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Co-Crystallization: A Novel Approach to Improve the Physicochemical Properties of Active Pharmaceutical Ingredients

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ABSTRACT

In recent years, there has been a lot of interest in the design and synthesis of pharmaceutical cocrystals. Co-crystals are made up of various molecules joined together by hydrogen bonds. Pharmaceutical Co-crystals are non-ionic supramolecular complexes and can be created through a variety of interactions, including hydrogen bonds, pi-stacking, and van der Waals forces. Two molecules of any size or shape with complementary hydrogen bond functions can be used to create co-crystals. Cogrinding and storing of amorphous phases produced by pharmaceutical operations results in the development of cocrystals. The production of new drug products with superior physical and pharmacological properties such as solubility, stability, hygroscopicity, dissolution rates, and bioavailability is greatly facilitated by the cocrystallization of drug ingredients. API and a stoichiometric amount of pharmaceutically acceptable co-crystal former (co-former) make up co-crystals. This review aims to present an extensive overview of the co-crystals, their difference from other states, co-crystallization methods, their physicochemical properties, and their application.

INTRODUCTION:

Solubility is the amount of solute that dissolves in a solvent. Fundamentally, a substance's solubility is influenced by the solvent being employed together with temperature and pressure. Due to its simplicity, high patient compliance, cost-effectiveness, lack of sterility restrictions, and flexibility in dosage form design, oral ingestion is the most practical and frequently used route of drug delivery. [1] Orally administered drug completely absorb only when they show fair solubility in gastric medium and such drugs show good bioavailability. Therefore, one of the most difficult components of the drug development process, particularly for the oral drug delivery system is to improve drug solubility to increase its oral bio-availability. [2]

COCRYSTALS:

Etter was the first to report the term "cocrystal" and the design guidelines for hydrogen bonding in an organic cocrystal. Desiraju was the first to introduce the idea of hydrogen bond creation in crystal formations using a supramolecular synthon. This marked the start of a new era in crystal engineering and cocrystal formation. In 2004, pharmaceutical cocrystals were described as a different class of innovative crystalline materials that may change the physicochemical properties of APIs.[3] Co-crystals are “homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds”. An API (in neutral or ionic form) and a cocrystal former, which is solid under ambient conditions are required to create a cocrystal for it to be considered a pharmaceutical cocrystal. In addition, a cocrystal solvate is a cocrystal made up of two or more solid components that are at room temperature and a liquid.[4] Pharmaceutical cocrystals have made it possible to build solid-state forms of active pharmaceutical ingredients (APIs) other than the typical solid-state forms including salts and polymorphs. This entails changing a drug's physical qualities, particularly its solubility without changing its pharmacological impact.[5]

Noncovalent interactions between the API and the coformer are the foundation of cocrystal structure. The interaction involved in intermolecular interactions such as van der Waals contact forces, π stacking, hydrogen bonds, electrostatic interaction, and halogen bonds between stoichiometric concentrations of different molecules. Typically, this fundamental structural unit found within supermolecules is referred to as a supramolecular synthon.[6] The

amide group (e.g., nicotinamide and urea), the amine group (e.g., benzamide, picolinamide, adenine), the alcohol group, and the acid group of carboxylic acids are the functional groups that are most frequently used for the creation of supramolecular synthons through H-bonding. [7] Coformers and API can both be acidic, basic, or neutral. Interactions between ionic chemicals should continue to be non-ionic permitting cocrystal formation rather than salt production. [8] Some of the examples of pharmaceutical co-crystals are co-crystals of fluoxetine HCl and benzoic acid; fluoxetine HCl and succinic acid; and fluoxetine HCl and fumaric acid.

CO-CRYSTAL VERSUS SOLVATES:

The physical state of the constituents is the only distinction between solvates and cocrystals. Solvates are substances where one component is liquid and the other is solid but on other hand, cocrystals are substances where both components are solid. [9]

CO-CRYSTAL VERSUS SALT FORMATION:

It is important to distinguish between salt formation and co-crystallization. There is a distinction between salt formation and co-crystallization, even though both are employed to improve the API's solubility, stability, and other properties. While salt formation requires an API charge to create its salt form but co-crystallization does not require any of these conditions. Hence co-crystallization presents a choice for API that doesn't have a charge and needs to be improved for solubility, stability, etc. While a co-former and an API are required for co-crystallization but three elements are required for salt formation such as an acid (A), a base (B), and a solvent. The salt formation can be explained by a simple reaction as below.

$$A\text{-}H \rightarrow (A^-)\ (B^+\text{-}H)$$

Proton transfer is thought to mainly depend on the pKa values of the components. The hydrogen packing rule leads to salt formation. When there is no such transfer and the components are instead present in the crystal as neutral entities, the product is generally defined as a co-crystal. In other words, a cocrystal is an A-B composite in which no proton transfer occurred.[10]

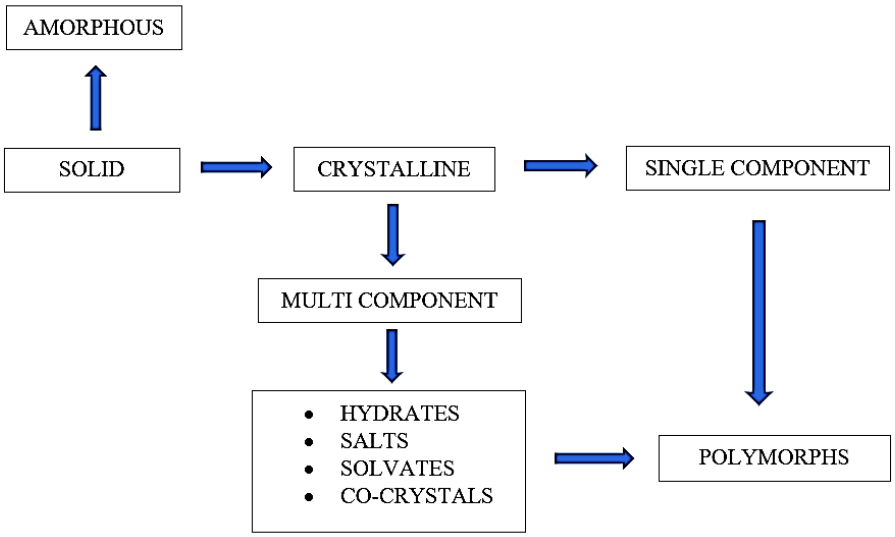


Figure 01: API solid form classification based on structure and composition[11]

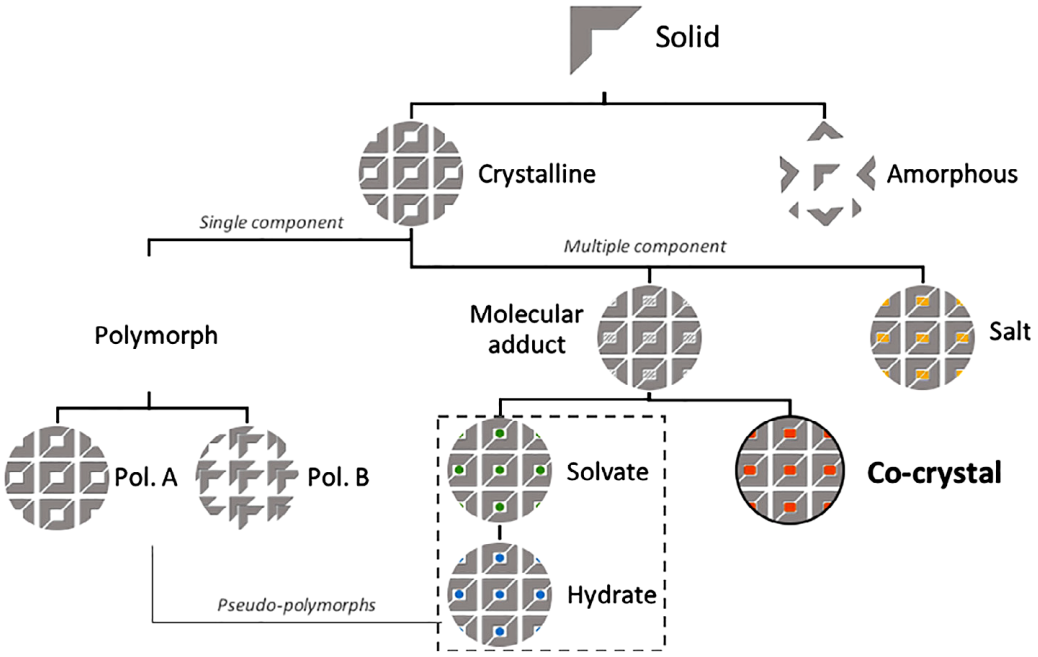


Figure 02: Schematic representation of API solid forms classification.

PROPERTIES OF CO-CRYSTALS:

Co-crystals, also known as counterions, are solid under ambient conditions and are formed when API and pharmaceutically acceptable (GRAS) compounds interact. This new approach to API formulation may help to address significant issues with the intellectual and physical

property in the context of drug development and delivery. Co-crystals are often described as "organic molecular compounds" or "addition compounds."[12]

Co-crystal technology use has only lately been recognized as a means to improve solubility, stability, and the intellectual property position of API development. An API's pharmacological activity is unaffected by co-crystallization with pharmaceutical excipients, although it can improve some of its physical characteristics such as solubility, hygroscopicity, and compaction behavior.[13] Depending on the makeup of the second component, co-crystals made of the same active pharmaceutical ingredient will exhibit glaringly different pharmacological characteristics (melting point, solubility, dissolution, bioavailability, moisture uptake, chemical stability, etc.). When compared to their components of pure forms, certain co-crystals generated had melting points that were higher and others that were lower. Examples include succinic acid (Mp=135.3), urea (Mp=188.9), and the succinic acid-urea co-crystal (Mp=149.9) (Walsh *et al.*, 2003).[14]

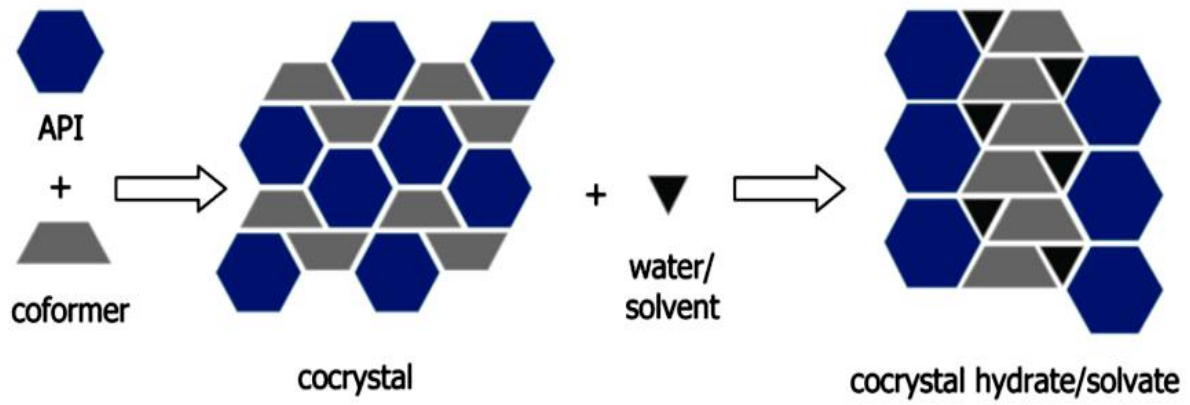


Figure 03: Possible multicomponent co-crystal

MECHANISM FOR CO-CRYSTAL SYNTHESIS:

When there is greater molecular mobility and complementarity, amorphous phases produced by pharmaceutical methods form cocrystals.[15] When solid mixtures with co-crystal reactants were exposed to deliquescent conditions, moisture uptake resulted in the formation of co-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, caffeine, or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid). These mechanisms include: (i) moisture uptake (ii) co-crystal aqueous solubility (iii) solubility and dissolution of co-crystal reactants and (iv) transition concentration. [16] There are

three stages in the mechanism of co-crystallization when moisture is present under deliquescent conditions: (i) moisture uptake (ii) reactant dissolution and (iii) cocrystal nucleation and growth. [17]

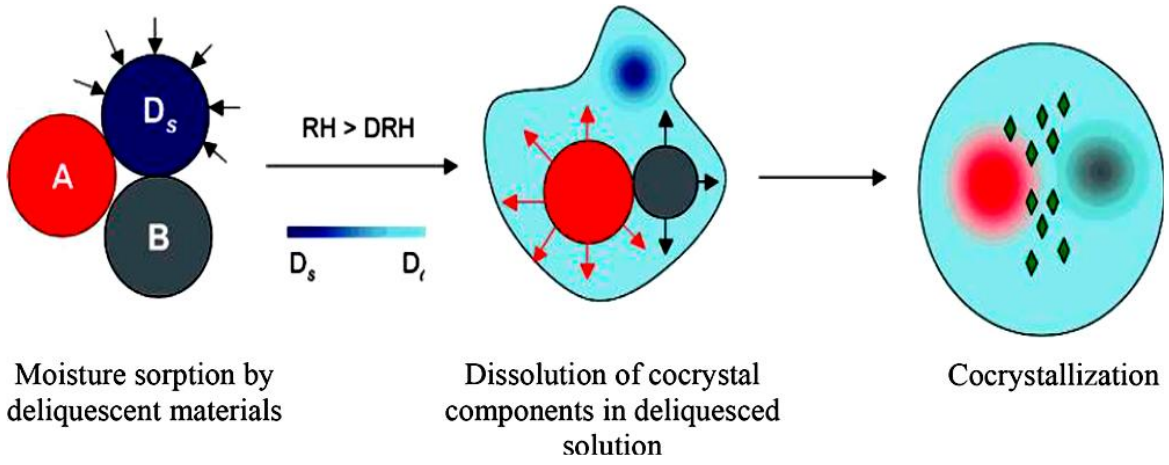


Figure 04: Illustration of the moisture uptake process leading to deliquescence, reactant dissolution, and cocrystal formation.

Where D_s is a solid deliquescent additive, A and B are cocrystal reactants and D_l is the solution phase produced by deliquescence at relative humidity higher than that of deliquescence relative humidity.

CHARACTERIZATION OF CO-CRYSTALS:

Characterization of co-crystals involves both structure (infrared spectroscopy, single crystal x-ray crystallography, and powder x-ray diffraction)[18] and physical properties (e.g., melting point apparatus, differential scanning calorimetry, thermogravimetric analysis).[19]To compare the solubility of molecular salts and co-crystals, plots of pH vs solubility were used. [20] Co-crystal phase diagrams in organic solvents were used to apply a mathematical model that was established to characterize the solubility of co-crystals by taking into account the equilibria between co-crystal, co-crystal components, and solution complexes. [21]

CRITERIA FOR CO-CRYSTAL FORMER SELECTION:

Cambridge Structural Database can be used to evaluate potential intermolecular hydrogen bonding between various molecules. If the projected lattice energy is large enough, computational methods for calculating crystal lattice energy can estimate the likelihood of co-crystal formation. One can readily construct supramolecular synthesis for the successful

creation of cocrystals between two different molecules with the use of systematic structural analyses. [22] Hansen solubility parameters (HSPs) can be used to forecast whether two distinct compounds will mix. HSPs is a simple mathematical approach, that necessitates an understanding of molecular chemical structure. [23]

METHODS OF PREPARATION OF CO-CRYSTALS:

Co-crystals can be prepared by solvent and solid-based methods.[24] Common methods used in the preparation of co-crystals are given below.[25]

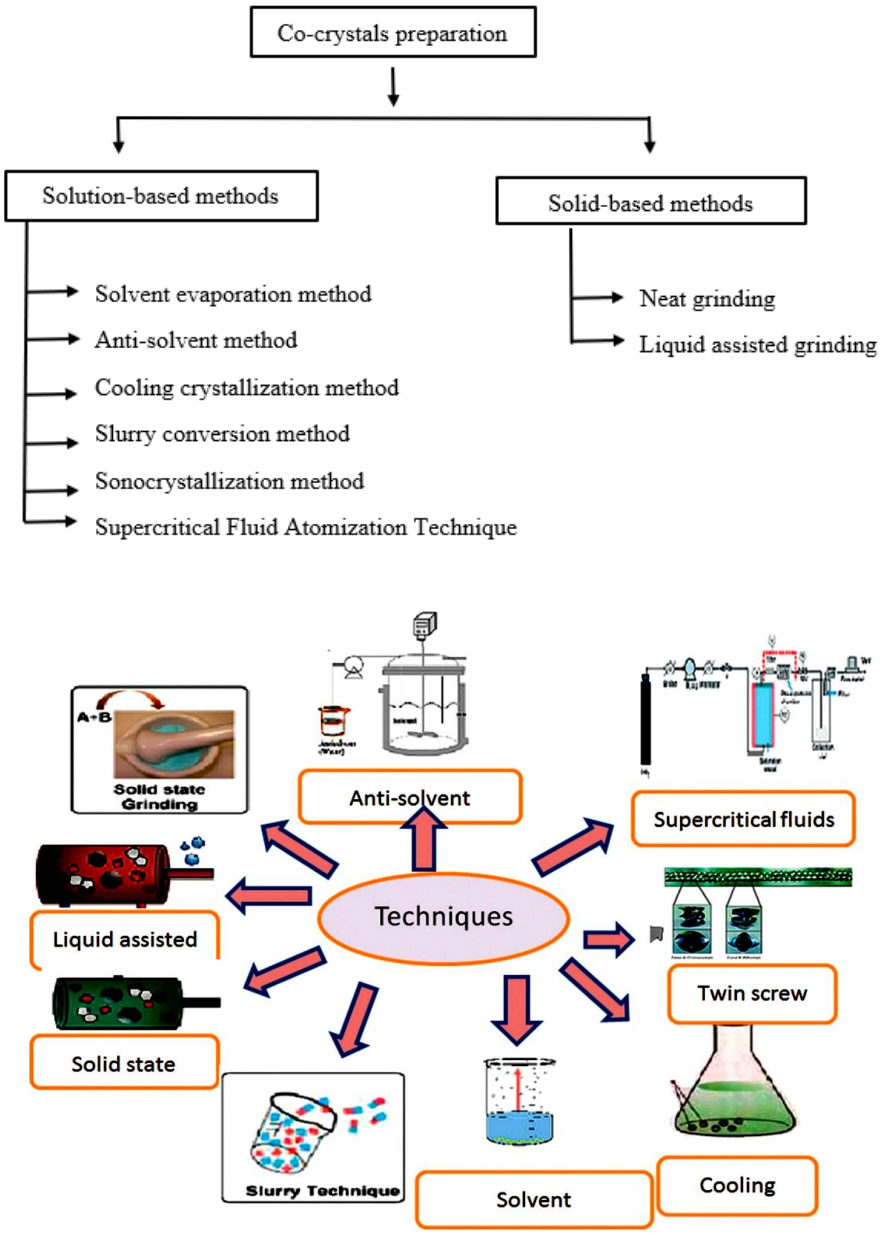


Figure 05: Techniques of cocrystal formation.[26]

SOLID-BASED METHODS:

1. Neat Grinding (Dry grinding):[27]

Drug + Coformer

(In a stoichiometric ratio)

Grind

(Mortar and pestle or ball mill)

Dry grinding can be accomplished in a variety of ways, including mechanically using a ball mill mixture, vibratory mill or manually using a motor and pestle. Piroxicam co-crystals were created by Prabhakar *et al.,* using the dry grinding process with sodium acetate as the coformer.[28]

2. Wet Grinding:

Drug + Coformer

(In a stoichiometric ratio)

Grind

Addition of some drops of solvent in mixture

(Mortar and pestle or ball mill)

Cocrystals have been manufactured by the grinding process, Sungyup *et al.*, created Adefovir dipivoxil Co-crystals by using glutaric acid and suberic acid as conformers by liquid-assisted grinding. [29] Ibuprofen-amino acid cocrystals were created by Muhamad *et al.*, using both a dry grinding approach and a liquid-aided grinding method. [30]

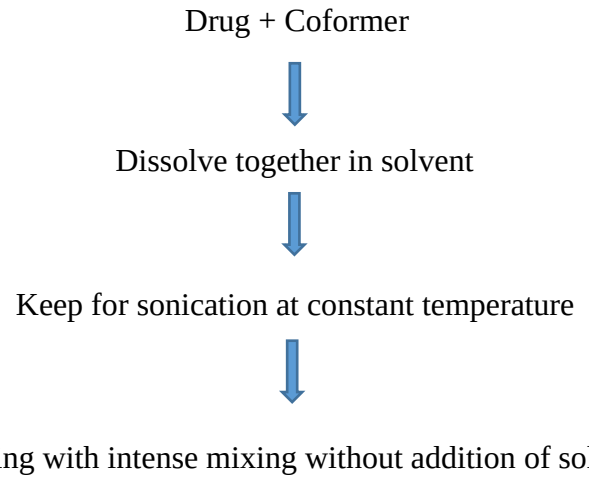
SOLUTION-BASED METHODS:

1. Anti-solvent method:

Heat-sensitive compounds benefit from anti-solvent crystallization, which uses less heat energy than a solvent evaporation method and can be carried out at temperatures close to

those found in the atmosphere. The difficulty in the separation of solvents from the mixture limits its reuse.[31]

2. Sonocrystallization method:[32]



3. Solvent evaporation method:

This approach involves dissolving the API and coformer in a common solvent at the proper stoichiometric ratio. To produce co-crystals, the solvent was then allowed to gradually evaporate at room temperature. When choosing a solvent, it is essential to take API and coformers solubilities into account. The quality of the co-crystal is significantly influenced by the solvent present during co-crystal formation. According to the theory behind this method, the functional division of pharmaceuticals and a complimentary coformer engage in intermolecular interactions such hydrogen bonding and make products that are thermodynamically advantageous. This methods drawback is that it doesn't work well on a broad scale.[33]

4. Cooling crystallization method:

The drug gets recrystallized by supersaturating the solution at a different temperature. At 40.0 ± 0.5^0C, an adequate amount of the drug was dissolved in a certain solvent volume. In a water bath, the solution was cooled to 10.0 ± 0.5^0C while being stirred continuously at a cooling rate of about 0.25^0C/min. Crystals were collected by vacuum filtration, cleaned three times in distilled water, allowed to dry for 24 hours at room temperature, and then stored in a desiccator.[34]

5. Supercritical Fluid Atomization Technique:

Rapid Expansion of Supercritical Solutions (RESS) is a process where a solution of the drug and coformer in supercritical CO_2 is rapidly depressurized (10–5 s) to atmospheric conditions. Cocrystallization with Supercritical Solvent (CSS) technique uses the solvent power of supercritical CO_2 to suspend the API and the coformer as a slurry in liquid or supercritical CO_2. Due to the fluid's drastic decrease in solvent power, the solute in the depressurized supercritical CO_2 is highly supersaturated. When a supersaturation forms quickly, it triggers nucleation and crystallization, which drives the fine particles to precipitate. The process employs non-toxic, extremely volatile solvents that don't leave any solvent residues on the crystals that are created. The limited solubility of the drug-coformer pairings in supercritical CO_2 and the low product yields are some drawbacks of RESS. [35]

APPLICATION OF PHARMACEUTICAL CO-CRYSTALS:

Cocrystal engineering is relevant to the production of energetic materials, pharmaceuticals, and other compounds. Drug development and more particularly formulation, design, and implementation of active pharmaceutical ingredients or APIs is the application that has received the greatest attention from researchers and practitioners. The bioavailability of a drug can be significantly affected by altering the structure and composition of the API. Cocrystal engineering makes use of each component's unique characteristics to create the best possible circumstances for solubility which may ultimately increase the drug's bioavailability. The principal idea is to develop superior physicochemical properties of the API while holding the properties of the drug molecule itself constant.[36]

CONCLUSION:

Cocrystal plays a significant part in the pharmaceutical industry. They reduce the overuse of solvents by improving solubility and they can improve the bioavailability and bio performance. As a result, there may be an easier distribution of particular drug products. To improve a drug's solubility, bioavailability, stability, and processability, cocrystals are an excellent choice. However, there are several challenges including coformer selection, physicochemical characterization, and formulation. Successful Cocrystals development can result from careful formulation design and drug coformer screening. In this review, we discussed in detail pharmaceutical co-crystals, how they differ from other states, co-

crystallization methods, their physicochemical properties, and their application to overcome the poor physicochemical properties of APIs.

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CONFLICTS OF INTEREST:

The authors declare that there is no conflict of interest.

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