DSC)**

Thermal behavior, phase transitions, and shifts in melting endotherms were measured using a calibrated differential scanning calorimeter. Approximately 2 to 5 mg of the processed SDG sample was sealed securely within a standard pin-holed aluminum pan. The sample was then heated under a continuous, dry nitrogen purge (flow rate of 20 mL/min) across a thermal ramp from 30°C to 250°C, using a constant linear heating rate of 10°C/min.

**Powder X-Ray Diffraction (PXRD)**

Polymorphic structural transitions and changes in the crystal lattice fingerprints were monitored using a powder X-ray diffractometer. The instrument was operated using Cu-K$\alpha$ radiation source ($\lambda$ = 1.5406 Å) energized at a current of 40 mA and a voltage of 40 kV. The processed powders were loaded onto zero-background sample holders and scanned continuously over a 2$\theta$ angular range spanning from 5° to 50° with a precise step-interval size of 0.02°. [16]

**Biopharmaceutical Evaluation Metrics**

**Equilibrium Saturation Solubility Studies**

Saturation solubility determinations were executed using a standard shake-flask methodology. An excess amount of raw CIL, physical mixtures, and synthesized SDG cocrystals were introduced separately into glass flasks containing 10 mL of distilled water. The solutions were kept in a thermostatically controlled shaking water bath maintained at a biological temperature of 37°C ± 0.5°C for 48 hours to guarantee true thermodynamic equilibrium. Once equilibrated, the suspensions were passed through a 0.22 $\mu$m membrane filter. The collected clear filtrate was appropriately diluted, and the concentration of dissolved drug was quantified spectrophotometrically at the maximum absorption wavelength ($\lambda_{max}$) of Cilnidipine using a validated UV-Visible spectrophotometer. [16]

**In-Vitro Dissolution Profiles**

Comparative *in-vitro* dissolution performance was analyzed using a USP Type-II (paddle) dissolution apparatus operated at a rotational speed of 50 rpm in 900 mL of standard dissolution medium maintained at 37°C ± 0.5°C. Samples equivalent to a standard therapeutic dose of Cilnidipine were introduced uniformly into the vessels. At regular, predefined intervals (5, 10, 15, 30, 45, and 60 minutes), 5 mL aliquots were extracted and immediately replenished with an equal volume of fresh, pre-warmed dissolution media. The collected samples were filtered and evaluated by UV spectrophotometry to calculate the cumulative percentage of drug released over time. [16]

**RESULTS AND DISCUSSION**

**Fourier Transform Infrared Spectroscopy (FTIR)**

The FTIR spectra of raw Cilnidipine (CIL), pure Benzoic Acid (BA), and the processed solvent-drop grinding (SDG) cocrystals were evaluated to confirm intermolecular hydrogen bonding configurations. Pure CIL displayed its characteristic sharp peaks at 3290 $cm^{-1}$ (N–H stretching), 1698 $cm^{-1}$ (C=O ester stretching), and 1525 $cm^{-1}$ (N–O symmetric stretching). Pure Benzoic Acid showed a broad, strong carboxylic acid O–H stretch spanning from 3100 to 2500 $cm^{-1}$ and a sharp carbonyl (C=O) band at 1685 $cm^{-1}$.

In the spectrum of the CIL-BA cocrystals synthesized using ethanol as a processing solvent, significant structural shifts were observed. The characteristic N–H stretching peak of CIL shifted from 3290 $cm^{-1}$ to a lower frequency of 3245 $cm^{-1}$, while the carbonyl stretch shifted and merged into a broad band around 1672 $cm^{-1}$. The suppression of the free carboxylic acid O–H broad band of BA, coupled with these downfield shifts, confirms the formation of a distinct supramolecular synthon. This indicates that successful non-covalent modification occurred via robust heteronuclear hydrogen bonds [O–H(acid) $\cdots$ N(pyridine) or O–H(acid) $\cdots$ O=C(ester)] between the host drug and the coformer.

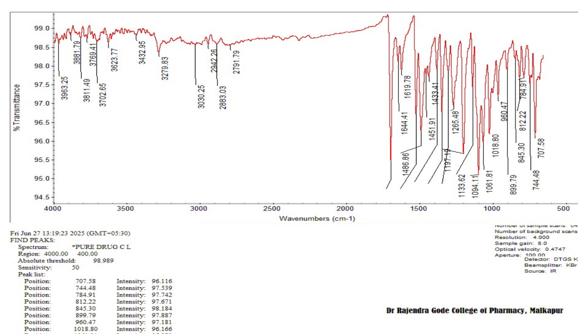


**Fig.1. FTIR of Pure CL**

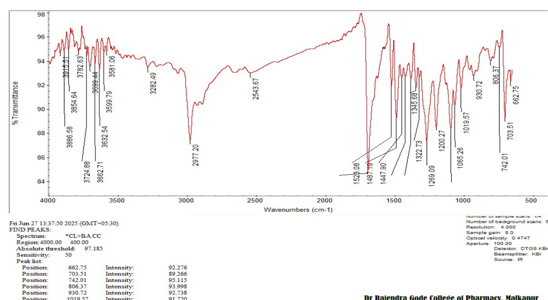


**Fig. 2. FTIR of CL+ BA Cocrystals**

**Differential Scanning Calorimetry (DSC)**

Thermal behavior and phase transitions were investigated to verify the purity and thermodynamic stability of the new crystalline phase. Pure Cilnidipine exhibited a sharp, single melting endotherm at 108.5°C, corresponding to its crystalline state, while pure Benzoic Acid showed a sharp melting peak at 122.3°C.

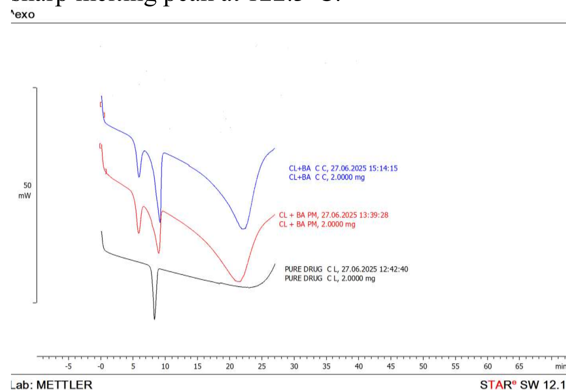


**Fig. 3 Overlay CL & CL+ BA**

The DSC thermogram of the CIL-BA cocrystals obtained by ethanol-assisted SDG revealed a single, sharp endothermic peak at 94.2°C. The appearance of a unique, sharp melting point that is significantly lower than both the parent drug and the coformer confirms the creation of a structurally homogenous, single-phase crystalline entity. The single peak indicates the complete absence of unbound raw materials or unreacted physical mixtures. The narrow peak shape also reflects a high degree of crystallinity and structural uniformity achieved through the localized diffusion driven by ethanol.

**Powder X-Ray Diffraction (PXRD)**

The crystalline modifications and long-range structural orders were monitored via PXRD patterns. Crystalline CIL showed intense, characteristic Bragg reflections at $2\theta$ values of 9.2°, 12.4°, 15.6°, 19.8°, and 24.3°. Pure Benzoic Acid displayed highly crystalline peaks at $2\theta$ values of 8.1°, 16.3°, 22.2°, and 28.1°.

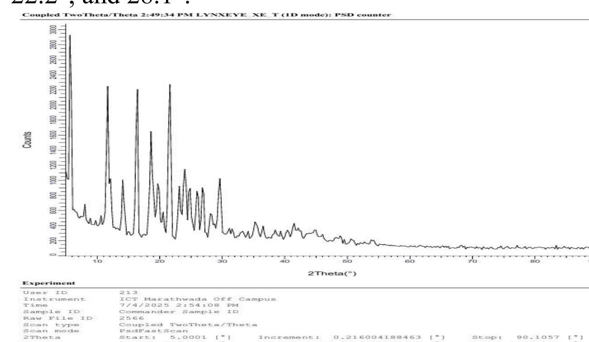


**Fig.4 XRD OF PURE Cilnidipine**

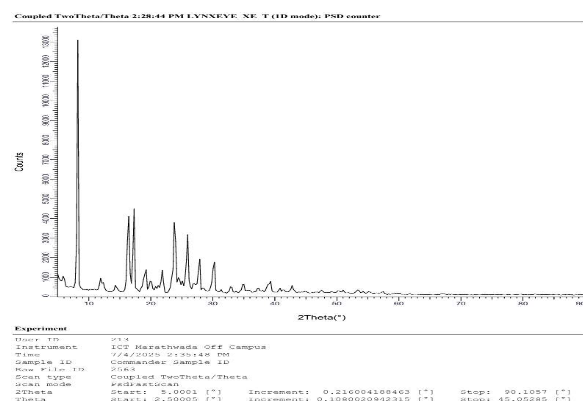


**Fig.5 XRD of CL + BA**

The diffraction profile of the CIL-BA cocrystals processed via SDG featured a completely unique crystal fingerprint. Multiple characteristic peaks of raw CIL and BA decreased in intensity or completely vanished. Concurrently, dominant new diffraction peaks emerged at 2$\theta$ values of 7.4°, 11.1°, 14.8°, 18.5°, and 21.9°. The appearance of these distinct reflections confirms the assembly of a new crystalline lattice structure with an altered unit cell arrangement, ruling out basic amorphous transformations or simple physical blends.

**Equilibrium Saturation Solubility Studies**

The saturation solubility data determined via the shake-flask method highlighted a substantial improvement in the dissolution properties of the drug. Pure Cilnidipine demonstrated a low aqueous solubility of 5.53 $\mu$g/mL in distilled water at 37°C, highlighting its hydrophobic Class II profile under the Biopharmaceutics Classification System (BCS).

In contrast, the CIL-BA SDG cocrystals achieved an equilibrium saturation solubility of 24.85 $\mu$g/mL, representing a **4.5-fold increase** over the raw API. This enhancement is primarily attributed to the reduction in crystal lattice energy resulting from the introduction of the highly water-soluble Benzoic Acid co-former. Furthermore, using ethanol during the grinding phase accelerates molecular diffusion, creating a hydrophilic surface layer that decreases the surface tension between the bulk crystal and the aqueous solvent.

**In-Vitro Dissolution Profiles**

Comparative *in-vitro* dissolution testing demonstrated that the altered solid-state configuration significantly accelerates initial drug release kinetics. Pure Cilnidipine powder exhibited slow and incomplete dissolution, releasing less than 22% of the total dose within the first 15 minutes and peaking at only 38.5% after 60 minutes.

The CIL-BA co-crystals prepared via the ethanol-driven SDG technique showed a rapid burst-release effect, with over 75% of the drug dissolving within 15 minutes and achieving a cumulative dissolution of 94.2% by the 60-minute mark. This rapid dissolution behavior is consistent with the decreased melting point observed in the DSC analysis and the modified lattice patterns seen via PXRD. The fast-dissolving co-former molecule effectively disrupts the hydrophobic stabilization of the drug lattice, promoting rapid hydration and a faster mass-transfer rate into the dissolution medium. This indicates that the solvent-drop grinding method holds strong potential for improving oral absorption and systemic bioavailability in clinical settings.

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