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Review

Cocrystallization approach: Dissolution rate enhancement of carbamazepine with various coformers and virtual screening tools

[Enfoque de cocristalización: mejora de la velocidad de disolución de la carbamazepina con diversos coformadores y herramientas de cribado virtual]

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Abstract

Context: Cocrystallization is a promising solid-state modification used to enhance the dissolution rate and solubility of poorly water-soluble drugs, such as carbamazepine. As a Biopharmaceutics Classification System class II antiepileptic drug, carbamazepine exhibits high permeability but low aqueous solubility. The enhancement of its dissolution rate through cocrystallization is primarily attributed to the formation of hydrogen bonds between carbamazepine and coformers.

Aims: To systematically review the effects of various coformers on the dissolution rate of carbamazepine. Furthermore, virtual screening techniques were employed to identify the coformer that demonstrates the strongest binding affinity with carbamazepine, thereby indicating the most favorable cocrystal formation.

Methods: Following PRISMA 2020 guidelines, studies (2013–2023) were retrieved from PubMed, ScienceDirect, and MDPI. Eligibility was determined using the PICO framework: Population—carbamazepine with low water solubility; Intervention—cocrystallization with various coformers; Comparison—pure carbamazepine; Outcome—enhanced dissolution rate. Study quality and bias risk were assessed with the American Dietetic Association checklist. Molecular docking using AutoDockTools 1.5.6 predicted coformer interactions.

Results: From 6,536 records, 14 studies met the inclusion criteria. Cocrystals with salicylic acid, nicotinamide, and para-hydroxybenzamide consistently improved dissolution compared to pure carbamazepine. Virtual screening results indicated that the cocrystal with salicylic acid exhibited the most favorable binding free energy (-3.67 kcal/mol), suggesting strong intermolecular interactions conducive to cocrystal stability.

Conclusions: Cocrystallization significantly enhances carbamazepine dissolution, with salicylic acid proving to be the most effective coformer. These findings support the potential application of cocrystals in improving the bioavailability of poorly soluble drugs.

Keywords: carbamazepine; cocrystal; coformer; dissolution; virtual screening.

Resumen

Contexto: La cocristalización es una prometedora modificación del estado sólido que se utiliza para mejorar la velocidad de disolución y la solubilidad de fármacos poco solubles en agua, como la carbamazepina. Como fármaco antiepiléptico de clase II del Sistema de Clasificación Biofarmacéutica, la carbamazepina presenta una alta permeabilidad, pero una baja solubilidad en agua. El aumento de su velocidad de disolución mediante la cocristalización se atribuye principalmente a la formación de enlaces de hidrógeno entre la carbamazepina y los coformadores.

Objetivos: Revisar sistemáticamente los efectos de diversos coformadores en la velocidad de disolución de la carbamazepina. Además, se emplearon técnicas de cribado virtual para identificar el coformador que muestra la mayor afinidad de unión con la carbamazepina, lo que indica la formación de cocristales más favorable.

Métodos: Siguiendo las directrices PRISMA 2020, se recuperaron estudios (2013-2023) de PubMed, ScienceDirect y MDPI. La elegibilidad se determinó mediante el marco PICO: Población: carbamazepina con baja solubilidad en agua; Intervención: cocristalización con diversos coformadores; Comparación: carbamazepina pura; Resultado: mayor velocidad de disolución. La calidad del estudio y el riesgo de sesgo se evaluaron con la lista de verificación de la Asociación Dietética Americana. El acoplamiento molecular con AutoDockTools 1.5.6 predijo las interacciones de los coformadores.

Resultados: De 6536 registros, 14 estudios cumplieron los criterios de inclusión. Los cocristales con ácido salicílico, nicotinamida y para-hidroxibenzamida mejoraron consistentemente la disolución en comparación con la carbamazepina pura. Los resultados del cribado virtual indicaron que el cocristal con ácido salicílico presentó la energía libre de unión más favorable (-3,67 kcal/mol), lo que sugiere fuertes interacciones intermoleculares que favorecen la estabilidad del cocristal.

Conclusiones: La cocristalización mejora significativamente la disolución de la carbamazepina, siendo el ácido salicílico el coformador más eficaz. Estos hallazgos respaldan la posible aplicación de los cocristales para mejorar la biodisponibilidad de fármacos poco solubles.

Palabras Clave: carbamazepina; cocristal; coformador; cribado virtual; disolución.

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INTRODUCTION

Solubility is a fundamental physicochemical property that critically influences the absorption, bioavailability, and therapeutic efficacy of orally administered drugs. Drugs exhibiting poor aqueous solubility often demonstrate limited dissolution rates, resulting in reduced systemic availability. According to the Biopharmaceutics Classification System (BCS), compounds classified under Class II are characterized by low solubility and high permeability, which poses significant formulation challenges (Sathisaran and Dalvi, 2019).

Various strategies have been employed to enhance the solubility of poorly water-soluble drugs. These include pH modification, salt formation, cosolvency, the use of surfactants, inclusion complexes (e.g., cyclodextrins), solid dispersions, nanoparticle formulations, and cocrystallization. Among these, cocrystallization has emerged as an effective approach for improving both the solubility and dissolution behavior of active pharmaceutical ingredients (APIs) without altering their pharmacodynamic properties. Cocrystals are defined as multicomponent crystalline materials composed of an API and a pharmaceutically acceptable coformer, held together in a specific stoichiometric ratio by non-covalent interactions such as hydrogen bonding and Van der Waals forces (Hou et al., 2019; Liang et al., 2020; Tănase et al., 2020).

The use of cocrystals offers several advantages in pharmaceutical development, including improved physicochemical properties (e.g., solubility, dissolution rate, stability) while preserving the intrinsic pharmacological activity of the API. The selection of suitable coformers is a critical aspect of successful cocrystal design. Ideal coformers are generally nontoxic, exhibit good aqueous solubility, are devoid of pharmacological activity, and are listed in regulatory databases such as the United States Food and Drug Administration's (USFDA) Everything Added to Food in the United States (EAFUS) and Generally Recognized as Safe (GRAS) lists (Bavishi and Borkhataria, 2016; Chaudhari et al., 2018).

Carbamazepine (Fig. 1), a dibenzoazepine derivative, is an antiepileptic drug categorized as a BCS Class II compound. Its poor solubility limits its dissolution rate and oral bioavailability. Previous studies have demonstrated that cocrystallization of carbamazepine with coformers such as cinnamic acid and para-hydroxybenzamide leads to a significant enhancement in its dissolution profile. For instance, the formation of carbamazepine–para-hydroxybenzamide cocrystals has been reported to improve dissolution rates by more than sixfold compared to the pure drug (Sathisaran and Dalvi, 2019; Shayanfar et al., 2013).

Although several reviews have been published on the use of cocrystallization to improve the solubility of carbamazepine, a comprehensive synthesis focused specifically on identifying the most effective coformer remains lacking. Therefore, the present systematic review was undertaken to compare dissolution data across various carbamazepine cocrystals and to determine the coformer that produces the highest enhancement in dissolution rate. Furthermore, computational docking simulations using virtual screening tools were employed to evaluate the molecular interactions and binding affinities between carbamazepine and the identified coformers. This approach provides a rational framework for selecting optimal coformers in the development of cocrystal-based formulations aimed at enhancing the bioavailability of poorly soluble drugs.

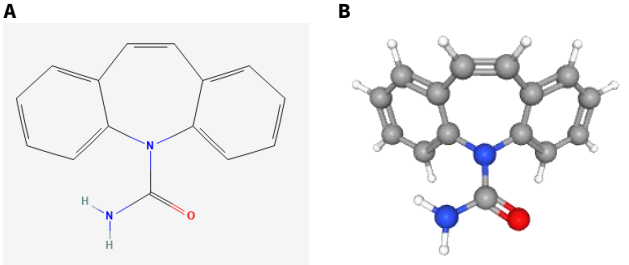

Figure 1. Chemical structure of carbamazepine.
(A) Two-dimensional representation; **(B)** Three-dimensional representation.
Source: National Center for Biotechnology Information (2024).

MATERIAL AND METHODS

Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The research was structured using the Population, Intervention, Comparison, and Outcome (PICO) framework to ensure a focused and evidence-based approach to article selection, as outlined in Table 1.

Articles were screened independently by two reviewers. Discrepancies were resolved through consensus with the assistance of additional reviewers. The quality of the study and the risk of bias were assessed with the American Dietetic Association (ADA) tool. The final decision was taken based on the agreement of all reviewers.

Table 1. PICO framework applied for the systematic review of carbamazepine cocrystals.

Component	Description
Population	Carbamazepine (BCS Class II), characterized by poor aqueous solubility.
Intervention	Cocrystallization with various pharmaceutically acceptable coformers.
Comparison	Pure (unmodified) carbamazepine.
Outcome	Improvement in dissolution rate compared to pure carbamazepine.

Note: This framework was used to define inclusion/exclusion criteria during article selection.

Eligibility criteria

The inclusion criteria for this review were defined as follows:

- Population (P): Carbamazepine, classified under BCS Class II, characterized by poor aqueous solubility.
- Intervention (I): Cocrystallization of carbamazepine with various coformers; studies must include experimental or computational characterization of cocrystal formation.
- Comparison (C): Pure or unmodified carbamazepine.
- Outcome (O): Enhancement in dissolution rate relative to pure carbamazepine.

Only original research articles published between January 2013 and December 2023 were considered. Eligible studies were required to be available in full text, published in English, and indexed in Scopus. Review articles, studies lacking dissolution rate data, and those not involving experimental validation of cocrystal formation were excluded.

Information sources and search strategy

Electronic literature searches were conducted using the following databases: PubMed, ScienceDirect, MDPI, the American Chemical Society (ACS), and the Royal Society of Chemistry (RSC). A combination of controlled vocabulary and keyword terms was used, including: "Carbamazepine cocrystal"; "Dissolution of carbamazepine"; "Cocrystal of carbamazepine"; "Dissolution rate of carbamazepine cocrystal". Search queries were tailored to each database's syntax and were limited to publications for the past 10 years. Supplementary searches were conducted through Google Scholar to screen for potentially relevant grey literature; however, studies retrieved from non-indexed sources were excluded from the final synthesis.

Study selection process

The selection of studies was conducted in four sequential stages: identification, screening, eligibility assessment, and inclusion. Duplicates were removed at the identification stage. Subsequently, titles and abstracts were screened for relevance to the predefined inclusion criteria. Full texts of potentially eligible articles were then retrieved and assessed independently by two reviewers. Discrepancies were resolved through discussion and consensus with a third reviewer. The PRISMA flow diagram was employed to illustrate the study selection process.

Data extraction and management

Data were extracted using a standardized form and included the following variables: publication year, identity of the coformer, method of cocrystal preparation, characterization techniques, and dissolution rate results. All data were reviewed by two independent investigators, and inconsistencies were resolved through mutual agreement. Data were organized and synthesized using spreadsheet software to facilitate comparison.

Quality assessment and risk of bias

The methodological quality and risk of bias for each included study were assessed using the ADA Quality Criteria Checklist. This tool evaluates 14 criteria across two domains: relevance and validity. Studies were rated as positive (+), neutral (Ø), or negative (–) based on their methodological rigor. The assessment was independently performed by two reviewers, with results cross-verified by the remaining authors (ADA, 2005).

Data synthesis

A qualitative synthesis approach was adopted. The primary outcome of interest was the relative increase in the dissolution rate of carbamazepine following cocrystallization with various coformers. Studies were grouped by coformer and preparation method to facilitate comparative analysis. Due to heterogeneity in experimental conditions and reporting formats, a meta-analysis was not performed.

Virtual screening protocol

To supplement the experimental data, a virtual screening study was conducted using AutoDockTools

version 1.5.6. Molecular docking simulations were employed to evaluate the binding affinity between carbamazepine and the top-performing coformers identified in the literature review. Binding free energy values were recorded and used as predictive indicators of the likelihood and strength of intermolecular interactions within the cocrystals.

RESULTS

Study selection

The initial literature search identified a total of 6,536 records across selected electronic databases. Following the removal of 3,692 irrelevant titles and abstracts during the screening phase, 2,800 records were excluded for not being indexed in Scopus. An additional 30 articles were eliminated due to the absence of dissolution rate data. After applying the inclusion and exclusion criteria, a final set of 14 eligible articles was included for qualitative synthesis. The study selection process is depicted in the PRISMA 2020 flow diagram (Fig. 2).

Study characteristics

The characteristics of the included studies are summarized in Table 2. Each article investigated the enhancement of carbamazepine's dissolution rate through cocrystallization with various coformers. A range of preparation techniques was employed, including solvent evaporation, solid-state grinding, slurry methods, hot melt extrusion, and reaction crystallization. Characterization techniques varied but commonly included differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (PXRD), Raman spectroscopy, and scanning electron microscopy (SEM).

A total of 12 distinct coformers were studied across the selected articles, including salicylic acid, nicotinamide, para-hydroxybenzamide, saccharin, cinnamic acid, trans-cinnamic acid, para-aminobenzoic acid, succinic acid, glutaric acid, vanillic acid, para-aminosalicylic acid, and 4-nitropyridine N-oxide.

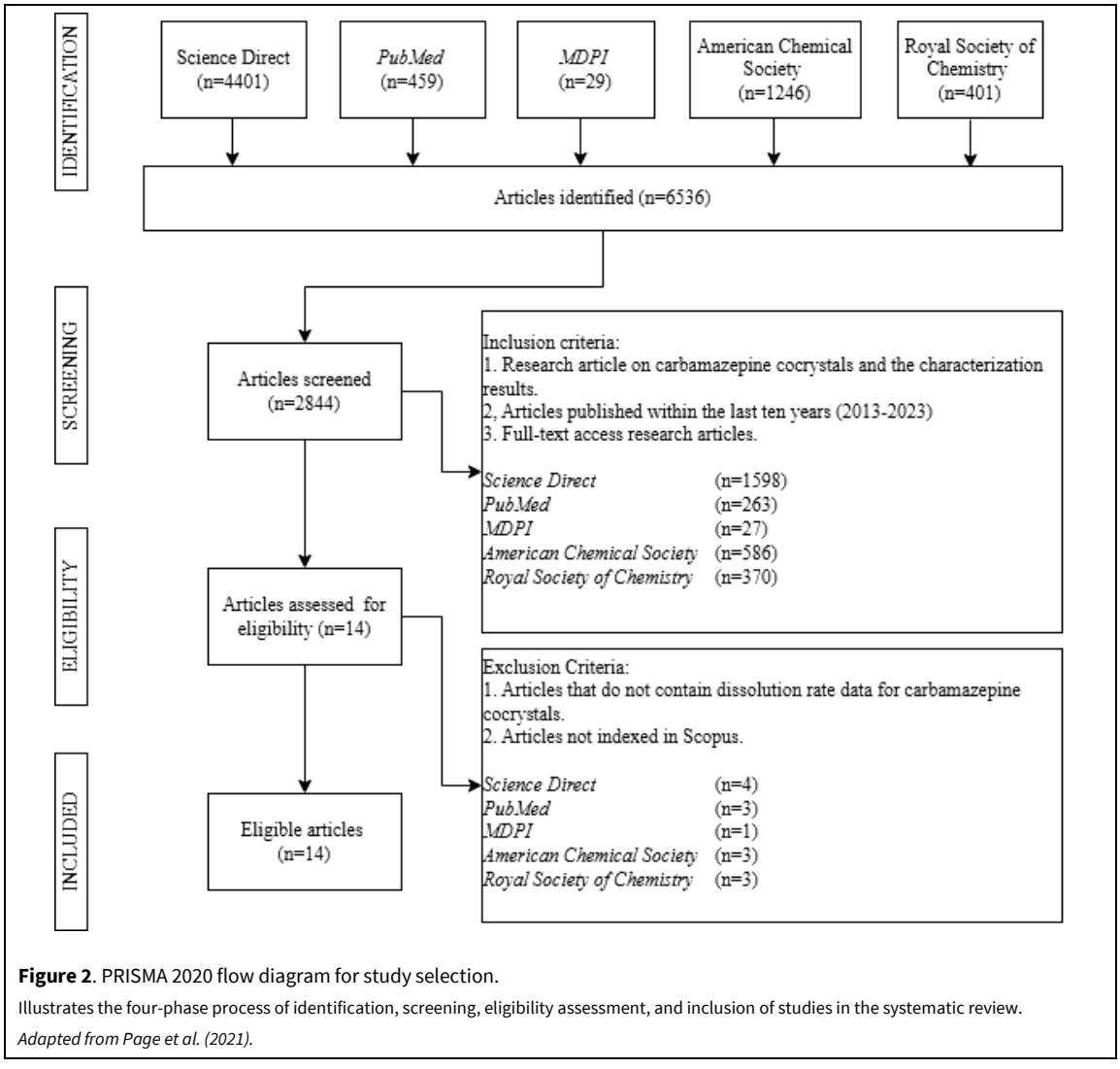

Figure 2. PRISMA 2020 flow diagram for study selection.

Illustrates the four-phase process of identification, screening, eligibility assessment, and inclusion of studies in the systematic review.

Adapted from Page et al. (2021).

Table 2. Summary of characteristics of included studies evaluating carbamazepine cocrystals.

No	Author	Coformers	Methods	Primary outcome	Secondary outcome
1	(Shayanfar et al., 2013)	Cinnamic Acid (CIN)	Solvent evaporation	Data on dissolution rate	Characterization of DSC, FTIR, and PXRD
2	(Sathisaran and Dalvi, 2019)	Para-hydroxy benzamide (PHBAD)	Solid state grinding	Data on dissolution rate	Characterization of DSC, PXRD, Raman and FTIR
3	(Yamashita and Sun, 2017)	Nicotinamide (NIC) with HPMCAS polymer addition	Reaction crystallization	Data on intrinsic dissolution rate	Characterization of XRD
		Glutaric acid (GLA) with HPMCAS polymer addition	Solvent evaporation	Data on intrinsic dissolution rate	Characterization of XRD
4	(Yamashita and Sun, 2016)	Nicotinamide (NIC) with NIC coformer addition	Reaction crystallization	Data on intrinsic dissolution rate	Characterization of XRD
5	(Tomaszewska et al., 2013)	Nicotinamide (NIC)	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, SEM, and PSD
		Nicotinamide (NIC) with microcrystalline cellulose addition	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, SEM, and PSD
		Saccharin (SAC)	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, SEM, and PSD
		Saccharin (SAC) with microcrystalline cellulose addition	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, SEM, and PSD
6	(Li et al., 2013)	Nicotinamide (NIC) with sodium lauryl sulfate and Tween 80 addition	Solvent evaporation	Data on intrinsic dissolution rate	Characterization of FTIR, Raman, and DSC
7	(Box et al., 2016)	Nicotinamide (NIC)	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, PSA, and SEM
		Saccharin (SAC)	Sonic slurry	Data on dissolution rate	Characterization of DSC, PXRD, PSA, and SEM
8	(Qiao et al., 2013)	Nicotinamide (NIC)	Solvent evaporation	Data on intrinsic dissolution rate	Characterization of SEM, FTIR, Raman, and DSC
9	(Li and Matzger, 2016)	Para-amino benzoate acid (PABA)	Solvent evaporation	Data on dissolution rate	Characterization of PXRD, Raman, and DSC
10	(Yamashita and Sun, 2018)	Glutaric acid (GLA)	Solvent evaporation	Data on intrinsic dissolution rate	Characterization of PXRD
11	(Dalpiaz et al., 2018)	Succinic acid (SUC)	Solvent evaporation	Data on dissolution rate	Characterization of XRD
		Vanillic acid VAN)	Solvent evaporation	Data on dissolution rate	Characterization of XRD
		4-nitropyridine N-oxide (NPO)	Solvent evaporation	Data on dissolution rate	Characterization of XRD
12	(Korde et al., 2018)	Salicylic acid (SAL) with polyethylene oxide addition	Solid state shear milling technology	Data on dissolution rate	Characterization of DSC, PXRD, NIR, FTIR, and SEM
		Salicylic acid (SAL)	Solvent evaporation	Data on dissolution rate	Characterization of DSC, PXRD, NIR, FTIR, and SEM
13	(Moradiya et al., 2014)	Trans-cinnamic acid (TCA)	Hot melt extrusion	Data on dissolution rate	Characterization of DSC, PXRD, NIR, PSD and SEM
		Trans-cinnamic acid (TCA)	Solvent evaporation	Data on dissolution rate	Characterization of DSC, PXRD, NIR, PSD and SEM
14	(Drozd et al., 2017)	Para-amino salicylic acid (PASA)	Solvent drop grinding	Data on dissolution rate	Characterization of DSC and PXRD

Abbreviations: DSC: Differential Scanning Calorimetry; PXRD: Powder X-ray Diffraction; FTIR: Fourier Transform Infrared Spectroscopy; SEM: Scanning Electron Microscopy; IDR: Intrinsic Dissolution Rate; PSA: Particle Size Analysis; NIR: Near Infrared Spectroscopy; TSE: Twin-Screw Extrusion; SSE: Single-Screw Extrusion.

Risk of bias assessment

All 14 studies underwent quality and bias assessment using the ADA Quality Criteria Checklist. Each study received a positive (+) rating, indicating that the methodologies employed were deemed robust and reliable. Key criteria, including inclusion/exclusion clarity, outcome specification, and data analysis transparency, were satisfactorily met across all articles. A summary of the quality ratings is presented in Table 3.

Table 3. Quality assessment of included studies using the ADA Quality Criteria Checklist.

Author and year	Relevance question				Validity question										Quality rating
	1	2	3	4	1	2	3	4	5	6	7	8	9	10	
(Shayanfar et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Sathisaran and Dalvi, 2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Yamashita and Sun, 2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Yamashita and Sun, 2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Ye s	No	No	+
(Tomaszewska et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Li et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Box et al., 2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Qiao et al., 2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Li and Matzger, 2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Yamashita and Sun, 2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Dalpiaz et al., 2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Korde et al., 2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Moradiya et al., 2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+
(Drozd et al., 2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	+

Relevance question	
1.	Will the answer if true, have a direct bearing on the health of patients?
2.	Is the outcome or topic something that patients/clients/population groups would care about?
3.	Is the problem addressed in the review one that is relevant to dietetics practice?
4.	Will the information, if true, require a change in practice?

If the answers to all of the above relevant questions are "Yes", the report is eligible for designation with a plus (+) on the evidence Quality Worksheet, depending on answers to the following validity question.

Validity question	
1.	Was the question for the review clearly focused and appropriate?
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate and reproducible?
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?
10.	Was bias due to the review's funding or sponsorship unlikely?

Minus/Negative (-)

If most (six or more) of the answers to the above validity questions are "No," the review should be designated with a minus (-) symbol on the Evidence Quality Worksheet

Neutral (Ø)

If the answer to any of the first four validity questions (1-4) is "No," but other criteria indicate strengths, the review should be designated with a neutral (Ø) symbol on the Evidence Quality Worksheet.

Plus/Positive (+)

If most of the answers to the above validity questions are "Yes" (must include criteria 1, 2, 3, and 4), the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet

Studies were rated based on relevance and validity domains. A positive (+) rating indicates high methodological quality. 'Yes' responses reflect criteria met. All studies fulfilled the four primary relevance questions and scored positively across most validity criteria.

Dissolution performance of carbamazepine cocrystals

The comparative dissolution profiles of carbamazepine cocrystals with various coformers are presented in Table 4. Significant enhancement in dissolution rate was reported for several coformers:

- **Salicylic acid (SAL):** The CBZ-SAL cocrystal demonstrated the most substantial improvement, with a dissolution rate exceeding 95% within 120 minutes using solvent evaporation and solid-state shear milling. The presence of hydrogen bonding between the hydroxyl and amide groups was considered pivotal in enhancing solubility.
- **Para-hydroxybenzamide (PHBAD):** Cocrystals prepared via solid-state grinding achieved a 6.5-fold increase in dissolution compared to pure CBZ, with 54% dissolution observed within 90 minutes.
- **Nicotinamide (NIC):** Multiple studies reported variable outcomes depending on the preparation method and dissolution medium. In modified compendial media, CBZ-NIC cocrystals reached up to 98% dissolution, whereas in standard conditions, values ranged between 5% and 50% over prolonged durations.
- **Cinnamic acid (CIN):** The CBZ-CIN cocrystal achieved 90% dissolution in 90 minutes, compared to 80% for unmodified carbamazepine, indicating moderate but consistent improvement.
- **Trans-cinnamic acid (TCA):** When prepared using hot melt extrusion, CBZ-TCA cocrystals exhibited dissolution rates up to 90% after 120 minutes, indicating that processing conditions significantly influenced performance.
- **Saccharin (SAC):** The CBZ-SAC cocrystal demonstrated variable outcomes depending on the dissolution medium. In modified conditions, dissolution rates reached 84%, whereas in compendial media, values were generally lower (34–58%).

Other coformers such as para-aminobenzoic acid (PABA), succinic acid (SUC), glutaric acid (GLA), vanillic acid (VAN), para-aminosalicylic acid (PASA), and 4-nitropyridine N-oxide (NPO) showed modest or minimal improvement in dissolution relative to pure carbamazepine. In certain cases, the presence of highly soluble coformers facilitated initial dissolution but also led to the recrystallization of less soluble carbamazepine forms (e.g., dihydrates), which limited the overall enhancement.

Table 4. Dissolution rate performance of carbamazepine cocrystals with various coformers.

No	Coformer	Method	Result	Reference
1	Cinnamic acid (CIN)	Solvent evaporation	After 90 minutes, the dissolution of CBZ-CIN cocrystals reached 90% and CBZ 80%	Shayanfar et al., 2013
2	Para-hydroxy benzamide (PHBAD)	Solid state grinding	After 90 minutes, the dissolution of the CBZ-PHBAD cocrystal was 54%, and that of CBZ was 8%.	Sathisaran and Dalvi, 2019
3	Nicotinamide (NIC)	Reaction crystallization	After 10 minutes, the IDR of CBZ-NIC/HPMCAS cocrystal (1:1) was 0.00035%, CBZ-NIC cocrystal 0.000075% and CBZ 0.000075%.	Yamashita and Sun, 2017
4	Nicotinamide (NIC)	Reaction crystallization	After 10 minutes, the IDR of CBZ-NIC/NIC cocrystal (1:3) was 0.0002%, CBZ-NIC cocrystal 0.00006% and CBZ 0.00006%.	Yamashita and Sun, 2016
5	Nicotinamide (NIC)	Sonic slurry	After 300 minutes, the dissolution of CBZ-NIC cocrystals was 5% and CBZ was 30%.	Tomaszewska et al., 2013
6	Nicotinamide (NIC)	Sonic slurry	After 300 minutes, the dissolution of CBZ-NIC cocrystals in compendial medium was 50% and CBZ 40%, while in modified medium, CBZ-NIC cocrystals were 98% and CBZ 44%.	Tomaszewska et al., 2013
7	Nicotinamide (NIC)	Solvent evaporation	After 60 minutes, the IDR of CBZ-NIC cocrystals in 10.4 mM SLS solution was 0.168% and CBZ 0.12%, while in 7.6 mM Tween 80 solution, the IDR of CBZ-NIC cocrystals was 0.09% and CBZ 0.06%.	Li et al., 2013
8	Nicotinamide (NIC)	Sonic slurry	After 130 minutes, the dissolution of CBZ-NIC cocrystal was 0.007% and after 130 minutes, the dissolution of CBZ was 0.03%.	Box et al., 2016
9	Nicotinamide (NIC)	Solvent evaporation	After 180 minutes, the IDR of CBZ-NIC cocrystals was 0.162% and CBZ 0.126%.	Qiao et al., 2013

Table 4. Dissolution rate performance of carbamazepine cocrystals with various coformers (continued...)

No	Coformer	Method	Result	Reference
10	Para-amino benzoate acid (PABA)	Solvent evaporation	After 60 minutes, the dissolution of CBZ-PABA (4:1) cocrystals in acetonitrile was 12.6% and CBZ 6.55%, while in Phosphate-Buffered Saline (PBS) medium, the dissolution of CBZ-PABA (4:1) cocrystals was 0.01% and CBZ 0.01%.	Li and Matzger, 2016
11	GLutaric acid (GLA)	Solvent evaporation	After 10 minutes, the IDR of CBZ-GLA/HPMCAS (1:1) cocrystals was 0.00005%, CBZ-GLA cocrystals 0.000075% and CBZ 0.000075%.	Yamashita and Sun, 2017
12	GLutaric acid (GLA)	Solvent evaporation	After 10 minutes, the IDR of CBZ-GLA/GLA cocrystals (1:3) was 0.00014% and CBZ-GLA cocrystals were 0.00007%.	Yamashita and Sun, 2018
13	Succinic acid (SUC)	Solvent evaporation	After 360 minutes, the dissolution of CBZ-SUC cocrystals in 10 mM PBS was 0.02% and CBZ 0.019%, while in 200 mM PBS, the dissolution of CBZ-SUC cocrystals was 0.011% and CBZ 0.012%.	Dalpiaz et al., 2018
14	Saccharin (SAC)	Sonic slurry	After 240 minutes, the dissolution of CBZ-SAC cocrystals was 0.0277% and CBZ 0.0285%.	Box et al., 2016
15	Saccharin (SAC)	Sonic slurry	After 300 minutes, the dissolution of CBZ-SAC cocrystals was 34% and CBZ was 30%.	Tomaszewska et al., 2013
16	Saccharin (SAC)	Sonic slurry	After 300 minutes, the dissolution of CBZ-SAC cocrystals in compendial medium was 58% and CBZ 40%, while in modified medium, CBZ-SAC cocrystals were 84% and CBZ 44%.	Tomaszewska et al., 2013
17	Salicylic acid (SAL)	Solid state shear milling technology	After 120 minutes, the dissolution of CBZ-SAL+25% PEO cocrystal was 100% and CBZ-SAL was 95%.	Korde et al., 2018
18	Salicylic acid (SAL)	Solvent evaporation	After 120 minutes, the dissolution of CBZ-SAL cocrystals was 95% and CBZ was 25%.	Korde et al., 2018
19	Trans-cinnamic acid (TCA)	Hot melt extrusion	After 120 minutes, the dissolution of CBZ-TCA cocrystal (SSE 125°C) was 60%, CBZ-TCA cocrystal (SSE 135°C) 76% and CBZ-TCA cocrystal (TSE 135°C) 90%.	Moradiya et al., 2014
20	Trans-cinnamic acid (TCA)	Solvent evaporation	After 120 minutes, the dissolution of CBZ-TCA cocrystals was 81% and CBZ was 49%.	Moradiya et al., 2014
21	Para-amino salicylic acid (PASA)	Solvent drop grinding	After 360 minutes, the dissolution of CBZ-PASA cocrystals was 0.0158% and CBZ 0.01127%.	Drozd et al., 2017
22	Vanillic acid (VAN)	Solvent evaporation	After 360 minutes, the dissolution of CBZ-VAN cocrystals in 10 mM PBS was 0.017% and CBZ 0.019%, while in 200 mM PBS, the dissolution of CBZ-VAN cocrystals was 0.013% and CBZ 0.12%.	Dalpiaz et al., 2018
23	4-nitropyridine N-oxide (NPO)	Solvent evaporation	After 360 minutes, the dissolution of CBZ-NPO cocrystals in 10 mM PBS was 0.018% and CBZ 0.019%, while in 200 mM PBS, the dissolution of CBZ-NPO cocrystals was 0.013% and CBZ 0.012%.	Dalpiaz et al., 2018

Comparison of the dissolution behavior of carbamazepine cocrystals and unmodified carbamazepine across various coformers and preparation methods. Values are expressed as percent dissolved at defined time points under specified conditions. Detailed references are provided for each result.

Virtual screening analysis

To evaluate the interaction strength between carbamazepine and selected coformers, molecular docking simulations were performed using AutoDockTools 1.5.6. Binding free energy values were calculated to predict the feasibility of forming stable cocrystals. The results are presented in Table 5.

- CBZ-SAL: Demonstrated the lowest binding free energy at –3.67 kcal/mol, indicating the strongest predicted interaction and highest cocrystal formation likelihood.
- CBZ-NIC: Exhibited a moderate binding affinity with a free energy of –3.33 kcal/mol.
- CBZ-PHBAD: Showed the least favorable interaction among the top three candidates, with a free energy value of –3.04 kcal/mol.

These findings support the experimental data, wherein CBZ-SAL consistently achieved the highest

Table 5. Predicted binding free energies from virtual screening of carbamazepine with selected coformers.

No	Cocrystal system	Binding free energy (kcal/mol)
1	CBZ-SAL	-3,67
2	CBZ-NIC	-3,33
3	CBZ-PHBAD	-3,04

Simulations were performed using AutoDockTools 1.5.6. Lower binding energy indicates a stronger predicted interaction between the drug and coformer.

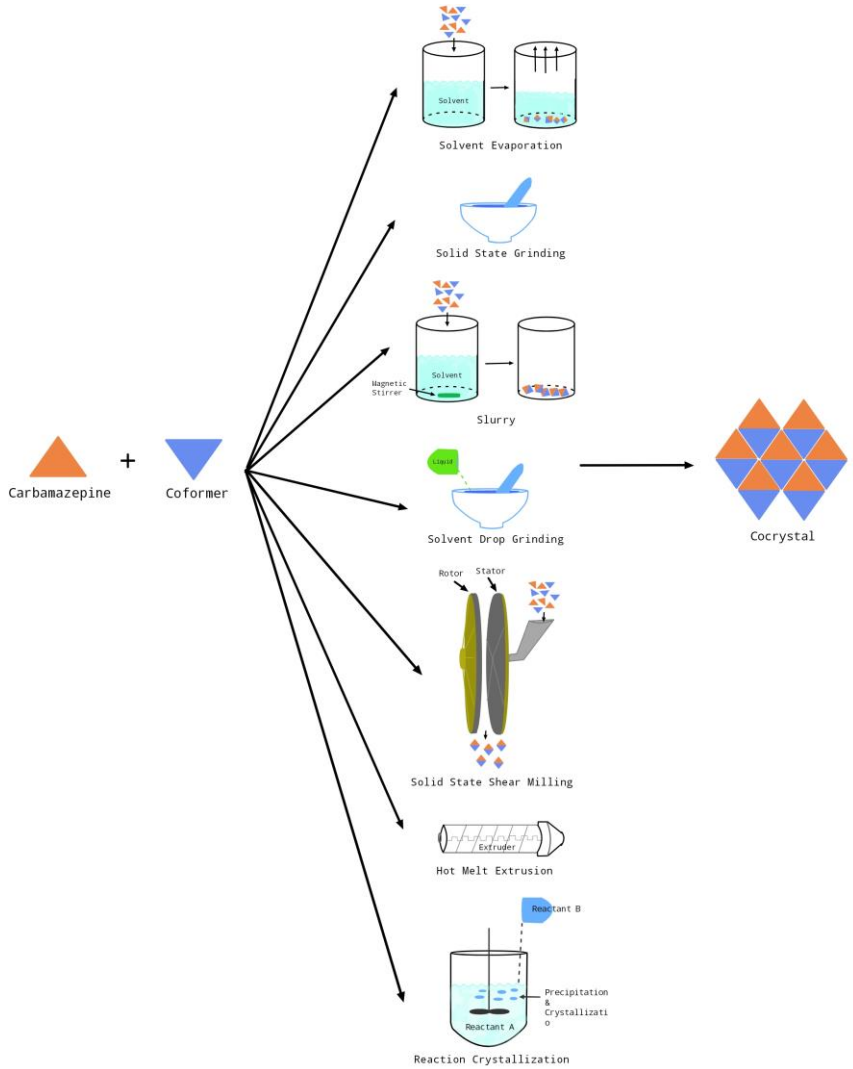

Figure 3. Overview of cocrystal preparation methods applied to carbamazepine.

Includes graphical summaries of solvent evaporation, solid-state grinding, slurry and sonic slurry, solvent drop grinding, solid-state shear milling, hot melt extrusion, and reaction crystallization.

Illustrates methodological diversity among included studies and their potential impact on cocrystal performance.

dissolution enhancement. The strong hydrogen bonding capability of salicylic acid with the amide group of carbamazepine was likely responsible for its superior performance.

Result of individual studies

Cocrystallization is one of the solid-state modification methods that changes the solid phase of a substance by altering its supramolecular makeup. The primary objective of solid-state modification is to enhance the solubility, stability, or other properties of the solid (Williams III et al., 2022). A summary of the cocrystal preparation methods used in the formation of carbamazepine + coformer, which have an impact on improving solubility and dissolution rate, is shown in Fig. 3.

Dissolution

Dissolution is a process of transferring drug molecules from solid form into the solution of a medium (body fluid). When the drug dissolves, the solid particles separate and enter the solution phase. Dissolution is one of the required tests for orally administered pharmaceutical dosage forms such as tablets, caplets, and capsules. This testing adheres to principles outlined in the Noyes-Whitney equation [1] (Krishna and Yu, 2008).

$$\frac{dc}{dt} = \text{K.A}\,(C_s - C) \qquad [1]$$

where K represents the dissolution rate constant, and A stands for the surface contact area of the undissolved compound. Cs denotes the saturation concentration of the solute within the dissolution medium at the specified experimental temperature. C refers to the concentration of the active substance in the solution at the time in the available solvent. The dissolution rate, symbolized by dc/dt, quantifies the alteration in drug concentration concerning time. Within this conceptual framework, the dissolution rate is modulated by surface area and drug solubility. Active pharmaceutical ingredients that have a high solubility in water have a higher dissolution rate, thereby increasing their bioavailability. Otherwise, for active pharmaceutical ingredients that have low solubility, the dissolution rate is also lower, thus decreasing their bioavailability (Krishna and Yu, 2008).

Cocrystal

A cocrystal is a multicomponent molecular crystal with all components in stoichiometric proportions and consisting of two or more chemically distinct molecules, including drug modification to alter the physical properties of the drug, especially drug solubility, without changing the pharmacologic performance. A cocrystal is a crystalline material consisting of an active pharmaceutical ingredient (API) and a cocrystal formulator (coformer) linked by hydrogen bonds (Chaudhari et al., 2018).

Cocrystal structure is based on noncovalent interactions between the API and the coformer. The interactions involved are intermolecular interactions, such as hydrogen bonding, van der Waals, π stacking, halogen bonding, and electrostatic interactions between stoichiometric amounts of various molecules. A coformer typically exhibits high water solubility and low volatility. Coformers that are used to form cocrystals should be non-toxic, have no side effects, be soluble in water, and be listed in the USFDA 'Everything Added to Food in the United States' (EAFUS) and Generally Recognized as Safe (GRAS) status. These compounds are considered safe enough for drug production so that they can be used as coformers in the cocrystallization process (Bavishi and Borkhataria, 2016; Desiraju, 2005).

The selection of a cocrystal screening method is very important for maximum performance. The properties of the active pharmaceutical ingredient and the coformer, such as thermal stability, melting temperature, and crystallization tendency of the active substance and excipients, influence the selection of the preparation method. Generally, cocrystal screening methods are divided into two, namely solution-based methods and solid-based methods.

Solvent evaporation

Solvent evaporation is the most common method for preparing cocrystals. The principle of the method is the dissolution of the API and coformer in a solvent or mixture of solvents, followed by slow evaporation. During evaporation, interactions occur between components to form hydrogen bonds. The choice of solvent affects the results of cocrystallization because it can change the intermolecular interactions between the active pharmaceutical ingredient and the coformer. Factors that influence the solvent evaporation process include the solvent removal rate and the temperature used during the solvent evaporation process. The advantages of solvent evaporation are that it is fast and quite simple, as it does not require the use of special tools. Besides, it is effective for lab-scale screening (Rodrigues et al., 2018; Singh and Van den Mooter, 2016).

Solid state grinding

Solid-state grinding or neat grinding is a method of making solid-based cocrystals by grinding the active substance with the coformer using a mortar and pestle, a ball mill, or a vibratory mill until a separable powder is formed. Solid-based methods are efficient and environmentally friendly as they require less or no solvent. Besides, it will avoid solvate formation. Manual grinding methods are not suitable for large-scale cocrystal manufacturing, so mechanical methods should be employed for efficient cocrystallization. Neat Grinding using a ball mill involves blending the components, loading them into a rotating chamber partially filled with small balls made from stainless steel, zirconium oxide, or tungsten carbide (Karki et al., 2007; Rodrigues et al., 2018).

Slurry

Slurry is a method of making cocrystals by adding a solid coformer into a solution, then the resulting suspension (slurry) is stirred until it forms a solid solution. The slurry formed between the two components will stimulate cocrystal formation and then be evaporated for 48 hours to induce cocrystallization. The difference between slurry and sonic slurry is the use of sonication to stir the slurry. In the sonic slurry method of cocrystal preparation, there is acoustic cavitation that will induce nucleation and crystallization, resulting in cocrystal formation. The advantages

of slurry is quite simple methodology and apparatus, single compounds crystal prevention, and effective for lab-scale screening (Box et al., 2016; Rodrigues et al., 2018; Tomaszewska et al., 2013).

Solvent drop grinding

Solvent drop grinding, also known as liquid-assisted grinding, represents a cocrystal synthesis technique in which grinding is coupled with the addition of a minimal solvent as a catalyst that enhances the kinetics of cocrystal formation. This method has higher efficiency and better control over cocrystal properties compared to solid-state grinding or neat grinding. The selection of solvent in this context demands precision, as the minute solvent volume must exhibit the capability to completely dissolve both the active ingredient and conformer. However, solvent drop grinding utilizes equimolar amounts of both components, which allows for the rapid production of cocrystals with high yields and crystallinity, facilitating structure determination (Guo et al., 2021; Rodrigues et al., 2018).

Solid state shear milling

Solid state shear milling (S3M) is a continuous solvent-free cocrystal grinding technology to solve the problem of cocrystal manufacturing. The S3M scheme consists of two disks, the stator and the rotor, placed opposite each other, made from wear-resistant materials with special surfaces. The stator is mounted on the equipment case, and the rotor is mounted on an axis with an electric motor. When the disk moves past the stationary point, there is a shift in the shape, volume, and position of the unit cell. The change in unit cell volume generates high pressure and shear force. The movement of the unit cell both radially and circularly causes continuous contraction and cleavage of the material. The high degree of shear at the interface and the presence of rising temperatures can provide sufficient energy to synthesize cocrystals with low residence times, thus minimizing degradation. S3M is characterized by low residence time, can be processed in the absence of solvents, and has already been proven in mechanochemical polymer applications. Mechanochemistry will provide energy to activate the co-crystallization reaction by subjecting the reactants to shear/collision forces (Korde et al., 2018; Tan et al., 2016).

Hot melt extrusion

Hot melt extrusion is a combined method that involves melting and simultaneously mixing active pharmaceutical ingredients and coformers using a heated screw extruder. The continuous preparation of cocrystals is carried out in a double extruder that mixes the active ingredient and coformer under temperature control. The temperature during the process must be considered, as it can pose a risk of decomposition of the compound. This is because sometimes high temperatures are required during the process to melt the active pharmaceutical ingredient and reduce the viscosity of the extrusion liquid. HME is an environmentally friendly technology, as it does not use organic solvents or water during processing; therefore, there is no solvent residue in the cocrystals, and no solvate formation occurs. Additionally, it is a continuous process that is easily scalable (Chaudhari et al., 2018; Dewi et al., 2021; Karimi-Jafari et al., 2018; Rodrigues et al., 2018).

Reaction crystallization

Reaction crystallization is effectively used for the preparation of cocrystals with different solubilities of cocrystal components. When the unstoichiometric concentrations of reactants are mixed, it results in a highly saturated solution of the cocrystals. The process of cocrystallization occurs when the solution reaches a state of supersaturation, which leads to the precipitation of cocrystals. Nucleation and cocrystal growth are controlled by the ability of the reactants to reduce the solubility of the cocrystal (Rodríguez-Hornedo et al., 2006; Yamashita and Sun, 2016).

To confirm the formation of intermolecular bonds within the cocrystals and the emergence of new crystal phases, it is necessary to analyze the crystal structure using X-ray diffraction (XRD). The diffraction patterns obtained through XRD analysis serve to identify the new crystalline phase of the cocrystal. Typically, the intensity of the peaks observed in the diffraction pattern correlates with the degree of crystallinity. The larger the peak area, the higher the degree of crystallinity of the crystal. The diffraction pattern of the CBZ-CIN cocrystal is different from that of CBZ, indicating the formation of a new crystal phase (Shayanfar et al., 2013).

Analysis of the physical interactions between mixed substances through melting point determination is facilitated by Differential Scanning Calorimetry (DSC). In cocrystals, the presence of hydrogen bonding induces a decrease in the melting point, altering the strength of intermolecular bonds and consequently reducing the energy required for the melting phase transition. The endothermic peak for carbamazepine was recorded at 190°C, while the endothermic peak for the carbamazepine-cinnamic acid cocrystal was observed at 144°C. This difference indicates a decrease in the melting point after the formation of the cocrystal (Shayanfar et al., 2013).

Fourier Transform Infrared (FTIR) analysis serves to elucidate the structure and chemical characteristics of the formed cocrystals. By observing the spectral differences between pure carbamazepine and the cocrystal, FTIR enables the identification of the cocrystal formation. This method distinguishes spectral irregularities attributed to the presence of hydrogen bonds in the cocrystals. The spectra of the cocrystals are different from those of pure carbamazepine and cinnamic acid, indicating the formation of hydrogen bonds. Shifts in the carbonyl of stretching group in CBZ-CIN to 1703 cm^{-1} and another shift in the N-H stretching bond at 3432 cm^{-1} indicate hydrogen bond formation between CBZ and CIN. However, the fingerprint region remains the same, indicating that the main functional groups remain. So it can be concluded that there is no change in the efficacy of cocrystals (Karagianni et al., 2018; Shayanfar et al., 2013).

Scanning Electron Microscopy (SEM) analysis served to visually inspect the cocrystal formation. Microscopic examination revealed the individual components that make up the cocrystals. The resulting cocrystals exhibited different morphologies, showing solid irregularities reminiscent of small rock-like formations and very rough surfaces. The shape of the cocrystals is varied, including large and small chunks, elongated needle-like structures, or powdery irregularities. These observations corroborate the formation of a new cocrystal phase, attributed to the interaction of hydrogen bonds between the drug and its conformer (Chhajed et al., 2020; Tomaszewska et al., 2013).

DISCUSSION

Table 4 shows the carbamazepine cocrystals with various conformers and their dissolution results.

This systematic review evaluated the enhancement of carbamazepine's dissolution rate through cocrystallization with various pharmaceutically acceptable coformers. The analysis of 14 eligible studies revealed that significant improvements in dissolution were observed when specific coformers were used, with salicylic acid demonstrating the highest performance both experimentally and computationally.

The improvement in dissolution rate can be attributed primarily to the formation of non-covalent interactions—particularly hydrogen bonds—between functional groups of carbamazepine and those of the coformers. This interaction is crucial in modifying the crystal lattice structure, resulting in improved wettability, reduced lattice energy, and increased surface area exposure, all of which are critical factors that facilitate enhanced dissolution.

Among the coformers studied, salicylic acid was identified as the most effective, achieving a dissolution rate exceeding 95% within 120 minutes. This enhancement was further supported by molecular docking analysis, which showed the strongest binding affinity between carbamazepine and salicylic acid, with a binding free energy of –3.67 kcal/mol. The carboxylic and hydroxyl functional groups of salicylic acid are capable of forming stable heterosynthon hydrogen bonds with the amide group of carbamazepine, promoting favorable cocrystal formation and stability.

Nicotinamide also demonstrated a substantial increase in dissolution, particularly under modified dissolution media conditions, where dissolution rates reached up to 98%. However, variability in outcomes was noted depending on the dissolution media and preparation techniques. The presence of highly soluble coformers such as nicotinamide may also increase the likelihood of phase transformation during dissolution, as previously reported with the formation of carbamazepine dihydrate, potentially offsetting the initial dissolution gains.

Para-hydroxybenzamide exhibited a dissolution rate improvement of approximately 6.5-fold compared to unmodified carbamazepine, which is attributed to its carboxamide group forming stable homosynthon interactions. Nevertheless, its binding affinity was slightly weaker than that of salicylic acid and nicotinamide, as indicated by docking scores.

Other coformers such as cinnamic acid, trans-cinnamic acid, and saccharin showed moderate improvements in dissolution. Interestingly, in cases such as saccharin and trans-cinnamic acid, the preparation method (e.g., hot melt extrusion vs. solvent evaporation) significantly influenced the extent of dissolution enhancement, highlighting the importance of processing conditions in cocrystal development.

Coformers such as vanillic acid, para-aminobenzoic acid, succinic acid, glutaric acid, and 4-nitropyridine N-oxide produced only marginal improvements in dissolution or failed to outperform pure carbamazepine under certain conditions. These results may be due to weak or unstable hydrogen bonding interactions, high melting points, or poor solubility of the coformers themselves.

The virtual screening results were generally consistent with the experimental dissolution outcomes. The coformers with the lowest binding free energy values correlated with those producing the highest in vitro dissolution rates, thereby validating the utility of molecular docking as a predictive tool in coformer screening.

Despite these promising findings, certain limitations were noted. First, dissolution testing protocols varied significantly across the included studies, in terms of both the dissolution media and the sampling time points. This heterogeneity precluded meta-analytic synthesis and made direct comparisons challenging. Second, only a limited number of studies have evaluated polymorphic stability or long-term storage, which are crucial for ensuring the clinical applicability of cocrystal formulations.

Furthermore, while computational methods such as docking offer valuable predictions, they must be complemented with experimental validation, including solubility profiling, stability studies, and potentially permeability testing (e.g., Caco-2 assays) to fully assess the bioavailability impact of cocrystals. Additional pharmacokinetic studies are warranted to evaluate the *in vivo* translation of improved dissolution into therapeutic efficacy.

Overall, the results of this systematic review reinforce the role of cocrystallization as a robust approach to overcoming solubility-limited bioavailability, particularly for BCS Class II drugs such as carbamazepine. The identification of salicylic acid as the most effective coformer provides a promising direction for further experimental development and formulation scaling.

Virtual screening tools

Following the identification of the coformer demonstrating the highest enhancement in dissolution rate, virtual screening is conducted to determine the strength of the interaction between carbamazepine and the coformer. The interaction strength between carbamazepine and the coformer was identified using the AutoDockTools 1.5.6 application. The prediction yields free energy binding data, which is the amount of energy required to form a bond between carbamazepine and the coformer. The predicted binding free energy of the cocrystal is shown in Table 5.

The CBZ-SAL cocrystal has the lowest binding free energy compared to other cocrystals, which is -3.67 kcal/mol. These findings suggest that the CBZ-SAL complex, with the lowest binding free energy (-3.67 kcal/mol), exhibits the most favorable interaction potential among the evaluated cocrystals.

CONCLUSION

This systematic review has demonstrated that cocrystallization is an effective solid-state modification strategy to enhance the dissolution rate of carbamazepine, a BCS Class II drug with inherently poor aqueous solubility. Among the various coformers evaluated, salicylic acid consistently exhibited the most significant enhancement in dissolution rate, achieving over 95% drug release within 120 minutes. This was further corroborated by virtual screening analysis, which indicated the strongest binding affinity between carbamazepine and salicylic acid.

Nicotinamide and para-hydroxybenzamide also showed notable improvements in dissolution, although to a lesser extent. The effectiveness of cocrystallization was found to depend not only on the choice of coformer but also on the preparation method and dissolution medium. These findings underscore the importance of systematic conformer selection and optimization of processing techniques in the design of cocrystal-based pharmaceutical formulations.

Virtual screening tools, such as AutoDock, have been validated as useful preliminary methods for predicting coformer interactions, providing a computational framework to support experimental efforts. However, further *in vitro* and *in vivo* studies, including assessments of permeability and stability, are recommended to confirm the translational potential of these findings for clinical applications.

In conclusion, the cocrystallization of carbamazepine with salicylic acid represents a promising approach to overcome its solubility limitations and may serve as a model for the development of improved formulations of other poorly soluble drugs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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The authors declare that no generative artificial intelligence (AI) tools were used in the creation of this document.

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Concepts or ideas	x	x		
Design	x	x		
Definition of intellectual content	x		x	
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Experimental studies	x	x		x
Data acquisition	x	x		x
Data analysis	x	x		x
Statistical analysis	x	x		x
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