SBIA-DMF Drug Substance Workshop

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Co-Crystal Active Pharmaceutical Ingredient: Recommended Documentation

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BACKGROUND

Pharmaceutical co-crystals, a subject of long known but little studied class of compounds, represent an emerging class of crystal forms in the context of pharmaceutical science. They can significantly diversify the number of crystal forms that exist for a particular active pharmaceutical ingredient and lead to improvements in physical properties of clinical relevance.

PURPOSE

A co-crystal with a pharmaceutically acceptable coformer that meets the conditions listed in FDA 2018 Guidance can be considered to have a regulatory classification similar to that of a polymorph of the API. When an API is weak base and conformer is weak acid, scientific evidence has to be shown to differentiate between the co-crystal and the salt.

METHOD(S)

1. Single X-ray to show that both API and coformer are present in the unit cell.
2. Measure pK_a of base and acid.
3. Provide orthogonal evidence to support the conclusion.

RESULT(S) AS SHOWN IN IBRUTINIB HEMI-FUMARIC ACID

1. Both API and coformer are present in the unit cell **via a Ibrutinib homodimer with a fumaric acid (WO201615612A1)**

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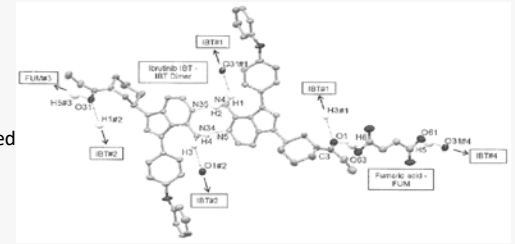
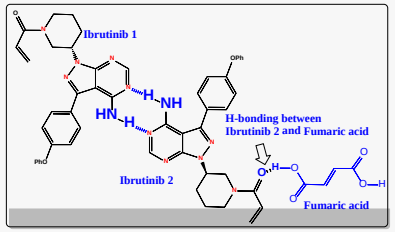




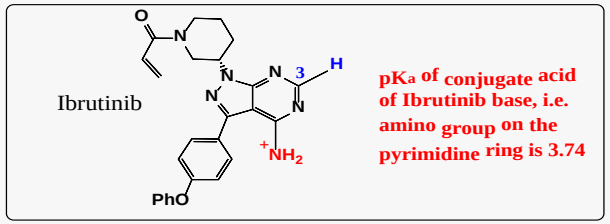
2. If API and its coformer meet ΔpK_a (pK_a (conjugate acid of base) - pK_a (acid)) < 1, this indicates no substantial proton transfer; thus co-crystal, not a salt. is formed. In Ibrutinib and fumaric acid case,

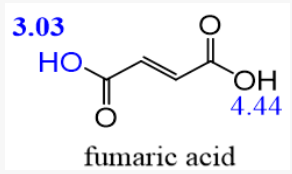
$\Delta pK_a = 3.74 - 3.03 = 0.71 < 1$;

no H^+ transfer. So not a salt, but a co-crystal

3. If pK_a criterion does not apply, or to add more evidence, orthogonal approaches such as spectroscopies can be provided (**US20170305914A1, US20180072737A1**).

- H3 chemical shift in ^{1}H NMR show 0.3 ppm difference for HCl salt (δ at 8.5 ppm) vs Ibrutinib free base (δ 8.2 ppm). No difference in chemical shift (δ) between free base and co-crystal (both δ at 8.2 ppm).
- Significant difference of bond length of C-O (1.32 Å) and C=O (1.20 Å) in fumaric acid revealed weak H-bonding, with no significant proton transfer.





CONCLUSION(S)

1. Single Crystal X-ray diffraction showed that both Ibrutinib API and coformer fumaric acid are present in the unit cell, consisting a homo-dimer of Ibrutinib with a fumaric acid.
2. It is observed in Ibrutinib Fumaric acid co-crystal that ΔpK_a of fumaric acid and conjugate acid of Ibrutinib base are < 1. This indicated no hydrogen transfer; thus, support co-crystal, not a salt.
3. Other spectroscopic evidences which support the co-crystal.
- ^{1}H NMR show 0.3 ppm difference for H3 in salt vs Ibrutinib free base. No difference in chemical shift of free base and cocrystal (δ at 8.2 ppm).
- Single X-ray showed distinction in bond lengths in fumaric acid between C-O and C=O; which signifies no ionization of acid but rather the hydrogen bonding between fumaric acid and Ibrutinib base.

WHERE TO GET MORE INFORMATION.

FDA Guidance 2019:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/determining-whether-submit-anda-or-505b2-application

FDA Co-crystal Guidance 2018:
https://www.fda.gov/media/81824/download

FDA Polymorph Guidance 2007:
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andaspharmaceutical-solid-polymorphism-chemistry-manufacturing-and-controls-information

FDA GRAS list for coformer selection:
https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras

Crystalline Forms of Ibrutinib:

WO2017029586A1, US20190002468A1

Co-Crystal Active Pharmaceutical Ingredient: Recommended Documentation

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Definition of Generic Drug

- Generic drug is **P**harmaceutically **E**quivalent (PE) and **T**herapeutically **E**quivalent (TE) to brand-name drug
- A generic drug works the same way and provides the same clinical benefit (efficacy and safety) as its brand-name product

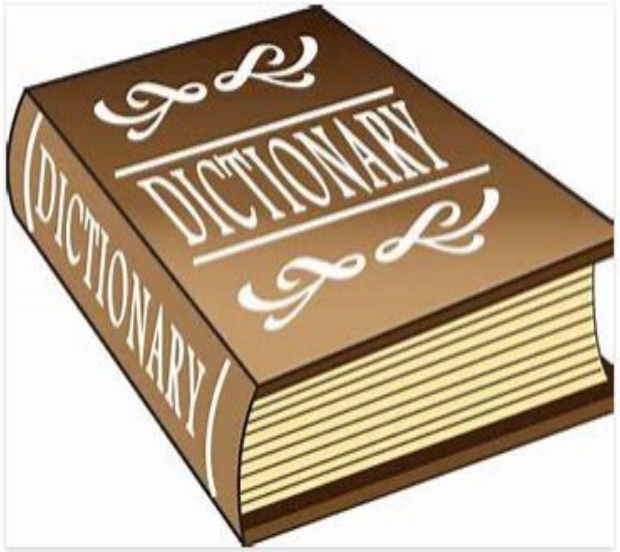
Pharmaceutical Equivalent vs. Pharmaceutical Alternative

- **Pharmaceutical equivalents (PE)** are drug products in identical dosage forms and route of administration that contain identical amount of the identical **A**ctive **P**harmaceutical **I**ngredient (API), i.e., the same salt or ester of the same therapeutic moiety.
- **Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form, or the same salt or ester (e.g., tetracycline hydrochloride, 250 mg capsules vs. tetracycline phosphate complex, 250 mg capsules).

Pharmaceutical Equivalence of Drug Substance conveyed by FDA Guidance on Solid Polymorphism

Polymorphic forms refer to **crystalline** and **amorphous** forms as well as **solvate** and **hydrate** forms

Definition of TERMS



- **Crystalline** forms have ordered or defined arrangements and conformations of the molecules in the crystal lattice.
- **Amorphous** (non-crystalline) forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice.
- **Solvates** are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a **hydrate**.

Salt, Polymorph, Co-Crystal

Name	Definition	Sameness
Salt	Is formed by proton (H^+) transfer from an acid to a base.	Different API NDA filed
Polymorph	Two or more crystalline forms of the same API, with different arrangements of conformations of the constituents in the X-ray crystal lattice.	Same API ANDA filed
Co-Crystal	Both neutral substances (API and coformer) are present in the crystal lattice without H^+ transfer.	Same API ANDA filed

Co-Crystal as Same API

- On August 16, 2016, the US food and drug administration (FDA) published a draft guidance Regulatory Classification of Pharmaceutical Co-Crystals. In this guidance, FDA suggested treating co-crystals as polymorphs, as long as proof is presented to rule out the existence of ionic bonds.
- In Feb 2018, this guidance has been updated to include specific criteria to distinguish between Co-Crystal and Salt.

WALK-THROUGH AN EXAMPLE USING PUBLICLY AVAILABLE DATA TO EXPLAIN PRINCIPLES LAID OUT IN THE CO-CRYSTAL GUIDANCE

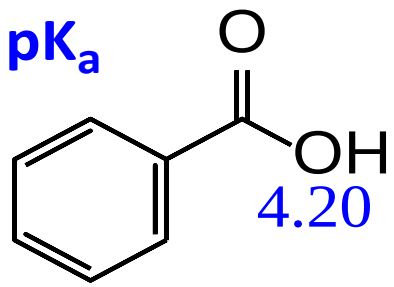
Anti-Leukemia Drug Ibruvica® (Ibrutinib)

- Approved 2013
- First-Line Treatment for Chronic lymphocytic leukemia [CLL]/Small lymphocytic lymphoma [SLL] and First Treatment for Marginal Zone Lymphoma
- **No. 5** annual sale in 2019 (8.085 billion) in USA
- Class 2 under BCS [**B**iopharmaceutical **C**lassification **S**ystem] (Low solubility, high permeability)

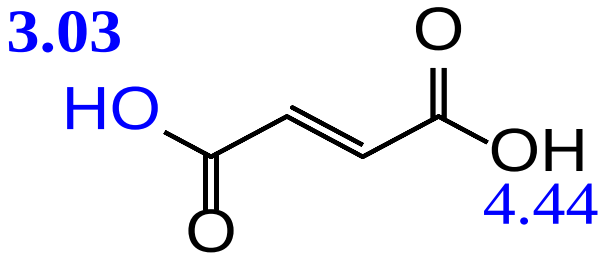
Ibrutinib Polymorph and Solvates and Their Stability

Ibrutinib Polymorph and Solvates (WO2016156127A1)	
Form A, B, C	Anhydrous/non-solvated
Form C and amorphous	More soluble than Form A. While stirring in suspension, convert into the less soluble form A.
Form D	Methyl isoButyl ketone solvated
Form E	Toluene solvated. Converted to Form A after 12 wk/40°C.
Form F	MeOH solvated.

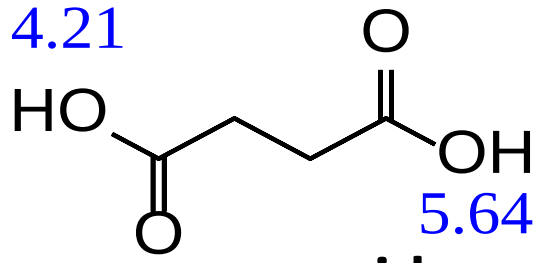
Ibrutinib Co-Crystal with Weak Acids



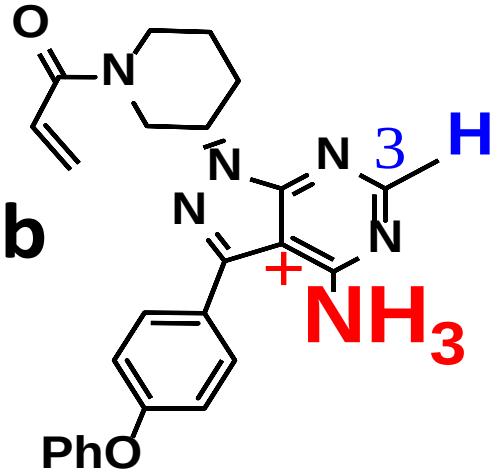
benzoic acid



fumaric acid



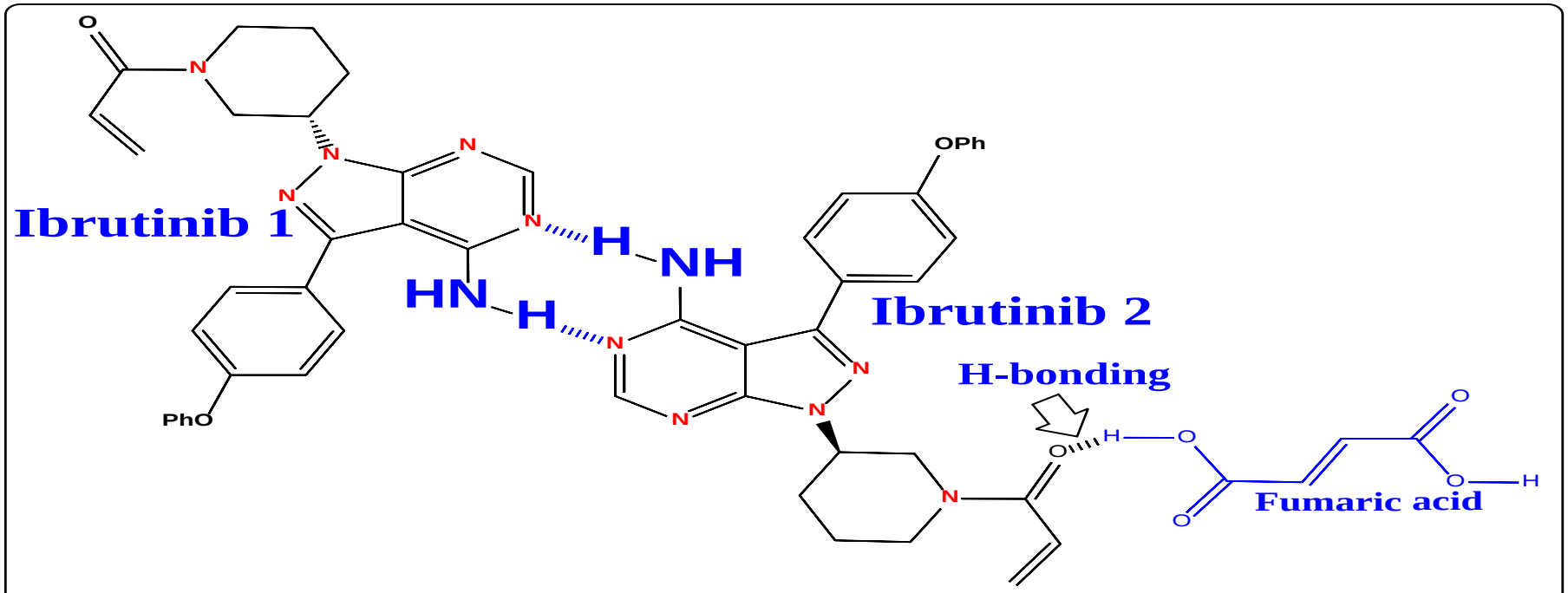
succinic acid



Ibrutinib

pK$_a$ of conjugate acid of Ibrutinib base: amino group on the pyrimidine ring is 3.74

Co-Crystal Information Conveyed by Single X-ray Diffraction



In Fumaric acid (FA), bond length C-O (1.32 Å) is significantly different from C=O (1.20 Å), indicating no ionization. **No H^+ transfer from Fumaric acid (FA) to Ibrutinib (IBU).**

Summary of Data and Comparison per Co-Crystal Guidance

U.S. FOOD & DRUG ADMINISTRATION

CDER Co-Crystal Criteria per Guidance	Reported Data
Both API and coformer are present in the unit cell	Ibrutinib homodimer with Fumaric acid are observed in crystal unit cell.
If API and its coformer have ΔpK_a [pK_a (conjugate acid of base) - pK_a (acid)] < 1, no substantial proton transfer; thus is co-crystal.	ΔpK_a = pK_a (conjugate acid of Ibrutinib) - pK_a (fumaric acid) =3.74 – 3.03 = 0.71 < 1; Indicate no H^+ transfer; so not a salt, but a co-crystal
If pK_a criterion does not apply, orthogonal approaches such as spectroscopy can supply evidence.	- ^1H NMR showed 0.3 ppm difference in chemical shift (δ) for H3 in salt (8.5 ppm) and Ibrutinib free base. No difference in chemical shift (δ) observed for Ibrutinib free base and fumaric acid cocrystal (δ 8.2 ppm). - Bond lengths differences of C-O and C=O in Fumaric acid support no proton transfer.

Conclusion

- The compliance of Ibrutinib fumaric acid co-crystal with criteria listed in FDA guidance has been demonstrated.
- Ibrutinib fumaric acid co-crystal is the same API as Ibrutinib free base.

Resources

FDA guidance for ANDAs: Pharmaceutical Solid Polymorphism

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andaspharmaceutical-solid-polymorphism-chemistry-manufacturing-and-controls-information

FDA Co-Crystal Guidance

https://www.fda.gov/media/81824/download

FDA GRAS (generally recognized as safe) list for coformer selection

https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras

DMF Questions inbox for DMF submission policies and procedures

dmfquestion@fda.hhs.gov

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on *March 3rd*
- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar
- Please refer to the following poster for cross-referenced materials: *Synthetic Therapeutic Polymers: Recommended documentation for* ***API sameness,*** *Bapu Gaddam et al.*
- Please refer to the following presentations on March 4th, 2021 for additional information: *Considerations for* ***complex APIs****, Bapu Gaddam et al.*