

QUERCETIN-HEXAHYDRIC ALCOHOL COCRYSTAL AND PROCESS FOR PREPARING THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

5 [0001] The embodiments herein claim the priority of the US provisional application filed on August 4, 2023, with the provisional application number 63/517,659 with the title, "QUERCETIN-HEXAHYDRIC ALCOHOL COCRYSTAL AND PROCESS FOR PREPARING THEREOF", and the contents of which are included in entirety as reference herein.

BACKGROUND

TECHNICAL FIELD

10 [0002] The inventive subject matter presented herein is generally directed toward a quercetin-hexahydric alcohol cocrystal. More particularly, embodiments are related to but are not limited to solid-state quercetin as a bioenhancer of active pharmaceutical ingredients, phytochemicals, vitamins, and minerals, process for preparing the quercetin-hexahydric alcohol cocrystal.

DESCRIPTION OF THE RELATED ART

15 [0003] The subject matter discussed in the background section should not be assumed to be prior art merely because of its mention in the background section. Similarly, a problem mentioned in the background section or associated with the subject matter of the background section should not be assumed to have been previously recognized in the prior art. The subject matter in the background section merely represents different approaches, which in and of themselves may also
20 be inventions.

[0004] Quercetin is a flavonoid found in many plants and foods, such as onions, moringa, apples, and berries. It is well-known for its anti-inflammatory and antioxidant effects. Quercetin has been widely used for the treatment of cancer, cardiovascular diseases, and diabetes. Previous research studies indicate quercetin's potential as a bioenhancer. Its ability to enhance the bioavailability of
25 drugs through various pathways is documented, such as the inhibition of the P-glycoprotein efflux pump and the inhibition of metabolic enzymes.

[0005] Despite these benefits, quercetin's poor solubility in water poses a significant challenge. Quercetin dihydrate is sparingly soluble in aqueous buffer. While quercetin is quite soluble in organic solvents, such as ethanol (2 mg/ml) and dimethylformamide (30 mg/ml), this solubility characteristic limits its application in the drug and nutraceutical industries where solubility in aqueous media is necessary for better bioavailability.

[0006] Several methods for improving the solubility of quercetin have been documented. For instance, steviol glycosides have been used to enhance quercetin's solubility by forming a complex. Additionally, quercetin cocrystals have been reported, including those formed with caffeine coformers, to increase quercetin's solubility.

[0007] However, there remains a need for novel formulations that further improve the solubility and bioavailability of quercetin in aqueous media, thereby enhancing its application in pharmaceutical and nutraceutical industries.

[0008] This invention addresses this need by developing quercetin-hexahydric alcohol cocrystals, which provide a method to improve the solubility and bioavailability of quercetin and enhance the bioactivity of bioactive compounds.

[0009] Thus, in view of the above, there is a long-felt need in the industry to address the described issues.

[0010] Further limitations and disadvantages of conventional and traditional approaches will become apparent to one of ordinary skill in the art through the comparison of described methods with some aspects of the present disclosure, as set forth in the remainder of the present application and with reference to the drawings.

SUMMARY OF THE INVENTION

[0011] A quercetin-hexahydric alcohol cocrystal and the process for preparing the same are provided and shown in and/or described in connection with the figures.

[0012] According to embodiments illustrated herein, there is provided a process for preparing a quercetin-hexahydric alcohol cocrystal as a bioenhancer for bioactive compounds. The process comprises a step of forming the cocrystal from a quercetin and a hexahydric alcohol by a kinetic-controlled cocrystallization process.

[0013] In an aspect, the kinetic-controlled cocrystallization process comprises a step of forming the cocrystal by cooling a solution at a cooling rate of 10 – 20 °C/min. In an aspect, the solution contains the quercetin and the hexahydric alcohol and has the temperature before said cooling in the range of 40 – 70 °C.

- 5 [0014] In an aspect, the kinetic-controlled cocrystallization process further comprises a step of aging the cocrystal.

[0015] In an aspect, the solution comprises a solvent that is selected from the group consisting of methanol, ethanol, and a combination thereof.

[0016] In an aspect, the quercetin is preferably a quercetin dihydrate.

- 10 [0017] In an aspect, a diffusion coefficient of the quercetin dihydrate in the solvent is preferably at $5 \times 10^{-10} \text{ m}^2/\text{s}$.

[0018] In an aspect, the hexahydric alcohol is selected from the group consisting of a straight-chain hexahydric alcohol and a cyclic hexahydric alcohol.

[0019] In an aspect, the hexahydric alcohol is preferably sorbitol.

- 15 [0020] In an aspect, a diffusion coefficient of the hexahydric alcohol in the solvent is preferably at $8 \times 10^{-10} \text{ m}^2/\text{s}$.

[0021] In an aspect, the molar ratio of the quercetin to the hexahydric alcohol in the solution is in the range of 1:1.

- 20 [0022] In an aspect, the kinetic-controlled cocrystallization process has a kinetic constant (k) in the range of $1 \times 10^{-16} - 1 \times 10^{-14} \text{ m}^3/\text{s}$.

[0023] In an aspect, the kinetic-controlled cocrystallization process has the kinetic constant (k) preferably at $10^{-15} \text{ m}^3/\text{s}$.

- 25 [0024] In an aspect, the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.

[0025] According to embodiments illustrated herein, there is provided a quercetin-hexahydric alcohol cocrystal as a bioenhancer for a bioactive compound. The cocrystal has a molar ratio of a quercetin to a hexahydric alcohol that is in the range of 1:1.

5 [0026] In an aspect, the quercetin-hexahydric alcohol cocrystal characterized by at least one of the following XRPD peaks: 10.7, 12.4, 13.8, 13.9, 14.7, 16.2, 16.4, 17.7, 18.0, 19.3, 21.6, 23.8, 25.9, 27.2, 28.7, 29.8, 33.5, 35.8, 36.6, and $37.0 \pm$ degree 2-theta [Cu K α radiation ($\lambda = 1.5406$ Å)].

[0027] In an aspect, the cocrystal preferably exhibits a thermal gravimetric in the range of 338.58 – 342.2 °C.

10 [0028] In an aspect, the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.

[0029] According to embodiments illustrated herein, there is provided a pharmaceutical composition includes the quercetin-hexahydric alcohol cocrystal and at least one pharmaceutically
15 acceptable carrier.

[0030] In an aspect, the pharmaceutical composition may be used in enhancing cell permeability and bioavailability of the bioactive compound.

[0031] In an aspect, the pharmaceutical composition may be used in the treatment of inflammation.

20 [0032] In one of the aspects, the present invention relates to cocrystal formations: a cocrystal of the quercetin with hexahydric alcohol, which can have either a straight-chain or cyclic structure. A cocrystal of the quercetin dihydrate with hexahydric alcohol, in a molar ratio of 1:1. In addition to the cocrystal compositions, this invention also describes: pharmaceutical compositions comprising the cocrystal described in the previous aspects. Methods of treating conditions that can
25 be addressed by administering the cocrystal are described in the earlier aspects. This multi-faceted invention covers the identification and characterization of various cocrystal systems, as well as its enhanced bio-accessibility applications of various active pharmaceutical ingredients, phytochemicals, vitamins, and minerals.

[0033] These features and advantages of the present disclosure may be appreciated by reviewing the following description of the present disclosure, along with the accompanying figures wherein like reference numerals refer to like parts.

BRIEF DESCRIPTION OF THE DRAWINGS

5 [0034] The accompanying drawings illustrate the embodiments of methods and other aspects of the disclosure. A person with ordinary skills in the art will appreciate that the illustrated element boundaries (e.g., boxes, groups of boxes, or other shapes) in the figures represent an example of the boundaries of such elements. In some examples, one element may be designed as multiple elements, or multiple elements may be designed as one element. In some examples, an element
10 shown as an internal component of one element may be implemented as an external component in another and vice versa. Furthermore, the elements may not be drawn to scale.

[0035] Various embodiments will hereinafter be described in accordance with the appended drawings, which are provided to illustrate, not limit, the scope, wherein similar designations denote similar elements, and in which:

15 [0036] FIG. 1 illustrates a graphical representation of an X-ray Powder Diffraction (XRPD) pattern of quercetin and quercetin dihydrate, in accordance with an embodiment of the present invention.

[0037] FIG. 2 illustrates a graphical representation of the XRPD pattern of hexahydric alcohol, in accordance with an embodiment of the present invention.

20 [0038] FIG. 3 presents the XRPD pattern of quercetin cocrystal-hexahydric alcohol, in accordance with an embodiment of the present invention.

[0039] FIG. 4 illustrates the DSC thermogram of quercetin-hexahydric alcohol cocrystals, revealing their thermal stability and decomposition behavior, in accordance with an embodiment of the present invention.

25 [0040] FIG. 5 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with resveratrol (representative flavonoid category), in accordance with an embodiment of the present invention.

[0041] FIG. 6A illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with lutein (representative carotenoid category), in accordance with an embodiment of the present invention.

5 [0042] FIG. 6B illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with β -carotene (representative carotenoid category), in accordance with an embodiment of the present invention.

[0043] FIG. 6C illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with lycopene (representative carotenoid category), in accordance with an embodiment of the present invention.

10 [0044] FIG. 7 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with nicotine (representative alkaloid category), in accordance with an embodiment of the present invention.

15 [0045] FIG. 8 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with glutathione (representative amino acid derivative category), in accordance with an embodiment of the present invention.

[0046] FIG. 9 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with cannabidiol (representative cannabinoid category), in accordance with an embodiment of the present invention.

20 [0047] FIG. 10 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with β -glucan (representative glucan category), in accordance with an embodiment of the present invention.

[0048] FIG. 11 illustrates a graphical representation of the bioenhancing activity of quercetin-hexahydric alcohol cocrystal in combination with collagen tripeptide (representative peptide category), in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS HEREIN.

[0049] The present disclosure is best understood with reference to the detailed figures and description set forth herein. Various embodiments of the present systems and methods have been discussed with reference to the figures. However, those skilled in the art will readily appreciate that the detailed description provided herein including the figures are presented for explanatory purposes and the embodiments extend beyond the currently described embodiments. For instance, the teachings and results presented in any particular described application may yield multiple alternative approaches and may be implemented in any suitable manner.

[0050] The described embodiments may be implemented manually, automatically, and/or a combination of thereof. The term “method” refers to manners, means, techniques, and procedures for accomplishing any task including, but not limited to, those manners, means, techniques, and procedures either known to the person skilled in the art or readily developed from existing manners, means, techniques and procedures by practitioners of the art to which the embodiments pertains. Persons skilled in the art will envision many other possible variations that are within the scope of the claimed subject matter.

[0051] The present disclosure provides solid-state quercetin as a bioenhancer of active pharmaceutical ingredients, phytochemicals, vitamins, and minerals, and the process of its preparation. The poor bioavailability of quercetin due to its limited solubility and absorption has hindered its full clinical translation. To address this challenge, the current invention discloses the preparation of novel quercetin cocrystals, which can be synthesized through either ball-milling or solvent evaporation processes. Cocrystallization is a well-established technique to improve the physicochemical properties of active pharmaceutical ingredients, including solubility, stability, and dissolution rate. The quercetin-hexahydric alcohol cocrystal was synthesized using a novel kinetic-controlled cocrystallization process. Its physicochemical properties were thoroughly characterized using various analytical techniques. The results demonstrate the successful formation of a new solid-state phase with distinct spectroscopic signatures compared to the individual components. The patentable aspects of the present invention lie in the remarkable bioenhancing activity of this solid-state quercetin. These novel cocrystals have been shown to enhance the bioactivity of a wide range of biomolecules, including cannabinoids, flavonoids, peptides, alkaloids, glucans, carotenoids, and amino acid derivatives. This enhancement in

bioactivity is attributed to the improved absorption and bioavailability of the co-formulated molecules when administered in conjunction with the quercetin cocrystals.

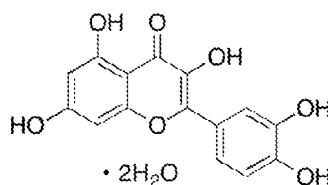
[0052] As a result, the use of quercetin cocrystals can potentially lead to reduced drug and/or nutrient-associated toxicity, decreased cost, and shorter duration of therapeutic interventions.

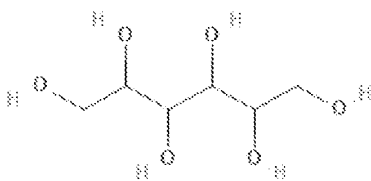
5 Thus, the present invention offers a promising solution to overcome the limitations of quercetin's bioavailability, thereby unlocking its full therapeutic potential. The development of quercetin cocrystals represents a significant advancement in the field of nutraceuticals and pharmaceutical formulations, with the potential to enhance the efficacy of a wide range of bioactive compounds.

[0053] The primary objective of this invention is to identify novel cocrystal formulations of the quercetin combined with hexahydric alcohol. The goal is to develop these quercetin-hexahydric
10 alcohol cocrystals in order to enhance the bioactivity of various active pharmaceutical ingredients, phytochemicals, vitamins, and minerals.

[0054] Another key aim of the invention is to synthesize and optimize the preparation methods for these quercetin cocrystals. Additionally, this work seeks to investigate and demonstrate the improved bioavailability or cellular uptake of active pharmaceutical ingredients, phytochemicals,
15 vitamins, and minerals when they are administered alongside the quercetin-hexahydric alcohol cocrystal formulation.

[0055] The structures of quercetin dihydrate and hexahydric alcohol are shown below:





[0056] A cocrystal is a unique crystalline material that is formed by the combination of two different molecular components - a primary compound and a coformer. When these two components come together, they assemble into a distinct crystallographic structure with specific properties that differ from the individual compounds. The coformer, often referred to as the "guest" molecule, interacts with the primary "host" compound to create this new cocrystalline structure. Unlike typical salts, which have a neutral net charge and balanced ionic species, cocrystals are composed of neutral molecular entities. As a result, the stoichiometric ratio between the compound and coformer in a cocrystal cannot be determined solely by charge balance considerations. The molar ratio of the compound to co-former in a cocrystal can vary and may be greater than, less than, or equal to 1:1. This variable stoichiometry makes the precise molar composition of a cocrystal unpredictable and dependent on the specific molecular interactions. The formation of this unique cocrystalline structure leads to distinct physicochemical properties that can differ from the individual starting materials. This makes cocrystals a valuable tool for modifying and enhancing the characteristics of compounds for various applications.

[0057] Cocrystals possess the ability to modify various physical and chemical properties of compounds. One of the key advantages of cocrystals is their potential to change the solubility and dissolution rate of the primary compound. Research has indicated that the formation of cocrystals can enhance the aqueous solubility and dissolution kinetics of the active compound compared to its standalone form. This can be particularly beneficial for improving the bioavailability of poorly soluble active pharmaceutical ingredients. In addition to solubility enhancement, cocrystals can also provide improvements in other important characteristics. For instance, they have been shown to enhance the stability of compounds under different humidity conditions, preventing unwanted changes or degradation. To achieve these specific property modifications, researchers often experiment with a variety of potential co-former molecules. By selecting the most suitable co-former, they can tailor the cocrystal composition to optimize the desired physical, chemical, or biopharmaceutical properties of the final product. The versatility of cocrystals allows for the

systematic exploration and tuning of compound characteristics, making them a valuable tool for formulation development and drug delivery applications.

- [0058] Cocrystals have emerged as an intriguing field in pharmaceutical research, offering a promising approach to enhance the physicochemical properties of active pharmaceutical ingredients (APIs) without modifying their chemical structure. The preparation of cocrystals involves the assembly of two or more distinct molecular or ionic components into a single crystalline lattice, held together by non-covalent interactions such as hydrogen bonding, π - π stacking, or halogen bonding. One of the primary benefits of forming cocrystals is the ability to enhance the solubility and bioavailability of drugs with poor solubility. By incorporating a second component, known as a coformer, the crystal packing and physicochemical properties of the drug can be modified, resulting in improved dissolution rates and oral absorption. Various strategies have been explored for cocrystal preparation, including solution-based methods like slow evaporation (thermodynamic-controlled), antisolvent addition, and cooling crystallization, as well as solid-state techniques such as grinding, kneading, and hot-melt extrusion.
- [0059] The precise makeup of a cocrystal, including the molar ratio between the co-former and the primary compound (such as an Active Pharmaceutical Ingredient, or API), can be determined using single crystal X-ray diffraction analysis. This analytical technique allows researchers to elucidate the crystallographic structure of the cocrystal and accurately quantify the molar stoichiometry between the co-former and the compound. However, in cases where single-crystal X-ray diffraction analysis may not be readily accessible, an alternative analytical method commonly used is solution-state proton nuclear magnetic resonance (^1H NMR) spectroscopy. ^1H NMR can be employed to confirm the composition of the cocrystal and identify the specific molar ratio between the co-former and the compound. This solution-state NMR approach provides a complementary analytical technique to the structural information obtained from X-ray diffraction. By utilizing these analytical methods, researchers can thoroughly characterize the makeup of a cocrystal, including the precise molar ratio between the co-former and the primary compound. This information is crucial for understanding the structure-property relationships and optimizing the cocrystal formulation for the desired applications.

- [0060] Verifying the formation of a cocrystal requires comparing the solid-state analytical data of the cocrystal product with that of the starting materials. The cocrystal's analytical response is distinct from a mere physical mixture of the initial components. For instance, X-ray powder

diffraction (XRPD) can be used to compare the patterns, as the XRPD pattern of a cocrystal will differ from that of a physical mixture of the starting substances. Single crystal analysis is also useful in confirming the cocrystal's solid-state structure, where the compound and co-formers occupy distinct positions within the crystal lattice unit cell. Furthermore, indexing can be
5 employed to ensure the presence of a single phase in the cocrystal product, rather than a mixture of phases.

[0061] A single crystal structure determination is not always necessary for characterizing a cocrystal. Various solid-state analytical methods can be used for this purpose instead. Techniques like X-ray powder diffraction (XRPD), Raman spectroscopy, infrared spectroscopy, and solid-
10 state ^{13}C NMR spectroscopy can be employed to analyze the crystallographic and spectroscopic properties of cocrystals. Additionally, cocrystals often exhibit unique thermal behavior compared to other forms of the same compound. Techniques such as capillary melting point, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) can be utilized to investigate this thermal behavior. By employing this range of solid-state analytical methods,
15 cocrystals can be identified and thoroughly characterized without relying solely on single crystal structure determination.

[0062] The full X-ray powder diffraction (XRPD) pattern obtained from a diffractometer can be used to characterize a cocrystal. However, a smaller subset of this XRPD data may also suffice for this purpose. For instance, a collection of one or more XRPD peaks can be utilized, and in some
20 cases, even a single XRPD peak can be enough to identify a cocrystal. Similarly, subsets of spectra from other analytical techniques, such as Raman, infrared, or solid-state NMR spectroscopy, can be used alone or in combination with XRPD data to characterize cocrystals. In these characterization examples, along with the XRPD peak data, information about the cocrystal's guest and host components, as well as their respective molar ratio, can also be provided as part of the
25 characterization process. The key point is that a full XRPD pattern is not always necessary, and selective use of XRPD peaks or data from other analytical methods can be effective for cocrystal identification and characterization.

[0063] An X-ray powder diffraction (XRPD) pattern is a graph that displays the diffraction angle (2θ) on the x-axis and the intensity on the y-axis. The peaks observed in the XRPD pattern are
30 crucial for characterizing a cocrystal. Instead of focusing on the peak intensity values on the y-axis, professionals in the pharmaceutical field typically prefer to identify and denote these peaks

based on their position on the x-axis, which represents the diffraction angle. This approach is preferred because the orientation of the sample can influence the peak intensity, making it a less reliable parameter for cocrystal characterization. By focusing on the peak positions ($^{\circ}2\theta$) rather than the peak intensities, the characterization of cocrystals becomes more robust and less susceptible to variations in sample orientation or preparation. This method allows for more reliable and consistent identification and analysis of cocrystal samples.

[0064] X-ray powder diffraction (XRPD) data, like any other measurement data, exhibits some degree of variability. This variability can be observed not only in the fluctuations of peak intensity but also in the positions of the peaks along the x-axis (diffraction angle, $^{\circ}2\theta$). However, for cocrystal characterization, this variability in peak positions can typically be taken into account and accounted for. The variability in peak positions can be attributed to various factors, including: Sample preparation: Even when dealing with the same crystalline material, preparing samples under different conditions (e.g., particle size, moisture content, solvent content, sample orientation) can result in slightly different diffraction patterns. Instrument parameters: Different X-ray diffractometers may operate with varying parameters, leading to minor differences in the obtained diffraction patterns, even when examining the same cocrystal sample. Data processing software: The use of different software packages for processing X-ray data can also contribute to the observed variability in the results. Experts in the pharmaceutical field are well aware of these sources of variability in XRPD data and can address them as part of their expertise in cocrystal characterization. Understanding and accounting for this variability is essential for reliable and consistent identification and analysis of cocrystal samples.

[0065] Due to the various factors that contribute to variability in X-ray powder diffraction (XRPD) data, it is a common practice to use the term "about" when stating the peak positions in degrees 2-theta ($^{\circ}2\theta$). This approach allows for approximating the data within a range, typically 0.1 or 0.2 $^{\circ}2\theta$, depending on the specific circumstances. In the context of this document, all XRPD peak positions mentioned are reported with a variability of approximately 0.2 $^{\circ}2\theta$. This level of variability is consistently applied throughout the document, whether the term "about" is explicitly used or not. This use of the "about" qualifier and the 0.2 $^{\circ}2\theta$ variability range acknowledges the inherent uncertainty and potential fluctuations in XRPD peak positions due to factors such as sample preparation, instrument parameters, and data processing methods. By accounting for this variability, the XRPD data can be more accurately and appropriately interpreted and used for cocrystal characterization.

[0066] Thermal analysis techniques are commonly used to characterize cocrystals. Cocrystals of the same compound often exhibit distinct melting temperatures, which can aid in their identification. Thermal measurement techniques, such as Differential Scanning Calorimetry (DSC), can also provide insights into the purity of cocrystal samples. To thoroughly characterize cocrystals, various thermal analysis methods can be employed, including melting point determination, DSC, and hot-stage microscopy. These thermal techniques can be used either alone or in combination with other analytical methods, such as X-ray powder diffraction (XRPD), Raman spectroscopy, and infrared spectroscopy. By utilizing a combination of these thermal and other analytical approaches, cocrystals can be effectively identified and analyzed. The distinct melting temperatures observed in thermal analysis, along with complementary data from techniques like XRPD and spectroscopy, provide a comprehensive characterization of cocrystal samples. This multi-pronged approach, employing both thermal and other analytical methods, allows for a thorough understanding and characterization of the physical and chemical properties of cocrystals, enabling their accurate identification and analysis.

[0067] Similar to other analytical techniques, the results of melting point analyses can exhibit some degree of variability. In addition to potential instrumental variability, other factors may contribute to the observed fluctuations in melting point measurements. The observed melting point of a cocrystal sample may be influenced by the presence of other cocrystals or contaminants in the sample. These competing or colliding properties within the sample can affect the measured melting point. To ensure precise and reliable findings, melting point determinations must account for these sources of variability. Factors such as sample purity, the presence of multiple cocrystal forms, and instrumental limitations need to be carefully considered when interpreting melting point data. By acknowledging and addressing these potential sources of variability, researchers and analysts can obtain more accurate and dependable melting point information for the effective characterization of cocrystal samples.

[0068] In one embodiment of the present invention, a cocrystal of quercetin dihydrate to hexahydric alcohol (either in straight-chain or cyclic structures) in a molar (or molar) ratio of 1:1 and 2:1 is disclosed. The structure of the cocrystal is outlined in FIG. 3.

[0069] The XRPD pattern corresponding to the quercetin dihydrate starting material used herein is in FIG. 1. FIG. 1 illustrates a graphical representation 100 of an X-ray Powder Diffraction

(XRPD) pattern of quercetin and quercetin dihydrate, in accordance with an embodiment of the present invention.

[0070] The pattern displays diffraction peaks characteristic of both forms. On the x-axis, the 2-theta (2θ) values represent the angles at which the X-rays are diffracted by the crystal lattice, while the y-axis denotes the intensity of the diffracted X-rays, indicative of the presence and concentration of certain crystal planes in the sample. The positions of the peaks correspond to specific interplanar distances in the crystal lattice, with each crystalline form exhibiting a unique set of peaks. Specific peaks in the pattern are attributed to the anhydrous form of quercetin, whereas other peaks are indicative of quercetin dihydrate, which includes water molecules in its crystal structure. Quercetin dihydrate is a crystalline form of quercetin that incorporates two water molecules per quercetin molecule, resulting in unique diffraction peaks distinct from the anhydrous form.

[0071] The database reference for quercetin indicates major peaks at 10.6° , 12.3° , 15.8° , 24.5° , and 27.9° 2θ , which correspond to its crystalline structure. These peaks serve as benchmarks for identifying quercetin in the sample. In contrast, quercetin dihydrate, due to the incorporation of water molecules, will exhibit distinct peaks, differentiating it from the anhydrous form. By comparing this XRPD pattern with reference patterns, including these specific peak positions for quercetin, the presence, and purity of quercetin and quercetin dihydrate in the sample can be confirmed, offering insights into the crystalline nature and stability of these compounds.

[0072] The XRPD pattern of hexahydric alcohol starting material is in FIG. 2. FIG. 2 illustrates a graphical representation 200 of the XRPD pattern of hexahydric alcohol, in accordance with an embodiment of the present invention.

[0073] Its XRPD pattern shows characteristic peaks that help identify and confirm its crystalline structure. The major peaks in the sorbitol XRPD pattern, as referenced in the database. These peaks correspond to the specific interplanar distances in the sorbitol crystal lattice. By comparing the XRPD pattern of the sample with these reference peaks, the presence and purity of sorbitol can be confirmed, offering insights into its crystalline nature and stability.

[0074] By comparing the XRPD patterns with reference patterns, including specific peak positions for quercetin, quercetin dihydrate, and sorbitol, the presence and purity of these

compounds in the samples can be confirmed, offering valuable insights into their crystalline nature and stability.

[0075] The XRPD pattern for the resulting cocrystal is in FIG. 3. FIG. 3 presents the XRPD pattern 300 of quercetin cocrystal, in accordance with an embodiment of the present invention.

5 When preparing quercetin cocrystals, the XRPD pattern shown reflects the crystalline structure of the resulting compound. The pattern displays distinct peaks at specific 2-theta (2θ) values, indicating the formation of quercetin cocrystals. The sharp, well-defined peaks suggest a high degree of crystallinity. These peaks can be compared to reference patterns of quercetin and its cocrystals to confirm the successful formation of the desired cocrystalline structure. This
10 comparison helps in identifying the unique crystal forms and verifying the purity of the cocrystals.

[0076] Quercetin cocrystals may be characterized by their thermal characteristics. For example, FIG. 4 is a DSC thermogram of quercetin cocrystals and it exhibits an endotherm at about 155° C. under the conditions set forth herein for DSC for the thermogram in FIG. 4. Quercetin cocrystals may be characterized by DSC alone or in combination with XRPD diffraction
15 pattern or one or more of the peaks set forth herein. FIG. 4 illustrates the DSC thermogram 400 of quercetin cocrystals, revealing their thermal stability and decomposition behavior, in accordance with an embodiment of the present invention. The thermogram shows an onset temperature of 313.25 °C, indicating the beginning of decomposition. The peak temperature, where the maximum rate of weight loss occurs, is 338.58 °C, followed by an endset temperature of 345.74 °C, marking
20 the end of the decomposition process. There are two significant weight loss events: a minor loss of 0.142 mg (2.868%) and a major loss of 4.478 mg (90.428%), suggesting initial moisture loss followed by substantial decomposition of the quercetin cocrystals. This analysis is crucial for understanding the thermal properties and potential applications of cocrystals in various industries.

[0077] This invention also relates to pharmaceutical compositions containing cocrystals of the
25 present invention. These compositions can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof including, treatment of other inflammation conditions. A patient, for this invention, is a mammal, including a human, in need of treatment for a particular condition or disease including, but not limited to, other inflammation conditions. Therefore, the present invention includes pharmaceutical compositions which are comprised of at
30 least one pharmaceutically acceptable carrier and a cocrystal of the present invention. A pharmaceutically acceptable carrier is any carrier that is relatively non-toxic and innocuous to a

patient at concentrations consistent with the effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compound of the cocrystals of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow, and timed-release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

[0078] With the kinetic-controlled cocrystallization of quercetin-hexahydric alcohol cocrystal in this invention, the diffusion coefficient of quercetin dihydrate in ethanol is $5 \times 10^{-10} \text{ m}^2/\text{s}$ and hexahydric alcohol is $8 \times 10^{-10} \text{ m}^2/\text{s}$. The nucleation rate (J) using the classical nucleation theory equation, $J = A \times \exp(-B / (\ln S)^2)$ where A and B are system-dependent constants ($A = 10^9$ and $B = 100$, then $J \approx 10^5 \text{ nuclei/m}^3 \cdot \text{s}$). The growth rate (G) assuming a diffusion-limited growth regime, $G = k \times (C - C^*) / C^*$ where k is the mass transfer coefficient, C is the bulk concentration, and C^* is the equilibrium concentration assuming $k \approx 10^{-5} \text{ m/s}$, $C \approx 10C^*$, then $G \approx 10^{-4} \text{ m/s}$. The overall kinetic constant (k) of quercetin-hexahydric alcohol cocrystal combining the nucleation and growth rates is $k = J \times G^3 \approx 10^{-15} \text{ m}^3/\text{s}$.

[0079] The equilibrium constant (Kd) for the dissolution of quercetin-hexahydric alcohol cocrystal represents the ratio of the dissolved species concentrations at equilibrium. A higher Kd value indicates greater solubility and dissolution of the quercetin-hexahydric alcohol cocrystal under the experimental conditions (ethanol-water mixture, pH = 6 – 7, temperature = 40 – 50 °C and stirring speed = 600 – 800 rpm). [quercetin] eq is 1.414 mol/L and [hexahydric alcohol]eq is 1.414 mol/L, then the equilibrium constant (Kd) is calculated as $Kd = [\text{quercetin}]_{\text{eq}} \times [\text{hexahydric alcohol}]_{\text{eq}}$. Therefore, the equilibrium constant (Kd) of quercetin-hexahydric alcohol cocrystal is 2 mol/L.

[0080] EXAMPLES

[0081] All chemicals were obtained from commercial sources and used without further purification.

[0082] XRPD patterns were collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu radiation produced using an Optix long, fine-focus source. An elliptically

graded multilayer mirror was used to focus Cu K α X-rays through the specimen and onto the detector. Before the analysis, a silicon specimen (NIST SRM 640d) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3- μ m-thick films and analyzed in transmission geometry. A beam-stop, short antiscatter extension, and antiscatter knife edge, were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 2.2b.

- 10 [0083] DSC analyses were performed using a TA Instruments 2920 and Q2000 differential scanning calorimeter. Temperature calibration was performed using NIST-traceable indium metal. Samples were placed into an aluminum DSC pan, covered with a lid (T0C—Tzero crimped), and the weight was accurately recorded. A weighed aluminum pan configured as the sample pan was placed on the reference side of the cell. The data acquisition parameters and pan configuration for each thermogram are displayed on images. The method code on the thermogram for each
- 15 corresponding Figure is an abbreviation for the start and end temperature as well as the heating rate; e.g., -30-250-10 means “from -30 °C. to 250 °C., at 10 °C./min”.

[0084] **Comparative Example 1: Quercetin Cocrystals Preparation 1**

- [0085] Solids of quercetin and hexahydric alcohol were added to MEK, with an excess of quercetin dihydrate, such that undissolved solids remained. The mixture was allowed to stir at ambient temperature for two days, resulting in an opaque white suspension. Solids were collected by vacuum filtration and washed with MEK on the filter.
- 20

[0086] **Comparative Example 2: Quercetin Cocrystals Preparation 2**

- [0087] Weighed amounts of quercetin dihydrate (45.0 mg) and hexahydric alcohol (27.12 mg) were added to a clean vial in a 1:1 molar ratio. Ethanol (30 mL) was added with sonication, resulting in a clear solution (this could be assisted with hexahydric alcohol to accelerate the solubility). The solution was uncapped and covered with perforated aluminum foil for slow evaporation at ambient conditions. After approximately 6 weeks, the sample contained solids with a small amount of solvent remaining. The solids were collected by vacuum filtration, resulting in
- 25
- 30 off-white, rectangular, and irregular plates exhibiting birefringence.

[0088] Example 1: Quercetin Cocrystals Preparation 3

[0089] The procedure for the kinetically controlled quercetin-hexahydric alcohol cocrystal formation involves first preparing a saturated solution of quercetin and sorbitol in a suitable solvent, such as ethanol, methanol, or a mixture of solvents, with a molar ratio of 1:1 for the two components. The solution is then heated to a temperature that ensures complete dissolution of the starting materials, typically between 40 – 50 °C. The key step is the rapid cooling of the solution, which is typically achieved by immersing the reaction vessel in an ice bath, leading to a cooling rate of around 10 – 20 °C/min. This rapid cooling induces rapid supersaturation and promotes the nucleation and growth of the desired quercetin-hexahydric alcohol cocrystal phase rather than the individual starting material crystals. The cocrystal slurry is allowed to stir or age for a short period, typically 10 – 30 minutes, to ensure complete cocrystal formation. Finally, the cocrystal product is collected by vacuum filtration or centrifugation, washed with a small amount of cold solvent, and dried under vacuum or in a desiccator to obtain the final product. This kinetically controlled approach typically results in smaller, more homogeneous cocrystal particles compared to other slower crystallization techniques.

[0090] In Comparative Examples 1 – 2 and Example 1, the final average crystal size was calculated using the provided data and the following equation:

$$L = k \left(\frac{C_0 - C_s}{G} \right)^{\frac{1}{n}}$$

[0091] Where:

- L represents the average crystal size
- C_0 represents the Initial Concentration
- C_s represents the Solubility Concentration
- G represents the Growth Rate
- n represents the Exponent
- k represents the Proportionality Constant

[0092] The conditions and corresponding crystal sizes for each cocrystallization process are tabulated below:

Sample	Cocrystallization Condition	Crystal size (um)
Comparative Example 2	Slow cocrystallization	812.5
Comparative Example 1	Fast cocrystallization	78.3
Example 1	Superfast cocrystallization	8.3

[0093] These calculated values illustrate the impact of the cocrystallization rate on the final crystal size, with slower cocrystallization producing significantly larger crystals compared to faster cocrystallization processes.

[0094] The relationship between particle size and bioavailability can be modeled using several equations from pharmaceutical sciences. In Comparative Examples 1 – 2 and Examples 1, the dissolution rate of the particles was calculated using the provided data and the Noyes-Whitney equation. This calculation helps illustrate how the particle size influences the dissolution rate, which in turn affects bioavailability and bioenhancing activity.

[0095] Noyes-Whitney Equation:

$$\frac{dC}{dt} = \frac{D \cdot A \cdot (C_s - C)}{h}$$

[0096] *Where:*

$\frac{dc}{dt}$ represents the dissolution rate

5 D denotes the diffusion coefficient

A denotes the surface area of the particle

C_s denotes the saturation solubility

C denotes the concentration of the solute in the bulk solution at time t

h is the thickness of the diffusion layer

10

$$A = 4\pi R^2$$

[0097] *Where:*

A denotes the surface area of the particle

R denotes the crystal sizes of the particle

Sample	Cocrystallization Condition	Crystal size (μm)	Diffusion Rate (mol/m ³ .s)
Comparative Example 2	Slow cocrystallization	812.5	2.073×10 ⁻¹⁰
Comparative Example 1	Fast cocrystallization	78.3	1.926×10 ⁻¹²
Example 1	Superfast cocrystallization	8.3	2.163×10 ⁻¹⁴

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[0098] The crystals formed by superfast cocrystallization have the smallest particle size (8.3 μm), resulting in the highest surface area and fastest dissolution rate. This leads to the highest potential bioavailability as the quercetin-sorbitol particles can dissolve quickly, allowing for more efficient absorption in the gastrointestinal tract.

[0099] To compare the yield of quercetin cocrystals across different preparations (Comparative Examples 1 – 2 and Example 3). Yield is calculated as the ratio of the mass of quercetin dihydrate in cocrystals obtained to the initial mass of the starting material (quercetin dihydrate), expressed as a percentage.

$$Yield (\%) = \left(\frac{\text{Mass of quercetin dihydrate in crystal obtained}}{\text{Mass of starting quercetin dihydrate}} \right) \cdot 100$$

Sample	Yield (%)
Comparative Example 1	62.8 ± 2.2
Comparative Example 2	71.1 ± 3.4
Example 1	84.2 ± 2.9

[00100] The yield analysis of quercetin-hexahydric alcohol cocrystals across different preparation methods indicates that Example 1 is the most efficient method, achieving a yield of 84.2%. This yield is significantly higher than the 71.1% yield observed in Comparative Example 1 and the 62.8% yield in Comparative Example 2. Example 1's superior yield can be attributed to the rapid cooling and kinetic control techniques employed in this method, which enhance the efficiency of the cocrystallization process and result in a higher conversion rate of quercetin dihydrate into the desired cocrystals. This substantial difference in yield underscores the effectiveness of the kinetic-controlled approach in maximizing the production of high-quality quercetin cocrystals compared to the slower, less efficient methods used in Comparative Examples 1 and 2.

[00101] Investigation of the effect of Comparative Examples 1 – 2 and Example 1 on Ascorbic acid permeability across human intestinal epithelial cells (Caco-2 cell line). The transport across the Caco-2 cell line was determined using a modified method based on Joshi G, et al [1]. Caco-2 cells at passage 10 – 20 were cultured in Transwell inserts (0.4 µm pore diameter, 1.13 cm² area) and used for transport experiments 14 – 21 days post-seeding. Before the experiment, the inserts were washed twice and equilibrated for 30 minutes with a pre-warmed transport medium (HBSS buffer containing 25 mM HEPES, pH 7.4).

[00102] The integrity of the monolayers was verified by monitoring the permeability of the paracellular leakage marker, Lucifer Yellow. Monolayers were deemed tight enough for transport

experiments when the apparent permeability coefficient (P_{app}) for lucifer yellow was less than 0.5×10^{-6} cm/s. All transport studies were conducted at 37 °C.

[00103] The transport buffer containing test compounds was added to the apical side (0.5 ml), while the basolateral side of the inserts contained 1.5 ml of transport buffer. After 6 hours of incubation, the concentrations of the test compounds in the transport medium were diluted with acetonitrile (for dissolved pigment) and analyzed immediately using a spectrophotometer at OD 453 nm.

[00104] The apical-to-basolateral permeability coefficient (P_{app}) was calculated using the equation:

$$P_{app} = \frac{dQ/dt}{A \cdot C_0 \cdot 60}$$

[00105] *Where:*

dQ/dt is the amount of compound in the basolateral compartment as a function of time (mg/min)

A is the monolayer area (1.13 cm²)

15 C_0 is the initial concentration of compounds in the apical compartment (0.4 mg/ml)

[00106] After 6 hours of incubation, the transport studies yielded the following data:

Sample	P_{app} (μg/sec)*
Ascorbic acid	$1.29 \times 10^{-5} \pm 3.85 \times 10^{-7}$
Ascorbic acid + Quercetin dihydrate	$1.39 \times 10^{-5} \pm 4.16 \times 10^{-7}$
Ascorbic acid + Comparative Example 1	$1.45 \times 10^{-5} \pm 4.35 \times 10^{-7}$
Ascorbic acid + Comparative Example 2	$1.58 \times 10^{-5} \pm 5.19 \times 10^{-7}$
Ascorbic acid + Comparative Example 3	$2.07 \times 10^{-5} \pm 6.37 \times 10^{-7}$

[00107] The transport study across Caco-2 cells demonstrated that combining Ascorbic acid with various forms of quercetin significantly enhances its permeability. Ascorbic acid alone showed the lowest permeability. Adding Quercetin dihydrate provided a moderate improvement. Greater enhancements were observed with quercetin cocrystals prepared by different methods, with the most significant improvement achieved using the kinetic-controlled cocrystallization process in

Example 3. This method markedly increased the permeability and transport of Ascorbic acid, suggesting significantly improved potential bioavailability compared to other forms. These findings support the superior performance and bioenhancing activity of the quercetin cocrystals prepared by the kinetic-controlled method.

5 [00108] To compare the stability of quercetin cocrystals prepared by different methods, we conducted a series of tests. The initial concentration of quercetin (C_0) in each sample was measured using high-performance liquid chromatography. These samples were then stored at accelerated conditions (40 °C and 75% relative humidity). At specific time intervals (1 week, 2 weeks, and 4 weeks), the concentration of quercetin (C_t) in each sample was measured using HPLC. The
10 percentage degradation of quercetin over time was calculated using the formula:

$$Degradation(\%) = \left(\frac{C_0 - C_t}{C_0} \right) \cdot 100$$

[00109] Where:

C_0 is the initial concentration of quercetin dihydrate

C_t is the concentration of quercetin dihydrate at time t

15 [00110] The results are summarized in the table below:

Sample	Initial Concentration (C_0)	Concentration after 1 week (C_1)	Degradation after 1 week	Concentration after 2 weeks (C_2)	Degradation after 2 weeks	Concentration after 4 weeks (C_4)	Degradation after 4 weeks
Comparative Example 1	100%	94.5%	5.5%	89.8%	10.2%	84.7%	15.3%
Comparative Example 2	100%	96.8%	3.2%	94.7%	5.3%	92.1%	7.9%
Example 1	100%	99.9%	0.1%	99.9%	0.1%	99.8%	0.1%

[00111] Example 1 demonstrated excellent stability, with no significant degradation observed after 4 weeks. This indicates that the cocrystals formed using the rapid cooling method are more stable under accelerated conditions compared to those obtained from Comparative Example 1 and
20 Comparative Example 2.

[00112] FIG. 5 illustrates a graphical representation 500 of the bioenhancing activity of quercetin cocrystal in combination with resveratrol (representative flavonoid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of resveratrol alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and

10%). The data reveals that the addition of quercetin cocrystal significantly enhances the permeability of resveratrol. As the concentration of quercetin cocrystal increases, the permeability of resveratrol also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of resveratrol when combined with quercetin cocrystal.

[00113] FIG. 6A illustrates a graphical representation 600A of the bioenhancing activity of quercetin cocrystal in combination with lutein (representative carotenoid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of lutein alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of lutein. As the concentration of quercetin cocrystal increases, the permeability of lutein also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of lutein when combined with quercetin cocrystal.

[00114] FIG. 6B illustrates a graphical representation 600B of the bioenhancing activity of quercetin cocrystal in combination with β -carotene (representative carotenoid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of β -Carotene alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data reveals that the addition of quercetin cocrystal significantly enhances the permeability of β -Carotene. As the concentration of quercetin cocrystal increases, the permeability of β -Carotene also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of β -Carotene when combined with quercetin cocrystal.

[00115] FIG. 6C illustrates a graphical representation 600C of the bioenhancing activity of quercetin cocrystal in combination with lycopene (representative carotenoid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of lycopene alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of lycopene. As the concentration of quercetin cocrystal increases, the permeability of lycopene also increases, with the highest enhancement observed at

10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of lycopene when combined with quercetin cocrystal.

[00116] FIG. 7 illustrates a graphical representation 700 of the bioenhancing activity of quercetin cocrystal in combination with nicotine (representative alkaloid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of nicotine alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of nicotine. As the concentration of quercetin cocrystal increases, the permeability of nicotine also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of nicotine when combined with quercetin cocrystal.

[00117] FIG. 8 illustrates a graphical representation 800 of the bioenhancing activity of quercetin cocrystal in combination with glutathione (representative amino acid derivative category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of glutathione alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of glutathione. As the concentration of quercetin cocrystal increases, the permeability of glutathione also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of glutathione when combined with quercetin cocrystal.

[00118] FIG. 9 illustrates a graphical representation 900 of the bioenhancing activity of quercetin cocrystal in combination with cannabidiol (representative cannabinoid category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of CBD alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of CBD. As the concentration of quercetin cocrystal increases, the permeability of CBD also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of CBD when combined with quercetin cocrystal.

[00119] FIG. 10 illustrates a graphical representation 1000 of the bioenhancing activity of quercetin cocrystal in combination with β -glucan (representative glucan category), in accordance

with an embodiment of the present invention. The graph shows the percent permeability of β -glucan alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of β -glucan. As the concentration of quercetin cocrystal increases, the permeability of β -glucan also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of β -glucan when combined with quercetin cocrystal.

[00120] FIG. 11 illustrates a graphical representation 1100 of the bioenhancing activity of quercetin cocrystal in combination with collagen tripeptide (representative peptide category), in accordance with an embodiment of the present invention. The graph shows the percent permeability of collagen tripeptide alone and in combination with varying concentrations of quercetin cocrystal (1%, 2%, 5%, and 10%). The data indicates that the addition of quercetin cocrystal significantly enhances the permeability of collagen tripeptide. As the concentration of quercetin cocrystal increases, the permeability of collagen tripeptide also increases, with the highest enhancement observed at 10% quercetin cocrystal. These results suggest a significant improvement in the bioavailability of collagen tripeptide when combined with quercetin cocrystal.

[00121] According to embodiments illustrated herein, there is provided a process for preparing a quercetin-hexahydric alcohol cocrystal as a bioenhancer for bioactive compounds. The process includes a step of forming the cocrystal from a quercetin and a hexahydric alcohol by a kinetic-controlled cocrystallization process. In an implementation, the kinetic-controlled cocrystallization process involves the swift removal of the solvent containing both quercetin and hexahydric alcohol under controlled temperature and humidity conditions. The technique leverages accelerated evaporation rates to induce quick nucleation and crystallization, resulting in high-quality cocrystals. Swift solvent removal creates a high degree of supersaturation, driving the molecules to arrange quickly into a stable crystalline lattice. This method is advantageous for its time efficiency, potential to form metastable polymorphs with enhanced properties, and scalability for industrial applications, making it particularly valuable in pharmaceutical development. The kinetic-controlled cocrystallization process differs from the normal process primarily due to its emphasis on accelerated kinetics and precise environmental control. In the traditional process, solvent evaporation occurs at a slower, more natural pace, often without stringent control over temperature and humidity, which can result in less uniform nucleation and potentially lower-quality crystals. In contrast, the kinetic-controlled method employs swift solvent removal to

achieve high supersaturation levels quickly, driving rapid nucleation and crystallization. This rapid kinetics fosters the formation of high-quality, defect-free cocrystals by reducing the time for molecules to move freely and potentially form unwanted phases or amorphous materials. Additionally, the controlled environment ensures reproducibility and consistency in the crystal formation, enhancing the purity and desired properties of the cocrystals. This method is particularly useful in pharmaceuticals for its efficiency and ability to produce cocrystals with enhanced solubility and bioavailability.

[00122] In an embodiment, the kinetic-controlled cocrystallization process includes a step of forming the cocrystal by cooling a solution at a cooling rate of 10 – 20 °C/min. In an aspect, the solution contains the quercetin and the hexahydric alcohol and has the temperature before said cooling in the range of 40 – 70 °C. In an embodiment, the kinetic-controlled cocrystallization process further comprises a step of aging the cocrystal. In an embodiment, the solution comprises a solvent that is selected from the group consisting of methanol, ethanol, and a combination thereof. In an embodiment, the quercetin is preferably a quercetin dihydrate. In an embodiment, a diffusion coefficient of the quercetin dihydrate in the solvent is preferably at 5×10^{-10} m²/s. In an embodiment, the hexahydric alcohol is selected from the group consisting of a straight-chain hexahydric alcohol and a cyclic hexahydric alcohol. In an embodiment, the hexahydric alcohol is preferably sorbitol. In an embodiment, a diffusion coefficient of the hexahydric alcohol in the solvent is preferably at 8×10^{-10} m²/s. In an embodiment, the molar ratio of the quercetin to the hexahydric alcohol in the solution is in the range of 1:1. In an embodiment, the kinetic-controlled cocrystallization process has a kinetic constant (k) in the range of 1×10^{-16} – 1×10^{-14} m³/s. In an embodiment, the kinetic-controlled cocrystallization process has the kinetic constant (k) preferably at 10^{-15} m³/s. In an embodiment, the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.

[00123] According to embodiments illustrated herein, there is provided a quercetin-hexahydric alcohol cocrystal as a bioenhancer for a bioactive compound. The cocrystal has a molar ratio of a quercetin to a hexahydric alcohol that is in the range of 1:1. In an embodiment, the quercetin-hexahydric alcohol cocrystal characterized by at least one of the following XRPD peaks: 10.7, 12.4, 13.8, 13.9, 14.7, 16.2, 16.4, 17.7, 18.0, 19.3, 21.6, 23.8, 25.9, 27.2, 28.7, 29.8, 33.5, 35.8, 36.6, and $37.0 \pm$ degree 2-theta [Cu K α radiation ($\lambda = 1.5406$ Å)]. In an embodiment, the cocrystal preferably exhibits a thermal gravimetric in the range of 338.58 – 342.2 °C. In an embodiment,

the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.

5 [00124] According to embodiments illustrated herein, there is provided a pharmaceutical composition includes the quercetin-hexahydric alcohol cocrystal and at least one pharmaceutically acceptable carrier. In an embodiment, the pharmaceutical composition may be used in enhancing cell permeability and bioavailability of the bioactive compound. In an embodiment, the pharmaceutical composition may be used in the treatment of inflammation.

10 [00125] According to an embodiment herein, the present invention provides a method of preparing the quercetin-hexahydric alcohol cocrystal composition. The method includes a step of combining quercetin and the hexahydric alcohol in a solvent system comprising an ethanol-water mixture. The method includes a step of controlling the pH of the solvent system to a range of 6 – 7. The method includes a step of maintaining the temperature of the solvent system at 40 – 50 °C. The method includes a step of stirring the solvent system at a speed of 600 – 800 rpm. The method
15 includes a step of allowing the system to reach equilibrium, whereby the equilibrium constant (Kd) of the quercetin-hexahydric alcohol cocrystal is within the range of 1.55 – 2 mol/L.

[00126] According to another embodiment herein, the present invention provides a method for the kinetically controlled formation of a quercetin-hexahydric alcohol cocrystal. The method includes a step of preparing a saturated solution of quercetin and a hexahydric alcohol in a suitable
20 solvent. The molar ratio of quercetin to hexahydric alcohol is 1:1. The method includes a step of heating the solution to a temperature between 40 – 50 °C to ensure complete dissolution of the starting materials. The method includes a step of rapidly cooling the solution, such as by immersing the reaction vessel in an ice bath, to achieve a cooling rate of 10 – 20 °C/min, thereby inducing rapid supersaturation and promoting the nucleation and growth of the quercetin-hexahydric alcohol cocrystal. The method includes a step of allowing the cocrystal slurry to stir
25 or age for 10 – 30 minutes to ensure complete cocrystal formation. The method includes a step of collecting the cocrystal product by vacuum filtration or centrifugation, washing the solid with a small amount of cold solvent, and drying the product under vacuum or in a desiccator. In an embodiment, the suitable solvent is ethanol, methanol, or a mixture thereof.

30 [00127] According to another embodiment herein, the present invention provides a method for the kinetically controlled formation of a quercetin-hexahydric alcohol cocrystal. The method

includes a step of preparing a saturated solution of quercetin and a hexahydric alcohol in a suitable solvent. The molar ratio of quercetin to hexahydric alcohol is 1:1. The method includes a step of heating the solution to a temperature between 50 – 70 °C to ensure complete dissolution of the starting materials. The method includes a step of rapidly cooling the solution, such as by
5 immersing the reaction vessel in an ice bath, to achieve a cooling rate of 10 – 20 °C/min, thereby inducing rapid supersaturation and promoting the nucleation and growth of the quercetin-hexahydric alcohol cocrystal. The method includes a step of allowing the cocrystal slurry to stir or age for 10 – 30 minutes to ensure complete cocrystal formation. The method includes a step of collecting the cocrystal product by vacuum filtration or centrifugation, washing the solid with a
10 small amount of cold solvent, and drying the product under vacuum or in a desiccator. In an embodiment, the suitable solvent is ethanol, methanol, or a mixture thereof. In an embodiment, the diffusion coefficient of quercetin dihydrate in ethanol is 5×10^{-10} m²/s and the diffusion coefficient of the hexahydric alcohol is 8×10^{-10} m²/s. In an embodiment, the nucleation rate (J) is approximately 10⁵ nuclei/m³·s, and the growth rate (G) is approximately 10⁻⁴ m/s, resulting in an
15 overall kinetic constant (k) of the quercetin-hexahydric alcohol cocrystal formation of approximately 10⁻¹⁵ m³/s.

[00128] A person skilled in the art will understand that the quercetin-hexahydric alcohol cocrystal and the method to produce thereof are described herein for illustrative purposes and should not be construed to limit the scope of the disclosure.

20 [00129] A person with ordinary skills in art will appreciate that the methods have been illustrated and explained to serve as examples and should not be considered limiting in any manner. It will be further appreciated that the variants of the above-disclosed system elements, modules, and other features and functions, or alternatives thereof, may be combined to create other different apparatuses, systems, or applications.

25 [00130] While the present disclosure has been described with reference to certain embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the present disclosure. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the present disclosure without departing from its scope. Therefore, it is intended that the present disclosure
30 not be limited to the particular embodiment disclosed, but that the present disclosure will include all embodiments falling within the scope of the appended claims.

CLAIMS

1. A process for preparing a quercetin-hexahydric alcohol cocrystal as a bioenhancer for bioactive compounds, the process comprising a formation of the cocrystal from a quercetin and a hexahydric alcohol by a kinetic-controlled cocrystallization process.
5
2. The process according to claim 1, wherein the kinetic-controlled cocrystallization process comprises forming the cocrystal by cooling a solution at a cooling rate of 10 – 20 °C/min, said solution containing the quercetin and the hexahydric alcohol and having the temperature before said cooling in the range of 40 – 70 °C
10
3. The process according to claim 2, further comprises a step of aging the cocrystal.
4. The process according to claim 2, wherein the solution comprises a solvent that is selected from the group consisting of methanol, ethanol, and a combination thereof.
15
5. The process according to claim 4, wherein the quercetin is preferably a quercetin dihydrate.
6. The process according to claim 5, wherein a diffusion coefficient of the quercetin dihydrate in the solvent is preferably at 5×10^{-10} m²/s.
20
7. The process according to claim 2, wherein the hexahydric alcohol is selected from the group consisting of a straight-chain hexahydric alcohol and a cyclic hexahydric alcohol.
8. The process according to claim 4, wherein the hexahydric alcohol is preferably sorbitol.
25
9. The process according to claim 8, wherein a diffusion coefficient of the hexahydric alcohol in the solvent is preferably at 8×10^{-10} m²/s.
10. The process according to claim 2, wherein a molar ratio of the quercetin to the hexahydric alcohol in the solution is in the range of 1:1.
30
11. The process according to claim 10, wherein the kinetic-controlled cocrystallization process has a kinetic constant (k) in the range of 1×10^{-16} – 1×10^{-14} m³/s.

12. The process according to claim 11, wherein the kinetic-controlled cocrystallization process has the kinetic constant (k) preferably at 10^{-15} m³/s.
- 5 13. The process according to claim 1, wherein the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.
- 10 14. A quercetin-hexahydric alcohol cocrystal as a bioenhancer for a bioactive compound, said cocrystal has a molar ratio of a quercetin to a hexahydric alcohol that is in the range of 1:1.
- 15 15. The quercetin-hexahydric alcohol cocrystal according to claim 14, characterized by at least one of the following XRPD peaks: 10.7, 12.4, 13.8, 13.9, 14.7, 16.2, 16.4, 17.7, 18.0, 19.3, 21.6, 23.8, 25.9, 27.2, 28.7, 29.8, 33.5, 35.8, 36.6, and $37.0 \pm$ degree 2-theta [Cu K α radiation ($\lambda = 1.5406$ Å)].
16. The quercetin-hexahydric alcohol cocrystal according to claim 15, said cocrystal preferably exhibits a thermal gravimetric in the range of 338.58 – 342.2 °C.
- 20 17. The quercetin-hexahydric alcohol cocrystal according to claim 16, wherein the bioactive compound is selected from the group consisting of an active pharmaceutical ingredient, a vitamin, a natural bioactive, a phytochemical, a mineral, and any combination thereof.
- 25 18. A pharmaceutical composition comprising the quercetin-hexahydric alcohol cocrystal according to claim 15 and at least one pharmaceutically acceptable carrier.
19. The pharmaceutical composition according to claim 18 for use in enhancing cell permeability and bioavailability of the bioactive compound.
- 30 20. The pharmaceutical composition according to claim 18 for use in the treatment of inflammation.