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CO-CRYSTALS OF CARBAMAZEPINE WITH NICOTINAMIDE: SOLUBILITY AND DISSOLUTION ENHANCEMENT

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Abstract

Carbamazepine is a long-established antiepileptic whose oral absorption is limited by slow, erratic dissolution and by a troublesome tendency to convert between polymorphs and a poorly soluble dihydrate. Pharmaceutical co-crystals with nicotinamide are among the best-studied attempts to improve this behaviour. This review draws on published work to describe the properties of the parent drug, the logic of coformer selection, methods of preparation, structural and thermal characterisation, and the solution behaviour that governs solubility and dissolution. A synthesis table compares representative studies. The review reports no new experimental data. The literature supports a real but conditional benefit, since supersaturation is transient and solution-mediated conversion, stability and regulatory classification remain decisive.

1. INTRODUCTION

Carbamazepine has been used since the 1960s for partial and generalised tonic-clonic seizures and for trigeminal neuralgia, and it remains on many national formularies. Its pharmacology is well understood, but its biopharmaceutics are awkward. The drug is neutral, practically insoluble in water, and highly permeable, which places it in class II of the biopharmaceutics classification system, where dissolution rather than permeation limits absorption [1, 2]. Its therapeutic window is narrow, and plasma concentrations have to be kept within a modest range to avoid both seizures and dose-related toxicity.

Under these circumstances, variation in the rate and extent of dissolution between batches or brands is not a trivial matter, and generic substitution has long been a topic of concern

among neurologists and pharmacists.

The usual formulation tools are not well suited to carbamazepine. Because it has no ionisable group within the physiological pH range, salt formation, the most common route to better solubility, is not available [3]. Micronisation helps only modestly, and solid dispersions and lipid systems add manufacturing complexity. Pharmaceutical co-crystals offer a different approach. A co-crystal is a crystalline solid in which the drug and a second molecule, the coformer, occupy defined positions in the same lattice, held together mainly by hydrogen bonds, and the resulting solid has its own melting point, solubility and dissolution rate [4, 5, 6]. For a neutral molecule with an amide group, like carbamazepine, the idea is particularly attractive.

Carbamazepine has become a model compound for co-crystal science. Early screening work identified several co-crystals, with nicotinamide, saccharin and other coformers among them, and these were examined in far more detail than most drug co-crystals [7, 8, 9]. This review collects what has been published about the carbamazepine and nicotinamide system in particular, covering the problems of the parent drug, how the combination was designed, how it is made and characterised, and how it behaves in solution. It reports no new experiments. Quantitative statements are limited to those that are widely reproduced or carry a clear citation, and the review also asks how far the results for this one pair can be generalised to co-crystals of other drugs.

2. THE PARENT DRUG AND ITS PROBLEMS

Carbamazepine exists in at least four anhydrous polymorphs, usually numbered I to IV, and as a dihydrate. Form III is the stable form at ambient temperature, form I is the stable form at higher temperature, and the others are metastable. Crystal structures, thermal behaviour and relative stability of these forms have been studied in detail [10, 11, 12]. Commercial products generally contain form III. The difficulty is that polymorphic transformation is possible during processing, for instance through wet granulation or compression, and that the anhydrous drug can take up water and convert to the dihydrate, whose solubility in water is lower. The stability relationships are known well enough to be controlled, but they add risk at every stage of manufacture and storage.

Molecular features explain much of this behaviour. Carbamazepine is a rigid, largely planar tricyclic dibenzazepine with a single carboxamide group, and its lipophilic ring system dominates its interaction with water. Its solubility in water at room temperature is of the order of a hundred micrograms per millilitre, and it differs somewhat among the solid forms, with the dihydrate lower than the anhydrous forms [12, 13]. The carboxamide supplies both hydrogen-bond donors and an acceptor, which is why the crystal packing is so strongly directed by the amide dimer, and why a coformer carrying a competing amide is a logical choice. A molecule with these traits is easy to crystallise but resists dissolving, an unfortunate combination for a drug that has to be taken for years.

The dihydrate matters most in the dissolution medium. When anhydrous carbamazepine dissolves in water or gastric fluid, the solution can become supersaturated with respect to the dihydrate, which then crystallises on the surface of the dissolving particles, forms a layer and slows further release [13]. Comparative studies of polymorphs and dihydrate have found differences in dissolution rate and, in animal work, in absorption, although the clinical significance in patients is more difficult to establish [12, 13]. Because the effect depends on the medium and on agitation, in vitro dissolution tests can give different rankings under different conditions, and the choice of test method has been a regular topic in the comparison of branded and generic products.

Carbamazepine also shows clinical features that make its pharmacokinetics unusually important. It is a potent inducer of its own metabolism through cytochrome P450 3A4, so clearance rises over the first weeks of treatment and doses are adjusted upward. Its absorption is slow and variable, with peak concentrations after oral tablets reached several hours after the dose, and it interacts

with many other drugs, including other antiepileptics. These traits mean that further variation from dissolution can push plasma concentrations outside the therapeutic range. Formulation scientists therefore have a strong reason to seek solid forms with more predictable and faster dissolution, provided that stability can be maintained and the new form is accepted by regulators.

Conventional approaches to improving poorly soluble drugs have been reviewed repeatedly, and they include particle size reduction, solid dispersions, complexation with cyclodextrins, lipid formulations and the use of salts [2, 3, 14]. Each has drawbacks for a neutral, high-dose drug like carbamazepine, whose daily dose is several hundred milligrams. Cyclodextrin complexes and lipid systems carry large excipient loads that are difficult to fit into a tablet, while amorphous dispersions face the risk of recrystallisation. Crystal engineering offers the possibility of altering solid-state properties without chemically modifying the molecule or adding bulky carriers, which is why co-crystals have drawn attention as an alternative route [4, 15].

Pharmacopoeial and regulatory history gives context. Carbamazepine tablets and chewable tablets are well established, and its dissolution specifications are product-specific in several markets. The classification of the drug as class II, with high permeability, makes it a candidate for in vitro-in vivo correlation, because dissolution should be the rate-limiting step, although the narrow therapeutic index has led some agencies to impose tighter bioequivalence limits than the standard range [1, 14]. A co-crystal that changes dissolution rate would, in principle, alter the bioequivalence picture, and that possibility has been considered in the few studies that go beyond solubility measurements in the laboratory.

3. CO-CRYSTAL DESIGN AND COFORMER SELECTION

Design starts from the hydrogen-bonding behaviour of the drug. In the crystal of carbamazepine, the carboxamide groups pair into centrosymmetric dimers through N–H···O bonds, leaving the anti N–H hydrogen of each amide free. A coformer that can compete for this motif by forming an amide–amide heterodimer is a promising candidate. Etter's rules of hydrogen-bond preference, and the concept of the supramolecular synthon that grew out of them, provide the framework, with best donors pairing with best acceptors [16, 17]. Nicotinamide is a textbook coformer in this sense. It carries a primary carboxamide that can replace one half of the carboxamide dimer of carbamazepine, and a pyridine nitrogen as an additional acceptor. In the reported structure the heterodimer is the main contact [7].

Coformer choice has other constraints beyond synthon fit. The coformer must be acceptable for oral use, with a clear safety record, which limits the search to substances on lists of approved excipients, food additives and vitamins. Nicotinamide, a form of vitamin B3, is widely used in food and pharmaceutical products and is highly water-soluble, which makes it appealing from a safety and a dissolution standpoint [7, 18]. Analyses of the Cambridge Structural Database suggest that co-crystal formation is more likely when the two components differ moderately in polarity and shape, and that complementarity in hydrogen-bonding functional groups is useful but not sufficient by itself [19]. In practice, selection still involves screening by experiment.

The relationship between co-crystals and salts needs care. Whether a drug and coformer form a salt, with proton transfer, or a co-crystal, without it, depends on the difference in pKa between the basic and acidic sites. Empirically, a difference below zero tends to give a co-crystal and a difference above about three gives a salt, with an uncertain zone in between where the proton may sit in a position that depends on the crystal environment [20, 21]. For carbamazepine and nicotinamide, both neutral at the relevant pH values, the issue does not arise, which is one reason why the pair is regarded as a clean example. The terminology matters for regulators because it determines how the solid is classified, as discussed later [6, 22, 23].

Stoichiometry and the presence of competing forms add to the complexity. Co-crystals of a

given pair can exist in more than one ratio, and the ratio that crystallises depends on solvent, temperature and concentration, as well as on the relative solubilities of the components [24, 25]. Carbamazepine and nicotinamide form a 1:1 co-crystal under most conditions. The existence of a stable stoichiometric form is useful, but it does not mean the product is easy to make on a large scale: the crystallisation window may be narrow and the competing phases, namely the individual components and the carbamazepine dihydrate, are always present as possible impurities [25, 26].

Practical screening combines several quick experiments. Typical programmes grind the drug with each candidate coformer, with and without a drop of solvent, and examine the products by powder diffraction, while parallel work evaporates solutions or slurries mixtures of the two solids [15, 27, 28]. Thermal screening with a hot-stage microscope offers a further inexpensive check. The earliest large demonstrations of the approach, such as the itraconazole co-crystals with dicarboxylic acids, showed that a rational choice of acid could produce dissolution close to that of a marketed amorphous product [29], and the carbamazepine work of the same period showed how general the behaviour of amide drugs might be [7]. A screen of this type is still the best route to a hit list, although prediction tools have narrowed the field of candidates.

Examples from other drugs show that the strategy generalises, with mixed results. Co-crystals of itraconazole with dicarboxylic acids gave dissolution close to that of an amorphous marketed product [29], a meloxicam–aspirin co-crystal showed improved solubility and pharmacokinetics in animals [18], and an AMG 517 sorbic acid co-crystal improved exposure of a very insoluble compound [30]. Not every attempt works. Many co-crystals are no more soluble than the parent drug, and some are less soluble because the coformer is poorly soluble or the lattice energy is high. Published studies are subject to publication bias, and the successes should be read in the knowledge that unsuccessful screens are rarely written up [27, 28].

4. PREPARATION METHODS

Solvent evaporation from a solution containing both components in stoichiometric ratio is the traditional method and the one used to grow single crystals for structure determination. It is simple and works well on a small scale, but it can fail when the components have very different solubilities, since the less soluble one crystallises first and the product is a mixture. Carbamazepine and nicotinamide differ greatly in solubility in most solvents, and the choice of solvent therefore has to be made with care, with attention to the ternary phase diagram [7, 24, 31]. Reports of unsuccessful attempts often turn out, on closer inspection, to reflect a poor choice of solvent more than any real inability of the pair to cocrystallise.

Reaction crystallisation, introduced by the group of Rodríguez-Hornedo, exploits the phase behaviour directly. A solution of coformer is prepared at a concentration above the transition point, and solid drug is added, so that the system is supersaturated with respect to the co-crystal and the added drug dissolves while the co-crystal nucleates. The method relies on the measurement of the solubility of the components and on plotting the stable regions of the phase diagram, and it has been applied to carbamazepine co-crystals [26]. A related slurry approach, in which the physical mixture is stirred in a small volume of solvent for hours or days, is a practical way to convert a mixture of components into the thermodynamically stable co-crystal, and is often used to confirm which form is stable.

Mechanochemical methods avoid large volumes of solvent. In neat grinding the two solids are milled together, and co-crystal forms through contact and local molecular mobility; in liquid-assisted grinding a few drops of solvent accelerate the process and often give a more crystalline product, sometimes selecting between polymorphs [32, 33]. Comparison of grinding with solution methods for several systems found that mechanochemistry could give co-crystals that were hard to obtain from solution, and that the products were the same phase when the system was well behaved [31]. For carbamazepine, grinding with nicotinamide is among the simplest ways to obtain the

co-crystal, and the method scales reasonably through ball milling and extrusion.

Scale-up is more demanding than laboratory work suggests. Cooling and antisolvent crystallisation, spray drying and melt-based processes have all been investigated for co-crystals, and each presents difficulties in controlling particle size, phase purity and residual solvent [15, 28]. Incongruent saturation is a particular trap: when one component is much more soluble than the other, the solution composition required for co-crystal growth differs from the stoichiometric ratio, and ordinary cooling crystallisation yields mixtures [24]. A manufacturing process has to be validated to show it consistently gives the co-crystal and not the parent drug or the dihydrate, a point of special relevance to carbamazepine because of the ease with which the latter forms.

Several authors have stressed the value of process analytical tools for co-crystal manufacture. In-line Raman spectroscopy and focused beam reflectance measurement can follow the appearance of the new phase during a crystallisation, and powder diffraction on samples withdrawn at intervals confirms identity [15, 28]. These techniques fit comfortably with the quality-by-design approach that regulators encourage, since they link process parameters to the critical attributes of the product. Published examples are mostly for model systems, and the carbamazepine and nicotinamide pair is one of the commonest choices. Industrial experience with a commercial co-crystal product remains limited, and the transfer from academic crystallisation studies to routine production is still largely unproven.

5. STRUCTURE AND CHARACTERISATION

A new solid phase must be shown to be a single-phase co-crystal, not a physical mixture or a salt. Powder X-ray diffraction is the primary tool, because the pattern of a co-crystal differs from the sum of the patterns of its components and shows new reflections at positions not present in either [7, 34]. Single-crystal diffraction, where crystals of adequate quality can be grown, gives the definitive answer by showing the hydrogen-bonding pattern and the location of the hydrogen atoms. In the reported structure of the carbamazepine and nicotinamide co-crystal, the amide groups of the two molecules pair, and this interaction replaces the carbamazepine dimer [7]. Powder diffraction of a bulk batch is then compared with the pattern calculated from the single-crystal structure.

Thermal analysis complements diffraction. Differential scanning calorimetry typically shows a single melting endotherm for the co-crystal at a temperature different from those of either component, and often between them, while thermogravimetric analysis rules out solvates or hydrates by showing the absence of mass loss before decomposition [27, 34]. Hot-stage microscopy lets the analyst watch melting and recrystallisation, which can reveal whether a melt of the co-crystal crystallises into the drug and coformer separately. For carbamazepine, thermal methods need to be interpreted carefully, since polymorphs interconvert on heating and a thermogram may reflect transitions that occurred during the experiment rather than properties of the sample as received [10, 12].

Vibrational and magnetic resonance spectroscopy provide evidence at the molecular level. Infrared and Raman spectra of the co-crystal show shifts in the amide stretching and bending bands that reflect the change of hydrogen-bonding partner, and solid-state nuclear magnetic resonance can distinguish the co-crystal from a physical mixture and show the number of independent molecules in the asymmetric unit [27, 34]. Spectroscopy is particularly valuable for quantifying the proportion of co-crystal in a mixture or tablet, where diffraction may lack sensitivity or be affected by preferred orientation. Dynamic vapour sorption adds information on hygroscopicity, an important property because water uptake is what drives conversion of anhydrous carbamazepine to the dihydrate [9, 13].

Control of phase purity is the main analytical task in a developed product. A residual fraction of free carbamazepine, whether from incomplete conversion or from dissociation in storage, can alter dissolution

disproportionately, because it can seed the dihydrate. Specifications for a co-crystal therefore need to cover identity by diffraction and spectroscopy, assay of both components in the correct ratio, and a limit for the free drug and coformer [15, 27, 34]. Quantitative methods based on powder diffraction, Raman mapping and solid-state NMR can detect a few percent of an impurity phase, and detection limits are often poorer for amorphous content. These requirements are close to those applied to a polymorphic drug substance, and the analytical experience gained with carbamazepine polymorphs transfers readily to its co-crystals [10, 12].

Physical and mechanical properties also come into the picture, since a solid that dissolves well but cannot be compressed is of little practical use. One systematic evaluation of the carbamazepine and nicotinamide co-crystal examined its behaviour on compression, its physical stability under different temperature and humidity conditions, and the dissolution of tablets made from it [9]. Co-crystals can show better or worse tableting properties than the parent drug, depending on crystal packing and slip planes, and the behaviour cannot be predicted reliably from structure alone. Evaluating these properties early in development helps identify problems before significant resources are committed to a candidate whose performance in the dissolution vessel is attractive but which cannot be manufactured.

6. SOLUBILITY AND DISSOLUTION BEHAVIOUR

The solubility of a co-crystal is not a fixed property like that of a single compound. It depends on the concentration of coformer in solution, since the co-crystal dissolves into its two components and its solubility product is the constant. A co-crystal formed from a drug and a highly soluble coformer can reach much higher drug concentrations than the drug alone, and the ratio of co-crystal to drug solubility is called the solubility advantage [35, 36]. For carbamazepine and nicotinamide, nicotinamide is so soluble that the co-crystal is predicted to be many times more soluble than the stable carbamazepine form in water. The measurement is difficult, because the co-crystal is unstable in water and converts to the dihydrate before equilibrium is reached.

That conversion explains much of the apparent inconsistency in the literature. When the co-crystal is added to water, the solution rapidly becomes supersaturated with carbamazepine relative to the stable phases, and the drug concentration climbs above that attainable from the parent drug. Then the dihydrate nucleates, concentration falls toward its much lower solubility, and the advantage disappears [26, 35]. Solution chemistry thus controls the outcome. The picture is often described as a spring and parachute: the co-crystal provides the spring of supersaturation, and additives or excipients that slow crystallisation of the stable phase provide the parachute, extending the useful window [25, 37]. Without a parachute, the benefit may be gone in minutes.

Behaviour in the gut adds assumptions that laboratory dissolution tests cannot test. When a co-crystal dissolves, the two components separate, and nicotinamide, which is very soluble and well absorbed, is expected to be taken up and cleared much faster than the drug. The concentration of coformer around a dissolving particle therefore falls with time, which lowers the solubility advantage of the co-crystal [35, 36]. Regulatory arguments that the co-crystal is simply an intermediate rely on rapid dissociation before the drug reaches its site of action [22]. For the carbamazepine and nicotinamide pair this assumption looks reasonable on solution chemistry, though it has been demonstrated more by modelling and by in vitro work than by direct measurement in humans.

Reported dissolution studies of the carbamazepine and nicotinamide co-crystal generally show a faster initial dissolution rate and a higher drug concentration at early time points than the parent drug, followed by a fall as the dihydrate forms [9, 35]. The details depend on the medium, the hydrodynamics and the particle size. Inclusion of polymeric precipitation inhibitors in the medium or the tablet can prolong supersaturation, and surfactants in biorelevant media change the picture further, since micellar solubilisation raises the apparent solubility of all forms [14, 37]. For this reason, dissolution tests in pure

water exaggerate differences, and comparisons in media that mimic gastric and intestinal fluids are more informative about likely in vivo behaviour.

The main published comparisons are brought together in table 1, which sets the carbamazepine studies beside work on other co-crystal systems that illuminate mechanisms. Three observations stand out. First, the clearest evidence of a benefit in vivo comes from the carbamazepine and saccharin co-crystal, which gave exposure in dogs comparable to that of a marketed product [8]. Second, the nicotinamide system has been examined mainly for its physical and solution behaviour [7, 9, 26, 35]. Third, the theoretical framework for predicting the effect of pH and coformer concentration has been developed to a level that allows quantitative prediction of solubility profiles [36]. The distribution of entries by category is given in fig. 1.

Reading table 1 and fig. 1 together shows how uneven the evidence base is. The largest group of entries concerns solution behaviour and design principles, not clinical performance, and in vivo data are few [8, 35, 36]. This pattern is not a flaw of the studies, which were mostly designed to explain mechanisms, but it limits what can be claimed. A statement that co-crystallisation with nicotinamide improves the bioavailability of carbamazepine is not directly supported by published pharmacokinetic work on that specific pair, though it is a reasonable expectation based on dissolution results and on the saccharin co-crystal in dogs [8, 9]. Careful authors express the conclusion in these conditional terms.

Table 1: Selected studies relevant to carbamazepine co-crystals and their dissolution behaviour

System or topic	Reported finding	Ref.
Carbamazepine and nicotinamide structure	Amide–amide heterodimer replaces the carbamazepine dimer; 1:1 co-crystal reported among several coformers	[7]
Carbamazepine and nicotinamide tablets	Compression behaviour, physical stability and tablet dissolution evaluated	[9]
Carbamazepine and saccharin dog study	Exposure comparable to a marketed product in an animal pharmacokinetic study	[8]
Anhydrous polymorphs and dihydrate parent drug	Dissolution and absorption differ between forms; dihydrate formation slows release	[10, 13]
Co-crystal solubility theory	Solubility depends on coformer concentration; conversion to the stable phase limits the advantage	[35]
Reaction crystallisation phase diagrams	Transition concentrations guide the choice of conditions for forming carbamazepine co-crystals	[26]
pH and ionisation prediction	Quantitative models predict co-crystal solubility as pH and coformer concentration change	[36]
Meloxicam and aspirin animal study	Improved solubility and pharmacokinetics reported for a co-crystal with a GRAS-type coformer	[18]
Indomethacin and saccharin dissolution	Faster dissolution than the parent drug in a preliminary pharmaceutical evaluation	[38]
AMG 517 and sorbic acid insoluble compound	Co-crystal improved exposure of a very poorly soluble compound in animals	[30]

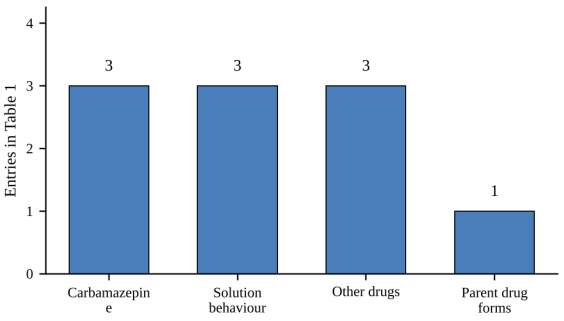


Fig. 1: Number of entries in table 1 by study category

Particle size and surface area interact with all of these effects. A fine co-crystal powder dissolves more quickly and reaches supersaturation sooner, but it also provides more nucleation sites for the dihydrate, so the net effect on peak concentration and its duration is not straightforward [35, 37]. Intrinsic dissolution measurements, in which

a compact of constant surface area is dissolved, remove the effect of particle size and are a better test of the true material property. They show the same trend as powder dissolution for the system, with a high initial rate followed by decline, and they also make it easier to see conversion on the surface of the compact by diffraction or microscopy after the experiment.

7. REGULATORY AND STABILITY CONSIDERATIONS

Regulatory treatment of co-crystals has become clearer in recent years. A guidance issued by the US Food and Drug Administration treats a co-crystal as a drug product intermediate, in the sense that the drug and coformer are expected to dissociate before reaching the site of action, and therefore not as a new active substance [22]. The European Medicines Agency took a broadly similar line in its reflection paper, which states that co-crystals can be regarded as comparable to salts for the purpose of identifying the active substance, provided that the case is supported by data [23]. Both positions reduce the burden compared with a new chemical entity, but they require evidence that the co-crystal dissociates, is controlled and does not alter the safety profile.

Stability determines whether a promising co-crystal is a viable product. The co-crystal has to survive manufacture and storage without reverting to carbamazepine or, worse, to the dihydrate. Humidity is the main hazard, and the physical stability of tablets made from the carbamazepine and nicotinamide co-crystal has been studied under elevated temperature and humidity [9]. Co-crystals of this type can be stable when dry and then convert when humidity exceeds a critical value, and this behaviour has to be mapped as part of development. Protective packaging and moisture-resistant formulations are possible mitigation measures, though they add cost and complexity that offset some of the benefit of improved dissolution [34, 39].

Limitations of the evidence should be stated plainly. Most studies are laboratory-scale, many use water as the dissolution medium, and few follow the co-crystal into a formulated tablet exposed to realistic conditions [27, 39]. In vivo data on the carbamazepine and nicotinamide pair itself are sparse. Because the drug has a narrow therapeutic index and strong auto-induction, any change in absorption rate would need careful clinical evaluation, and the benefit of faster dissolution is not self-evident when the drug is already well absorbed over time in most patients. Future work should focus on supersaturation maintenance, relevant biorelevant testing, pharmacokinetics in suitable animal models and process scale-up with in-line monitoring [15, 28, 39].

A broader question concerns intellectual property and commercial feasibility. Co-crystals of known drugs can be patented as new solid forms, and companies have used them to extend the life of products, but regulators and courts have sometimes questioned whether the incremental benefit justifies protection. For an off-patent, low-cost drug like carbamazepine, where generic competition is intense, a co-crystal product would face a tough commercial test unless it offered a clear clinical advantage. The research value of the system is therefore likely to remain greater than its commercial value, with carbamazepine continuing to serve as a reference compound for method development in crystal engineering [4, 6].

8. CONCLUSION

Co-crystallisation of carbamazepine with nicotinamide shows how crystal engineering can alter the solid-state behaviour of a neutral, poorly soluble drug. The design rests on a well-understood hydrogen-bonding interaction, the coformer is a safe and familiar vitamin, and the co-crystal can be made by solution, slurry or grinding methods [7, 26, 32, 33]. In laboratory dissolution tests it generally gives faster dissolution and a higher early concentration than the parent drug, followed by a decline as the dihydrate crystallises [9, 35]. The system has also yielded general lessons about solubility advantage, supersaturation and phase behaviour that apply to many other drugs [25, 36].

The practical value of the pair remains less certain than its scientific interest. In vivo

evidence for nicotinamide itself is limited, the benefit depends on maintaining supersaturation, and stability under humidity must be controlled [8, 9, 37]. Regulatory guidance has become more permissive, which improves the prospects for co-crystal products in general [22, 23]. Future studies should test biorelevant conditions, include precipitation inhibitors, report pharmacokinetics in animals and examine scale-up, so that claims about bioavailability rest on direct evidence and not on inference from dissolution alone [15, 28, 39].

9. ABBREVIATIONS

API-Active pharmaceutical ingredient, BCS-Biopharmaceutics classification system, DSC-Differential scanning calorimetry, GRAS-Generally recognised as safe, PXRD-Powder X-ray diffraction, CBZ-Carbamazepine, NMR-Nuclear magnetic resonance, TGA-Thermogravimetric analysis, pKa-Acid dissociation constant, EMA-European Medicines Agency, FDA-Food and Drug Administration

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All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

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