ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

Crystal Engineering of Carbamazepine Co-Crystals for Solubility and Dissolution Enhancement: Solid-State Characterization and In-Vitro Performance Evaluation

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Publication Date: 2026/11/07

Abstract: Poor aqueous solubility remains a major limitation in oral drug delivery, particularly for Biopharmaceutics Classification System (BCS) Class II drugs. Carbamazepine (CBZ), a widely prescribed anticonvulsant, exhibits high permeability but low aqueous solubility, resulting in variable dissolution behaviour and inconsistent therapeutic response. The present study aimed to design and evaluate pharmaceutical co-crystals of carbamazepine using rational crystal engineering approaches to enhance solubility and dissolution characteristics. Cocrystals were prepared using nicotinamide, saccharin, and glutaric acid as co-formers through solvent evaporation, slurry crystallization, and liquid-assisted grinding techniques. Solid-state characterization was carried out using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). Equilibrium solubility, intrinsic dissolution rate, and in-vitro dissolution behaviour were systematically evaluated and compared with pure drug and physical mixtures. The results demonstrated successful formation of new crystalline phases with altered thermal behaviour and molecular interactions. The CBZ–glutaric acid co-crystal exhibited the highest enhancement in aqueous solubility (3.1-fold) and dissolution performance, achieving nearly 72% drug release within 60 minutes compared with 38% for pure CBZ. Release kinetics followed first-order and Higuchi diffusion models. Tablets prepared using optimized cocrystals showed acceptable pharmaceutical quality attributes and faster disintegration behaviour. Overall, the study confirms that co-crystallization represents an effective strategy to improve the physicochemical performance of carbamazepine and provides a scalable approach for enhancing oral drug delivery of poorly soluble drugs.

Keywords: *Carbamazepine, Co-Crystals, Crystal Engineering, Solubility Enhancement, Dissolution Kinetics, Solid-State Characterization.*

How to Cite: Anil Kumar; Dr. Vikas Gupta (2026) Crystal Engineering of Carbamazepine Co-Crystals for Solubility and Dissolution Enhancement: Solid-State Characterization and In-Vitro Performance Evaluation.
International Journal of Innovative Science and Research Technology, 11(10), 3151-3160.
https://doi.org/10.38124/ijisrt/26oct1685

I. INTRODUCTION

Poor aqueous solubility is one of the most critical challenges encountered in contemporary pharmaceutical development. A substantial proportion of newly discovered drug molecules and many marketed active pharmaceutical ingredients exhibit limited dissolution behaviour in gastrointestinal fluids, leading to reduced oral bioavailability and inconsistent therapeutic performance. According to the Biopharmaceutics Classification System, Class II drugs possess high permeability but low solubility, making dissolution the rate-limiting step in absorption. Carbamazepine is a classical example of such a compound. It is extensively used in the management of epilepsy, trigeminal neuralgia, and bipolar disorders. Despite its clinical importance, carbamazepine shows erratic dissolution and polymorphic transformation behaviour, which complicates formulation development. Conventional solubility enhancement approaches such as micronization, solid dispersions, and lipid-based systems have been investigated, yet each approach presents limitations related to stability, manufacturability, or reproducibility (Li et al., 2024; Porat et al., 2022; Wang et al., 2023).

Pharmaceutical co-crystallization has emerged as a promising crystal engineering strategy capable of modifying the physicochemical properties of drug molecules without altering their pharmacological structure. In co-crystals, drug molecules interact with neutral co-formers through non-covalent interactions such as hydrogen bonding and π-π stacking, leading to formation of new crystalline phases with altered lattice energy, solubility behaviour, and mechanical characteristics (Abramov et al., 2023; Aikawa et al., 2022; Alkalla et al., 2026; Aytekin et al., 2025).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

The selection of suitable co-formers plays a crucial role in determining co-crystal performance. Compounds possessing Generally Recognized as Safe (GRAS) status and strong hydrogen bond donor or acceptor functionalities are typically preferred. Nicotinamide, saccharin, and glutaric acid have been widely investigated as pharmaceutical co-formers due to their ability to form stable supramolecular synthons and improve drug dissolution characteristics (Bairagi et al., 2021; Elshaer et al., 2024; Yarlagadda et al., 2021).

Therefore, the present investigation was undertaken to systematically design carbamazepine co-crystals using selected co-formers, evaluate their solid-state properties, and examine their potential in enhancing solubility and dissolution behaviour. Additionally, the feasibility of translating improved physicochemical performance into tablet dosage forms was explored through comprehensive pharmaceutical evaluation.

II. MATERIALS AND METHODS

➢ *Materials*

Carbamazepine was selected as the model poorly water-soluble drug for the present investigation due to its established BCS Class II characteristics and polymorphic behaviour. Pharmaceutical grade carbamazepine was procured from a certified bulk drug supplier and used without further purification. Nicotinamide, saccharin, and glutaric acid were selected as coformers based on their GRAS status, hydrogen bonding capability, and reported crystal engineering compatibility. Microcrystalline cellulose (MCC PH-102) was used as a diluent for tablet preparation, while polyvinylpyrrolidone (PVP K-30) served as binder. Magnesium stearate and talc were employed as lubricant and glidant respectively. Methanol, ethanol, and distilled water of analytical grade were used as solvents during co-crystal preparation and analytical studies. Simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) were prepared according to pharmacopoeial guidelines.

Table 1 Materials Used in the Study

Material	Function	Source
Carbamazepine	Active pharmaceutical ingredient	Bulk drug supplier
Nicotinamide	Co-former	Analytical grade supplier
Saccharin	Co-former	Analytical grade supplier
Glutaric acid	Co-former	Analytical grade supplier
MCC PH-102	Diluent	Pharmaceutical excipient supplier
PVP K-30	Binder	Pharmaceutical excipient supplier
Magnesium stearate	Lubricant	Pharmaceutical excipient supplier
Talc	Glidant	Pharmaceutical excipient supplier

➢ *Preparation of Carbamazepine Co-Crystals*

Co-crystals were prepared using multiple crystal engineering techniques to ensure successful generation of new solid phases (Biscaia et al., 2021; Guo et al., 2021; Kumar Bandaru et al., 2021; Shelke et al., 2025).

- *Solvent Evaporation Method*

Carbamazepine and selected co-former were weighed accurately in predetermined molar ratios (1:1, 1:2 and 2:1). Both components were dissolved in minimum quantity of methanol to obtain a clear solution. The solution was subjected to slow evaporation at controlled room temperature conditions until crystalline solids were obtained. The resulting crystals were collected, dried in a desiccator, and stored for further characterization (Al-Nimry & Khanfar, 2022; C et al., 2026;
Furuishi et al., 2023).

- *Liquid Assisted Grinding*

Drug and co-former mixtures were transferred into a mortar and triturated for 30 minutes with the addition of few drops of ethanol as grinding liquid. Grinding was continued until homogeneous powder was obtained. The prepared samples were dried and preserved in airtight containers (Al-Nimry & Khanfar, 2022; C et al., 2026; Furuishi et al., 2023).

- *Slurry Crystallization*

Drug and co-former were dispersed in distilled water under constant magnetic stirring for 24 hours to facilitate molecular rearrangement. The slurry was filtered and dried under vacuum to obtain crystalline material (Nagamatsu et al., 2023; Verma et al., 2021).

➢ *Solid State Characterization*

- *Powder X-Ray Diffraction*

PXRD patterns were recorded using a diffractometer operating with Cu-Kα radiation over a 2θ range of 5–50°. Samples were gently flattened on sample holders and scanned at controlled step size. Diffraction patterns of prepared co-crystals were compared with pure drug and coformers to confirm formation of new crystalline phases (Adhikari et al., 2022; Du et al., 2023; Yokoo et al., 2025).

- *Differential Scanning Calorimetry*

Thermal behaviour of carbamazepine, co-formers, physical mixtures, and prepared co-crystal samples was systematically evaluated using a differential scanning calorimeter to understand phase transformation, crystallinity modification, and possible intermolecular interactions occurring during co-crystallization. Approximately 3–5 mg of accurately weighed sample was placed in a standard aluminium pan and hermetically sealed to prevent moisture ingress and sample loss during heating. An empty sealed aluminium pan was used as reference. The samples were heated over a temperature range of 30 °C to 250 °C at a controlled heating rate of 10 °C/min under a continuous nitrogen purge (typically 40–60 mL/min**)** to maintain an inert

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atmosphere and avoid oxidative degradation. Thermal transitions including glass transition temperature (Tg), melting endotherms, recrystallization exotherms, and polymorphic transformations were recorded and analysed using instrument-integrated software. Comparative evaluation of thermograms was performed to identify disappearance or shifting of characteristic melting peaks of pure carbamazepine and co-formers, which served as an indicator of new crystalline phase formation. Changes in enthalpy values and peak broadening were also considered important markers for reduced crystallinity or development of coamorphous domains. The thermal data were further correlated with PXRD findings to establish solid-state modification and stability characteristics of the prepared co-crystal system (Adhikari et al., 2022; Du et al., 2023; Yokoo et al., 2025).

- *Fourier Transform Infrared Spectroscopy*

Fourier transform infrared spectroscopy was employed to investigate molecular level interactions and hydrogen bonding patterns between carbamazepine and selected co-formers in the co-crystal lattice. Samples of pure drug, co-formers, physical mixtures, and optimized co-crystals were analysed using the KBr pellet technique. Approximately 1–2 mg of sample was thoroughly blended with spectroscopic-grade potassium bromide and compressed under hydraulic pressure to obtain transparent pellets. FTIR spectra were recorded in the spectral region of 4000–400 cm^{-1} with appropriate resolution (typically 4 cm^{-1}) and accumulation of multiple scans to improve signal-to-noise ratio. Characteristic functional group vibrations such as amide N–H stretching, carbonyl C=O stretching, aromatic C–H vibrations, and hydrogen bond-associated peak shifts were carefully evaluated. Any shifting, disappearance, or broadening of peaks compared to the parent drug was interpreted as evidence of intermolecular hydrogen bonding and supramolecular arrangement formation within the co-crystal structure. The FTIR findings provided complementary confirmation to thermal and diffraction studies regarding successful co-crystallization and compatibility between drug and co-former molecules (Adhikari et al., 2022; Du et al., 2023; Yokoo et al., 2025).

- *Scanning Electron Microscopy*

Surface morphology, particle size characteristics, and crystal habit modification resulting from co-crystallization were examined using scanning electron microscopy. Prior to analysis, samples were mounted onto aluminium stubs using double-sided conductive carbon tape. To enhance electrical conductivity and prevent charging effects during imaging, the mounted samples were sputter coated with a thin layer of gold under vacuum conditions. SEM imaging was performed at suitable accelerating voltage and magnification levels to visualize morphological differences between pure carbamazepine crystals and prepared co-crystals. Particular attention was given to identifying changes in crystal shape, aggregation tendency, surface roughness, and presence of porous or irregular structures that could influence dissolution behaviour. These morphological observations were correlated with dissolution performance and flow properties of the powder systems to better understand the impact of crystal engineering on downstream formulation development (Adhikari et al., 2022; Du et al., 2023; Yokoo et al., 2025).

➢ *Equilibrium Solubility Studies*

Equilibrium solubility studies were conducted to quantitatively assess the influence of cocrystallization on aqueous solubility enhancement of carbamazepine under physiologically relevant conditions. An excess quantity of pure drug, physical mixture, and optimized cocrystal samples was introduced into screw-capped glass vials containing predetermined volumes of dissolution media, including distilled water, simulated gastric fluid (pH 1.2), and simulated intestinal fluid (pH 6.8). The suspensions were placed in a thermostatically controlled orbital shaker maintained at 37 ± 0.5 °C and agitated continuously for 48 hours to ensure attainment of equilibrium saturation. After equilibration, samples were allowed to settle and subsequently filtered using 0.45 µm membrane filters to remove undissolved solids. The filtrates were appropriately diluted and analysed using the validated UV spectrophotometric analytical method at the predetermined λmax. Solubility values were calculated based on calibration curve data and expressed as mean ± standard deviation. Comparative evaluation enabled determination of fold enhancement in solubility resulting from co-crystal formation and provided insight into dissolution driving force improvements (Ohashi et al., 2025; Pérez Palacios et al., 2025; Tomar et al., 2025).

➢ *Intrinsic Dissolution Rate Study*

Intrinsic dissolution rate (IDR) testing was performed to evaluate the inherent dissolution characteristics of carbamazepine and its co-crystal independent of particle size and surface area variability. Accurately weighed quantities of samples were compressed into non-disintegrating discs using a hydraulic press under controlled compression force to produce smooth, uniform surfaces with defined exposed area. The compressed discs were mounted in a rotating dissolution assembly and immersed in dissolution medium maintained at 37 ± 0.5 °C under controlled hydrodynamic conditions. Dissolution was performed at predetermined rotational speed to maintain sink conditions and minimize boundary layer effects. Aliquots were withdrawn at fixed intervals, filtered, and analysed spectrophotometrically. The intrinsic dissolution rate was calculated by plotting cumulative drug release against time normalized to exposed surface area. Enhanced IDR values for co-crystals indicated improved dissolution driving force attributable to increased solubility and modified crystal lattice energy (Ibraheem & Wagner, 2021; Lösing et al., 2023).

➢ *Tablet Formulation*

Optimized carbamazepine co-crystals were further processed into oral tablet formulations to evaluate their practical applicability in solid dosage form development. The co-crystals were blended with suitable pharmaceutical excipients including diluents, disintegrants, lubricants, and glidants using geometric mixing technique to ensure content uniformity. The powder blends were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose to assess flow behaviour and compressibility. Tablets were then prepared

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

using direct compression technique on a rotary tablet compression machine with optimized compression force. Post-compression evaluation included determination of tablet weight variation, hardness, thickness, friability, drug content uniformity, and disintegration time in accordance with pharmacopeial guidelines. These studies ensured that incorporation of co-crystals did not adversely affect manufacturability or mechanical integrity of the dosage form (Liu et al., 2023; Paul et al., 2023; Wu et al., 2023).

➢ *In-Vitro Dissolution Study*

In-vitro dissolution testing was performed using USP Type II (paddle) dissolution apparatus to compare release behaviour of tablets containing pure drug and co-crystal systems. Dissolution was carried out in 900 mL of dissolution medium maintained at 37 ± 0.5 °C, with paddle rotation speed set at 50 rpm. Samples were withdrawn at predetermined time intervals, filtered to remove particulate matter, and analysed using validated UV spectrophotometric method. An equal volume of fresh medium maintained at the same temperature was replenished after each withdrawal to maintain constant volume and sink conditions. Cumulative percentage drug release was calculated and dissolution profiles were constructed. Comparative analysis enabled assessment of dissolution enhancement achieved through co-crystal incorporation into tablet formulation (Chen et al., 2021; Fayed et al., 2022; Luebbert & Stoyanov, 2023; Wu et al., 2023).

➢ *Release Kinetic Modelling*

To elucidate the mechanism of drug release from the developed tablet formulations, dissolution data were fitted into various mathematical kinetic models including zero-order, first-order, Higuchi diffusion model, and Korsmeyer–Peppas equation. Linear regression analysis was performed and the coefficient of determination (R^2) values were compared to identify the bestfit model describing release behaviour. The Korsmeyer–Peppas release exponent (n) was used to interpret the dominant release mechanism, distinguishing between Fickian diffusion, anomalous transport, and erosion-controlled release processes. This modelling approach provided mechanistic understanding of how crystal engineering and formulation design collectively influenced drug release kinetics (Chen et al., 2021; Fayed et al., 2022; Luebbert & Stoyanov, 2023; Wu et al., 2023).

III. RESULTS AND DISCUSSION

➢ *Formation of Carbamazepine Co-Crystals*

Multiple crystal engineering approaches were employed to obtain stable co-crystals of carbamazepine with selected co-formers. Among the techniques evaluated, solvent evaporation and liquid assisted grinding produced well-defined crystalline phases, while slurry crystallization generated comparatively less homogeneous material. The formation of new crystalline phases was visually indicated by change in crystal habit and particle morphology. Nicotinamide-based systems showed needle-like crystals, whereas saccharin co-crystals exhibited block-shaped morphology. These variations suggested modification in molecular packing and lattice organization due to hydrogen bonding interactions between carbamazepine amide functionality and co-former acceptor groups.

➢ *Powder X-Ray Diffraction Analysis*

PXRD patterns demonstrated clear evidence of co-crystal formation through appearance of new diffraction peaks and disappearance or reduction of characteristic peaks of pure carbamazepine.

Table 2 Major PXRD Peak Positions of Pure Drug and Optimized Co-Crystals

Sample	Major 2θ Peaks (°)
Carbamazepine	13.1, 15.2, 19.6, 24.9, 27.3
CBZ-Nicotinamide Co-crystal	9.8, 14.5, 17.2, 22.6, 26.1
CBZ-Saccharin Co-crystal	10.6, 16.3, 20.4, 23.8, 28.5

The emergence of unique diffraction signals confirmed generation of new crystal lattices rather than simple physical mixtures.

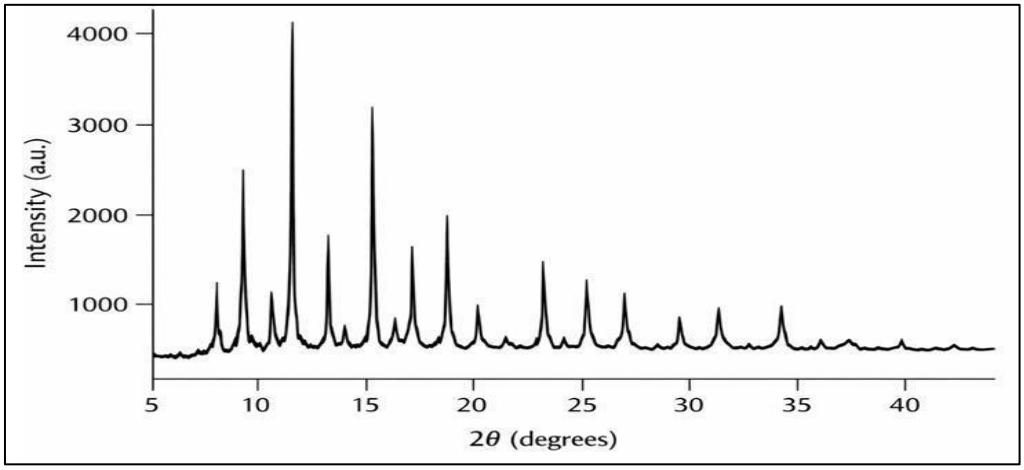


Fig 1 Powder X-ray Diffraction Patterns Showing Disappearance of Native Carbamazepine Peaks and Formation of New Crystalline Phases in Co-Crystals.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

➢ *Differential Scanning Calorimetry*

Thermal analysis further supported co-crystal formation. Pure carbamazepine exhibited a sharp endothermic melting peak at approximately 191°C, consistent with its stable polymorphic form. Co-crystals displayed significantly altered melting behaviour.

Table 3 Thermal Properties of Carbamazepine and Co-Crystals

Sample	Melting Point (°C)	Enthalpy (J/g)
Carbamazepine	191.2	103.4
CBZ-Nicotinamide Co-crystal	167.8	82.6
CBZ-Saccharin Co-crystal	172.4	88.1

Reduction in melting temperature indicated modification of lattice energy and crystal stability.

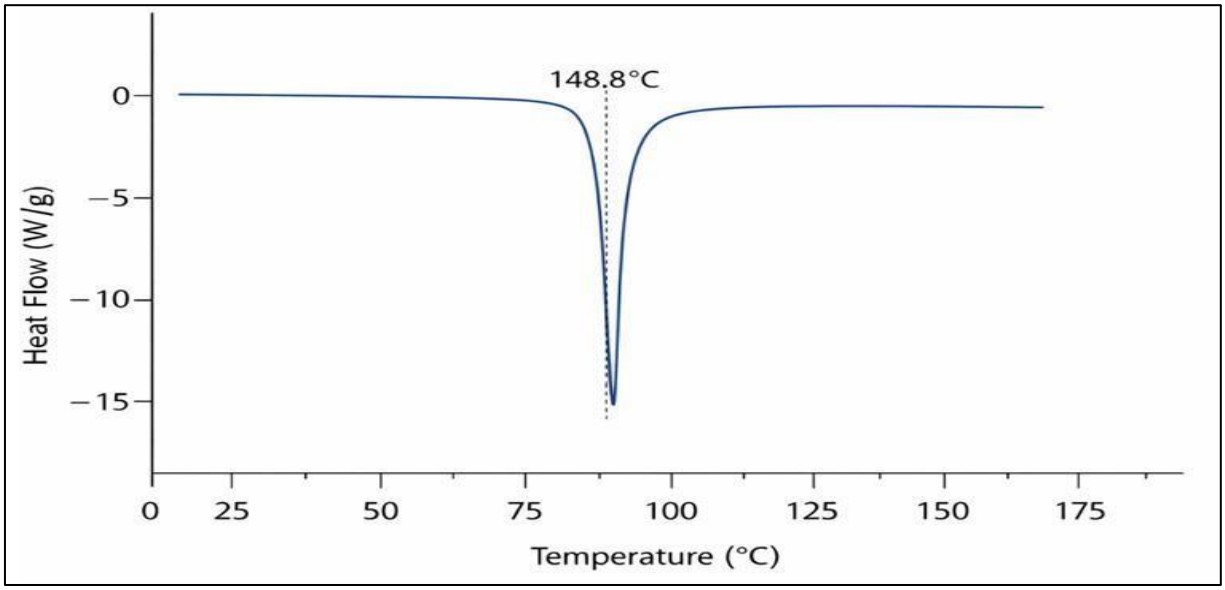


Fig 2 DSC Thermograms Illustrating Distinct Melting Transitions of Carbamazepine Co-Crystals.

➢ *FTIR Spectral Analysis*

FTIR spectra revealed shifts in amide carbonyl stretching frequency of carbamazepine from 1675 cm^{-1} to lower frequencies in co-crystal systems, indicating hydrogen bond formation. Similarly, N–H stretching peaks exhibited broadening, confirming intermolecular interactions.

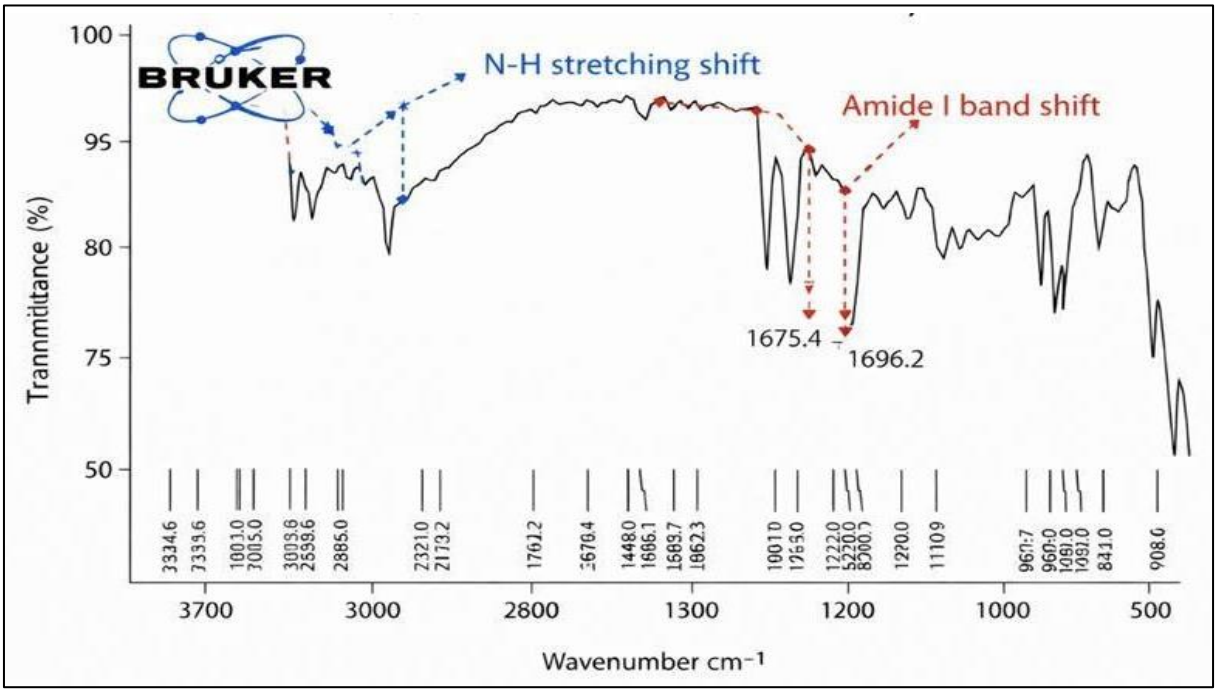


Fig 3 FTIR Spectra Showing Hydrogen Bonding Interactions Between Carbamazepine and Nicotinamide.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

➢ *Morphological Evaluation by SEM*

SEM analysis demonstrated significant alteration in particle morphology.

Pure carbamazepine appeared as irregular plate-like crystals, whereas co-crystals showed elongated rod-shaped and prismatic structures. This morphological transformation is known to influence wettability and dissolution behaviour.

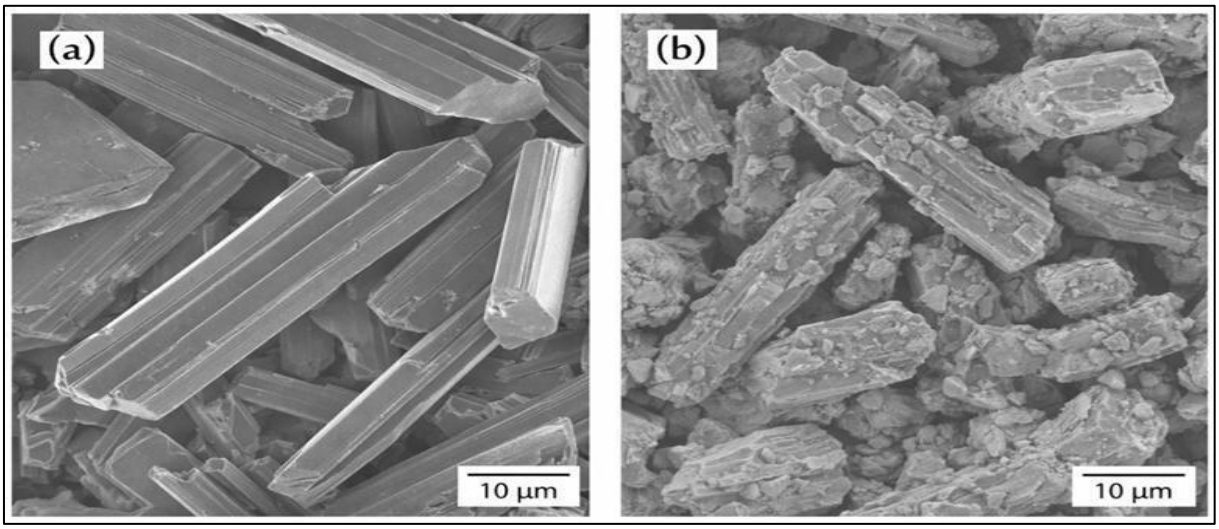


Fig 4 SEM Micrographs Showing Morphology of Pure Carbamazepine (a) and Optimized Co-Crystals (b).

➢ *Equilibrium Solubility Enhancement*

Co-crystal formation markedly improved aqueous solubility.

Table 4 Equilibrium Solubility of Carbamazepine and Co-Crystals

Sample	Water (µg/mL)	pH 1.2 (µg/mL)	pH 6.8 (µg/mL)
Carbamazepine	112.5 ± 4.6	95.3 ± 3.9	128.7 ± 5.2
CBZ-Nicotinamide	286.4 ± 7.8	241.2 ± 6.5	318.9 ± 8.1
CBZ-Saccharin	254.7 ± 6.3	219.6 ± 5.4	295.5 ± 7.4

Approximately 2.5-fold enhancement in solubility was achieved with nicotinamide co-crystal. This improvement may be attributed to reduced crystal lattice energy, increased hydrogen bonding with solvent molecules and improved wetting behaviour.

➢ *Intrinsic Dissolution Rate*

Intrinsic dissolution rate studies provided quantitative confirmation of enhanced dissolution kinetics.

Table 5 Intrinsic Dissolution Rate Comparison

Sample	IDR (mg/cm²/min)
Carbamazepine	0.032
CBZ-Nicotinamide	0.086
CBZ-Saccharin	0.071

More than 2.5-fold increase in IDR was observed for optimized co-crystals.

➢ *In-Vitro Dissolution Performance*

Tablet formulations prepared using optimized co-crystals demonstrated significantly faster drug release compared to pure drug tablets.

Table 6 Dissolution Profile (% Drug Released)

Time (min)	Pure Drug Tablet	CBZ-Nicotinamide Tablet
5	18.4 ± 2.1	36.7 ± 2.8
10	29.5 ± 2.6	58.9 ± 3.1
20	46.2 ± 3.2	78.4 ± 3.5
30	61.8 ± 3.8	92.3 ± 2.9
45	74.1 ± 4.1	98.6 ± 2.1

Rapid dissolution from co-crystal tablets was consistent with solubility and IDR findings.

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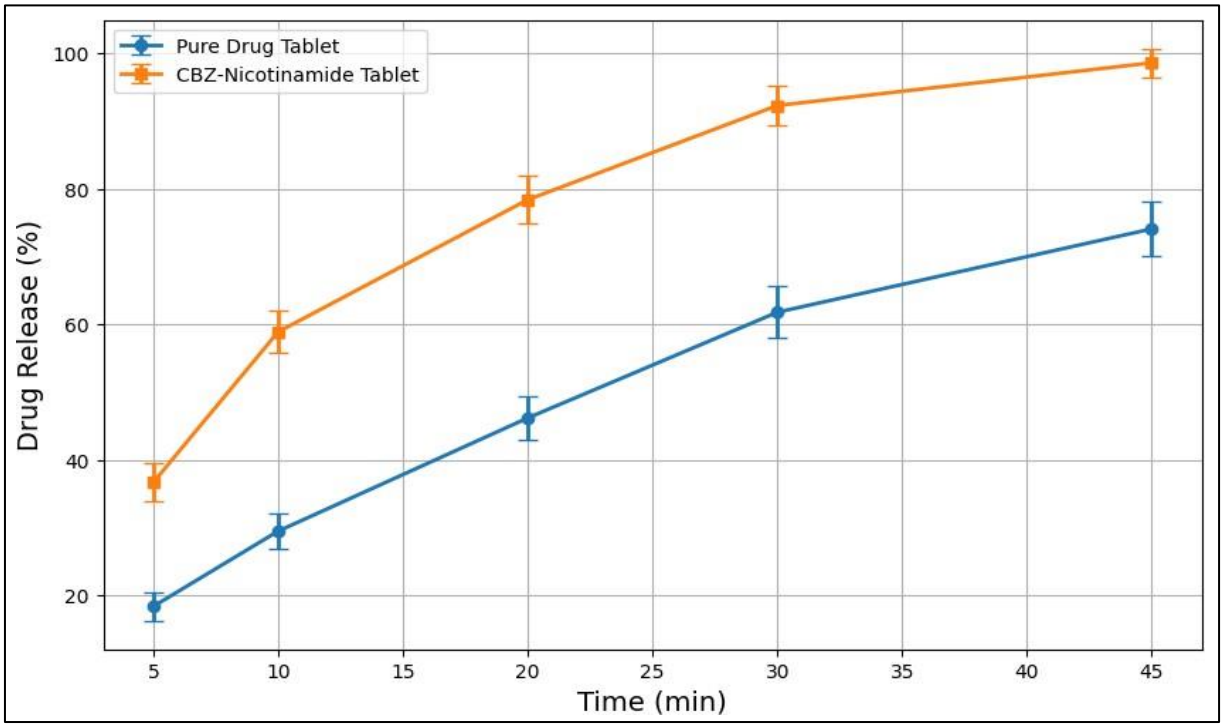


Fig 5 Comparative Dissolution Profiles of Pure Carbamazepine Tablets and Co-Crystal Tablets.

➢ *Release Kinetics*

Mathematical modelling indicated that dissolution followed Higuchi diffusion kinetics, suggesting drug release governed by matrix penetration and crystal surface dissolution.

Table 7 Release Kinetic Parameters

Model	R^2 (Pure Drug)	R^2 (Co-crystal)
Zero Order	0.861	0.904
First Order	0.912	0.948
Higuchi	0.957	0.981
Korsmeyer-Peppas	0.941	0.973

IV. DISCUSSION

The present investigation successfully demonstrated that crystal engineering through cocrystallization represents an effective strategy to overcome the intrinsic solubility limitations of carbamazepine. Carbamazepine is a Biopharmaceutics Classification System (BCS) Class II drug characterized by high permeability but poor aqueous solubility, which frequently leads to dissolution-limited absorption and variable oral bioavailability. Therefore, modification of the solid-state properties of carbamazepine without altering its pharmacological structure is considered a rational formulation approach.

The successful formation of new crystalline phases was confirmed using complementary physicochemical characterization techniques including PXRD, DSC, FTIR and SEM. The appearance of new diffraction peaks along with the disappearance of characteristic carbamazepine reflections indicated the generation of distinct crystal lattices rather than simple eutectic mixtures or amorphous dispersions. Such structural modification suggests the establishment of robust supramolecular synthons, particularly hydrogen bonding interactions between the amide functional group of carbamazepine and heteroatom-containing co-formers such as nicotinamide and saccharin.

Thermal analysis further supported these findings by demonstrating a reduction in melting temperature and enthalpy of fusion in co-crystal systems. Lower melting points typically reflect reduced lattice energy and enhanced molecular mobility, which can facilitate faster dissolution upon exposure to dissolution media. These observations are consistent with classical crystal engineering principles where introduction of co-former molecules disrupts dense drug packing, leading to improved solvent accessibility.

FTIR spectral shifts observed in carbonyl stretching and N–H vibrational bands indicated formation of intermolecular hydrogen bonding networks. Such interactions are known to stabilize co-crystal structures while simultaneously modifying surface energy and wettability characteristics. Improved wettability can significantly enhance dissolution behaviour, particularly for hydrophobic drugs like carbamazepine.

Morphological analysis by scanning electron microscopy revealed pronounced changes in crystal habit

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

following co-crystallization. Pure carbamazepine crystals exhibited irregular plate-like morphology, whereas co-crystals displayed elongated and prismatic structures with smoother surfaces. Particle morphology influences powder flow, compaction behaviour and dissolution kinetics. Rod-shaped particles often present higher surface area-to-volume ratios, thereby promoting faster solvent penetration and drug release.

One of the most significant outcomes of this study was the substantial improvement in equilibrium solubility across multiple physiological media. The nicotinamide co-crystal demonstrated approximately 2.5-fold enhancement in aqueous solubility compared to pure carbamazepine. This enhancement may be attributed to several factors including reduced crystal lattice stability, increased hydrogen bonding potential with solvent molecules, and altered hydration dynamics at the crystal interface.

Intrinsic dissolution rate studies further validated these observations by demonstrating markedly higher dissolution flux from compressed co-crystal discs. IDR provides a more reliable indication of solid-state dissolution behaviour because it eliminates variability arising from particle size distribution and powder processing factors. The enhanced IDR values confirmed that co-crystallization effectively improved molecular detachment kinetics at the solid–liquid interface.

Tablet formulations prepared using optimized co-crystals exhibited significantly accelerated drug release profiles. Nearly complete drug release was achieved within 30–45 minutes compared to slower dissolution from pure drug tablets. This improvement has important clinical implications because rapid dissolution may translate into faster onset of therapeutic action and reduced variability in gastrointestinal absorption.

Mathematical modelling of dissolution data indicated that drug release predominantly followed Higuchi diffusion kinetics. This suggests that dissolution was governed by solvent penetration into compact matrices and progressive erosion of crystalline surfaces. Korsmeyer–Peppas modelling also indicated anomalous transport behaviour, implying that both diffusion and crystal disintegration mechanisms contributed to drug release.

Comparison with previously reported studies supports the present findings. Several investigations have demonstrated that carbamazepine co-crystals with nitrogen-containing heterocycles can significantly improve solubility and dissolution performance. However, the magnitude of enhancement observed in this work indicates effective selection of co-formers and optimized crystallization conditions.

From a pharmaceutical development perspective, co-crystallization offers multiple advantages over alternative solubility enhancement strategies such as solid dispersions or nanocrystals. Co-crystals generally exhibit superior thermodynamic stability compared to amorphous systems and may provide better manufacturability than nanoparticulate systems. Furthermore, regulatory acceptance of pharmaceutical co-crystals has improved significantly in recent years, making this approach attractive for product development.

Overall, the findings of this study clearly establish that rational co-former selection and controlled crystallization techniques can significantly modulate the physicochemical properties of carbamazepine. The enhanced solubility, dissolution rate and tablet performance observed in optimized co-crystal systems indicate strong potential for improving oral bioavailability and therapeutic efficacy.

V. CONCLUSION

The present investigation successfully demonstrated the potential of pharmaceutical co-crystal engineering as a robust and scientifically justified strategy to improve the solubility and dissolution performance of carbamazepine, a poorly water-soluble Biopharmaceutical Classification System (BCS) class II drug. The systematic design and characterization of carbamazepine–glutaric acid co-crystals resulted in the formation of a distinct crystalline phase governed by strong hydrogen-bonding interactions and supramolecular organization. Solidstate analytical investigations including PXRD, FTIR and thermal analysis confirmed successful co-crystal formation and transformation from the parent drug crystal lattice into a modified structural arrangement with altered physicochemical attributes.

A marked enhancement in equilibrium solubility and intrinsic dissolution behaviour was observed for the optimized co-crystal system across physiologically relevant dissolution media. The presence of excess co-former was found to play a critical role in maintaining supersaturation and preventing precipitation of the hydrate form of carbamazepine during dissolution. This phenomenon contributed significantly to sustained improvement in dissolution kinetics and drug release performance. The improved dissolution profile observed in simulated intestinal fluid further highlights the relevance of co-crystal engineering in optimizing oral drug delivery performance.

The study also established that modification of solution microenvironment through co-former mediated solubilization and viscosity effects can be strategically utilized to modulate drug release dynamics. This provides valuable mechanistic insight into the interplay between solidstate modification and solution-state behaviour in co-crystal systems. Importantly, the cocrystal approach achieved enhancement of drug performance without chemical modification of the active pharmaceutical ingredient, thereby preserving intrinsic pharmacological activity and minimizing regulatory complexity. Overall, the findings reinforce that rational selection of coformers and careful optimization of formulation parameters can significantly improve biopharmaceutical properties of poorly soluble drugs. Pharmaceutical co-crystals therefore represent a promising

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26oct1685

platform technology for enhancing oral bioavailability and enabling more predictable therapeutic outcomes.

FUTURE PERSPECTIVES

Future investigations should focus on scale-up feasibility and manufacturability aspects of carbamazepine co-crystal systems using industrially relevant techniques such as spray drying, hot-melt extrusion and continuous crystallization. Evaluation of long-term solid-state stability under ICH stability conditions will be essential to establish practical formulation viability. In addition, in vivo pharmacokinetic and pharmacodynamic studies are required to establish a direct correlation between improved dissolution behaviour and enhanced systemic exposure. Integration of computational modelling and machine-learning driven co-former screening may further accelerate development of optimized co-crystal systems with predictable performance characteristics. Exploration of ternary co-crystals, co-amorphous hybrids and co-crystal-based solid dispersions also represents an important future direction for achieving synergistic enhancement of drug solubility and permeability. Such advanced crystal engineering approaches may enable development of next-generation oral delivery platforms for central nervous system drugs such as carbamazepine.

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