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# FORMULATION AND EVALUATION OF NOVEL CO-CRYSTALS OF CITALOPRAM HYDROBROMIDE USING A FULL FACTORIAL DESIGN APPROACH

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## ABSTRACT

**Background:** Citalopram Hydrobromide, a selective serotonin reuptake inhibitor (SSRI), exhibits limited aqueous solubility, restricting its bioavailability. Co-crystallization has emerged as a promising approach to enhance solubility and dissolution without chemical modification. To formulate and evaluate co-crystals of Citalopram Hydrobromide with different co-formers (urea, citric acid, tartaric acid) in molar ratios of 1:2 and 1:3, and to assess their impact on solubility, dissolution rate, and tablet formulation performance. **Methods:** Co-crystals were prepared using the co-grinding method and characterized by UV, FTIR, PXRD, melting point, saturation solubility, and electron microscopy. Tablets were prepared by wet granulation, optimized using $2^2$ full factorial design, and evaluated for weight variation, hardness, friability, disintegration, and in vitro dissolution. **Results:** Co-crystals with tartaric acid (1:3) showed the highest drug content (98.89%), saturation solubility (0.809 mg/ml), and dissolution (100.2% in 60 min). Among 12 tablet formulations, F11 (tartaric acid 1:3) demonstrated superior performance with optimal disintegration and dissolution profiles. **Conclusion:** Co-crystallization significantly improved the physicochemical properties of Citalopram Hydrobromide. Tartaric acid (1:3) co-crystal tablets showed the most promising results, offering a simple and effective approach to enhance oral bioavailability of poorly soluble drugs.

**KEYWORDS:** Citalopram Hydrobromide, Co-crystals, Tartaric Acid, Solubility Enhancement, Dissolution, Full Factorial Design.

## INTRODUCTION

Poor solubility remains a significant challenge in pharmaceutical formulation, particularly for Biopharmaceutical Classification System (BCS) Class II drugs like Citalopram Hydrobromide, which exhibit low solubility and high permeability. Approximately 40% of drugs in the development pipeline fall into this category, which can result in reduced bioavailability and suboptimal therapeutic response. Several conventional approaches such as salt formation, micronization, and solid dispersions have been employed to enhance solubility, but these methods have limitations like stability issues, complex processing, or limited scalability.[1,2]

In recent years, **pharmaceutical co-crystallization** has emerged as an innovative and promising strategy to improve the physicochemical properties of poorly soluble APIs. Co-crystals are multicomponent crystalline systems composed of the active drug and one or more co-formers, bound together through non-covalent interactions such as hydrogen bonding. Unlike salts, co-crystals can be formed even for non-ionizable drugs and without altering the pharmacological identity of the API. Moreover, co-crystals can enhance not only solubility but also other properties such as dissolution rate, stability, and mechanical behavior, making them attractive for industrial application.[3,4]

**Citalopram Hydrobromide** is a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for the treatment of major depressive disorder and generalized anxiety disorder. Despite its efficacy, its therapeutic potential is hampered by its low aqueous solubility, leading to erratic absorption and delayed onset of action. The use of co-crystal technology, particularly with GRAS (Generally Recognized As Safe) co-formers such as urea, citric acid, and tartaric acid, offers a rational and efficient solution to enhance its solubility and optimize its oral bioavailability.[5,6]

This study focuses on the **formulation and evaluation of novel co-crystals of Citalopram Hydrobromide** using a solvent-free co-grinding method. The prepared co-crystals were subjected to thorough characterization using FTIR, PXRD, SEM, solubility, and melting point studies. The optimized co-crystal was then formulated into tablets using wet granulation and statistically evaluated using a $2^2$ full factorial design. This approach ensures not only enhancement in dissolution but also reproducibility, robustness, and optimization of formulation parameters to achieve a superior dosage form.[7,8]

## MATERIALS AND METHODS

### Materials

- **API**: Citalopram Hydrobromide (gift sample)
- **Co-formers**: Urea, Citric Acid, Tartaric Acid (AR grade)
- **Excipients**: MCC, PVP K30, Talc, Magnesium Stearate

### Co-crystal Preparation

Co-crystals were synthesized using the solvent-free **co-grinding method** in 1:2 and 1:3 molar ratios of drug: co-former using a mortar and pestle for 30 minutes, followed by vacuum drying.

### Characterization of Co-Crystals

- **FTIR**: To determine intermolecular interactions between drug and co-former.
- **PXRD**: To evaluate crystalline structure and identify new diffraction peaks.
- **Melting Point**: To confirm crystal structure changes.

- **SEM**: To observe surface morphology of crystals.
- **Saturation Solubility**: In distilled water and buffer pH 6.8.
- **UV-Vis Spectrophotometry**: λmax at 239 nm used for quantification.

**Tablet Formulation**

Using **wet granulation technique**, the prepared co-crystals were formulated into tablets. Each batch contained 10 mg equivalent of Citalopram HBr. Formulations were developed as per a **$2^2$ full factorial design** with 12 different batches (F1–F12).

**Evaluation of Tablets**

- **Pre-Compression Studies**: Flow properties (angle of repose, bulk density, tapped density, Carr's Index, Hausner's Ratio).
- **Post-Compression Studies**:
  - Weight variation
  - Hardness
  - Friability
  - Disintegration time
  - Drug content
  - In-vitro dissolution
  - Release kinetics (Zero-order, First-order)

## RESULTS

**1. Calibration and λmax Determination**

The λmax of Citalopram Hydrobromide was found to be **293 nm** in pH 6.8 phosphate buffer.

**Table 1: Calibration Data of Citalopram Hydrobromide.**

| Concentration (µg/ml) | Absorbance (Distilled Water) | pH 1.2 (0.1N HCl) | pH 6.8 Phosphate Buffer |
|---|---|---|---|
| 0 | 0.000 | 0.000 | 0.000 |
| 0.5 | 0.056 | 0.109 | 0.215 |
| 1.0 | 0.109 | 0.228 | 0.410 |
| 1.5 | 0.166 | 0.428 | 0.616 |
| 2.0 | 0.217 | 0.624 | 0.797 |
| 2.5 | 0.241 | 0.763 | 0.986 |

**2. FTIR Analysis**

**Table 2: FTIR Spectral Shifts Indicating Co-Crystal Formation.**

| Sample | Key Functional Groups | Shift Observed ($cm^{-1}$) | Inference |
|---|---|---|---|
| Pure CH | N–H: 3337, C–H: 2814 | — | Base reference |
| CH + Urea (1:3) | N–H: 3336, C=O: 1249 | Slight shift | H-bond with urea |
| CH + Tartaric Acid (1:3) | O–H: 3335, C–H: 1047 | Moderate shift | Strong H-bonding |
| CH + Citric Acid (1:3) | O–H: 3339 | Stronger broadening | Confirmed co-crystal |

Interpretation: Peak shifts and broadenings confirm intermolecular hydrogen bonding and non-covalent interactions responsible for co-crystal formation.

**3. Melting Point Analysis**

**Table 3: Melting Point Depression of Co-Crystals.**

| Sample | Melting Point (°C) | Observation |
|---|---|---|
| Pure CH | 147.0 | Sharp melting |
| CH + Urea (1:3) | 144.2 | Slightly reduced |
| CH + Citric Acid (1:3) | 142.6 | Reduced by 4.4°C |
| CH + Tartaric Acid (1:3) | **140.8** | **Maximum depression** |

Interpretation: Depression of melting points indicates new crystalline phases, confirming successful co-crystallization.

**4. SEM (Scanning Electron Microscopy)**

**Table 4: Particle Morphology and Size.**

| Formulation | Avg. Size (µm) | Morphology |
|---|---|---|
| Pure CH | 63 | Irregular |
| CH + Urea (1:3) | 67.2 | Cone-shaped |
| CH + Citric Acid (1:3) | 61.0 | Tetragonal |
| CH + Tartaric Acid (1:3) | **60.4** | Rod-shaped |

Interpretation: Morphological changes confirm altered crystal habit; smaller size in tartaric acid co-crystal supports enhanced solubility and dissolution.

**5. Saturation Solubility Study**

**Table 5: Aqueous Solubility (mg/mL).**

| Formulation | Solubility | Fold Increase | pH Equilibrium |
|---|---|---|---|
| Pure CH | 0.166 | — | 3.1 |
| CH + Urea (1:3) | 0.715 | 4.30× | 6.02 |
| CH + Citric Acid (1:3) | 0.711 | 4.28× | 4.54 |
| CH + Tartaric Acid (1:3) | **0.809** | **4.87×** | 4.70 |

Prepared co-crystals exhibited significantly higher solubility than the pure drug, with the **tartaric acid (1:3)** formulation showing the highest increase (**4.87-fold**).

**6. PXRD Analysis**

**Table 6: PXRD Pattern Data.**

| Sample | Peak Range (2θ) | Max Intensity | Crystallinity (%) |
|---|---|---|---|
| Pure CH | 10.68–22.17 | 12137 | 48.57 |
| CH + Urea (1:3) | 10.71–22.18 | 6040 | 52.77 |
| CH + Citric Acid (1:3) | 6.98–22.50 | 726 | 61.04 |
| CH + Tartaric Acid (1:3) | **14.04–22.24** | **2669** | **71.12** |

PXRD patterns confirmed the formation of new crystalline phases in co-crystals, especially with tartaric acid.

**7. Flow properties**

**Table 7: Flow properties of prepared co-crystal tablet blend.**

| Formulation code | BD (g/CC) | TD (g/CC) | CI (%) | HR | AR($^0$) | Flow properties |
|---|---|---|---|---|---|---|
| F1 | 0.85 | 0.97 | 12.37 | 1.14 | 31.3 | Good |
| F2 | 0.52 | 0.67 | 22 | 1.28 | 41.4 | Passable |
| F3 | 0.82 | 0.90 | 8.8 | 1.09 | 25.1 | Excellent |
| F4 | 0.43 | 0.65 | 33.8 | 1.51 | 57.2 | Very poor |
| F5 | 0.65 | 0.75 | 13.3 | 1.15 | 33.1 | Good |
| F6 | 0.57 | 0.76 | 24 | 1.31 | 42.2 | Passable |

| | | | | | | |
|---|---|---|---|---|---|---|
| F7 | 0.88 | 0.98 | 10.0 | 1.11 | 26.2 | Excellent |
| F8 | 0.35 | 0.55 | 36.3 | 1.57 | 55.8 | Very poor |
| F9 | 0.58 | 0.66 | 12.12 | 1.13 | 32.5 | Good |
| F10 | 0.52 | 0.69 | 24.6 | 1.32 | 41.5 | Passable |
| F11 | 0.90 | 0.99 | 9.09 | 1.1 | 25.5 | Excellent |
| F12 | 0.45 | 0.66 | 32.1 | 1.46 | 58.4 | Very poor |

The angle of repose of drug and prepared co-crystals formulations were assessed by fixed funnel method. The formulations like F3, F7, and F11 are showing excellent flow properties while compared to other formulations. While in case of prepared formulations like F1, F5, F9 are showing good flow properties.

**8. Post Formulation**

**Table 8: Post Formulation Studies of prepared co-crystal tablet formulations**

| Formulation code | Weight variation | Thickness [mm] | Hardness [Kg/Cm2] | Friability [%] | Disintegration [Min] | %Drug Content | %CDR at 60Min |
|---|---|---|---|---|---|---|---|
| F1 | 197 | 3.15 | 5.9 | 0.64 | 19.3 | 97.4 | 88.05 |
| F2 | 194 | 3.19 | 6 | 0.7 | 20 | 96.02 | 87.01 |
| F3 | 198 | 3 | 5.8 | 0.62 | 19.2 | 98.2 | 91.25 |
| F4 | 196 | 3.17 | 5.92 | 0.69 | 19.85 | 96.24 | 86.01 |
| F5 | 199 | 2.89 | 4.9 | 0.56 | 17.58 | 98.2 | 98.25 |
| F6 | 195.2 | 2.98 | 5.01 | 0.62 | 17.95 | 97 | 97.25 |
| F7 | 199 | 2.8 | 4.8 | 0.54 | 17.5 | 99.8 | 101.01 |
| F8 | 197 | 2.9 | 4.95 | 0.59 | 17.75 | 97.3 | 96.01 |
| F9 | 199.9 | 2.75 | 4.35 | 0.46 | 14.28 | 99.4 | 98.25 |
| F10 | 196.5 | 2.84 | 4.54 | 0.5 | 15 | 98.01 | 97.02 |
| F11 | 200 | 2.65 | 4.25 | 0.42 | 14.2 | 100.4 | 100.2 |
| F12 | 199 | 2.78 | 4.44 | 0.48 | 14.3 | 98.4 | 97.25 |

The prepared batches of formulations were evaluated for weight variation and the values are in a range of 194 to 200 mg, thickness values are in a range of 2.65 to 3.17 mm, hardness values arein a range of 4.25 to 5.92 kg/cm$^2$, friability values are in a range of 0.42 to 0.7, disintegration values are in a range of 14.2 to 20 min, drug content values are in a range of 96.02 to 100.4 %, and % CDR values are in a range of 87.01 to 100.2% at the end of 60 min.

**9. In-Vitro Dissolution**

**Table 9: Drug Release (%) in pH 6.8 Buffer.**

| Time (min) | Pure CH | Urea Co-crystal | Citric Acid | Tartaric Acid (F11) |
|---|---|---|---|---|
| 10 | 18.2 | 48.7 | 45.2 | **58.6** |
| 30 | 48.5 | 75.3 | 70.2 | **88.9** |
| 60 | 65.2 | 91.8 | 89.2 | **100.2** |

Interpretation: Tartaric acid (1:3) co-crystal (F11) exhibited complete drug release within 60 mins, significantly outperforming the pure drug.

**10. Drug Release Kinetics**

**Table 10: Kinetic Model Fit for F11.**

| Model | $R^2$ Value |
|---|---|
| Zero-order | 0.9634 |
| **First-order** | **0.9927** |
| Higuchi | 0.9812 |
| Korsmeyer–Peppas | 0.9865 |

Interpretation: Drug release followed first-order kinetics with non-Fickian diffusion.

**11. Drug content and percentage yield of prepared co-crystals**

**Table 11: Drug content and percentage yield of prepared co-crystals**

| Formulation Code | Drug content | % Yield |
|---|---|---|
| Citalopram Hydrobromide +Urea 1:2 | 95.24 | 84 |
| Citalopram Hydrobromide +Tartaric acid1:2 | 97.94 | 75 |
| Citalopram Hydrobromide +Citric acid 1:2 | 95.28 | 79 |
| Citalopram Hydrobromide +Urea 1:3 | 96.68 | 92.40 |
| Citalopram Hydrobromide +Tartaric acid 1:3 | 98.89 | 80.5 |
| Citalopram Hydrobromide +Citric acid 1:3 | 98.28 | 82.50 |

The prepared multicomponent co-crystal formulations are evaluated for drug content and percentage yield. In case of Citalopram Hydrobromide with tartaric acid 1:3 had showing high drug content 99.89 and 1:2 ratio shows 98.94. While in case of percentage yield Citalopram Hydrobromide with urea 1:3 (93.40 %) and 1:2 (85%) had showing high percentage yield.

**DISCUSSION**

The main goal of this study was to improve the solubility and dissolution of Citalopram Hydrobromide, a BCS Class II drug with poor water solubility. We successfully prepared co-crystals of the drug using urea, citric acid, and tartaric acid as co-formers through a solvent-free co-grinding method. These co-crystals were then evaluated and compared with the pure drug.

**FTIR results** showed shifts in important peaks, which confirmed that hydrogen bonding occurred between the drug and the co-formers. This is a clear indication that co-crystals were formed. The **melting points** of the co-crystals were lower than the pure drug, supporting the formation of new crystalline structures.

**SEM analysis** showed changes in particle shape and size. The tartaric acid co-crystals were smaller and rod-shaped, which can help increase solubility. This was confirmed by the **saturation solubility test**, where the tartaric acid co-crystals had the highest solubility (4.87 times more than the pure drug).

**PXRD analysis** also confirmed changes in the crystal structure. New peaks appeared in the co-crystals, especially in the tartaric acid ones, showing the formation of different crystal forms.

We then made tablets using these co-crystals and tested their **flow properties**, which were found to be good in most cases, especially for the F11 formulation (tartaric acid 1:3), which had excellent flow and compressibility.

When we tested the **tablet properties**, F11 again showed the best results, with quick disintegration, good hardness, and high drug content. In the **dissolution test**, F11 showed 100.2% drug release within 60 minutes, much higher than the pure drug, which released only 65.2%.

The **release kinetics** showed that F11 followed first-order kinetics, meaning the release rate depends on how much drug is left. It also followed non-Fickian diffusion, which means both diffusion and erosion contributed to drug release.

In summary, the tartaric acid co-crystal (1:3) showed the best performance in terms of solubility, dissolution, and tablet quality. This study shows that co-crystal technology is a simple, effective, and scalable method to improve the oral delivery of poorly soluble drugs like Citalopram Hydrobromide.

Lastly, the **drug content and percentage yield** of co-crystals confirmed the efficiency of the preparation method. Tartaric acid (1:3) co-crystals showed the highest drug content (98.89%), and the highest percentage yield (92.4%) was seen with urea (1:3).

## CONCLUSION

This study successfully demonstrated that co-crystallization is an effective strategy to improve the solubility and dissolution rate of Citalopram Hydrobromide, a poorly water-soluble antidepressant. Co-crystals were prepared using safe and pharmaceutically accepted co-formers—urea, citric acid, and tartaric acid—through a solvent-free co-grinding method.

Among all the formulations, the tartaric acid co-crystal in a 1:3 ratio (F11) showed the best results in terms of solubility enhancement, tablet characteristics, and drug release profile. It released 100.2% of the drug within 60 minutes, compared to only 65.2% from the pure drug.

The optimized formulation followed first-order kinetics with a non-Fickian diffusion mechanism, indicating both diffusion and erosion-controlled release. Overall, this approach offers a promising, simple, and scalable method to enhance the performance of Citalopram Hydrobromide and potentially other BCS Class II drugs in oral dosage forms.

## CONFLICT OF INTEREST

None.

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