Polymorphism basics and cocrystal technology.

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Received: January 21, 2023; *Accepted:* February 7, 2023

Review Article

ABSTRACT

The adoption of cocrystals into oral pharmaceutical formulations is expected to propel this, as yet, moribund field into clinical and monetary prominence. The increase in resources and research that will inevitably follow is expected to address long standing problems in crystal engineering. *Ab initio* predictions of heterosynthon structure, identification of molecular descriptors to enable bioavailability enhancing coformer selection and a priori prediction of the cocrystal lattice have thus far been insoluble. Solutions to the prediction of supersaturation levels and polymorphic transition of the cocrystal formulated API in GI fluids, and solvation barrier and solubilization free energies, remain empirical. Properties such as on-demand/environment, formulation enabled, proton transfer between API and coformer and the development of neural networks or AI, trained on empirical data to predict ideal API-coformer pairs without the need to explicitly understand mechanisms, remain obscure, and hence un-researched. It is ironic that failure mechanisms that result in the delayed appearance of a less-soluble polymorph in pharmaceutical formulations (disappearing polymorphs) could (and should) be gainfully utilized to facilitate the delayed appearance in vivo of less-soluble polymorph(s) in cocrystal formulations. The bioavailability increase afforded by cocrystal formulations has the potential to enable greater patient compliance due to favorable posology, introduce more efficacious drugs into the therapeutic armamentarium, enable line-extensions and expand intellectual property portfolios, reduce the cost-of-goods; and hence of medicines, and add one more valuable tool in the repertoire of the pharmaceutical formulation scientist.

KEY WORDS: Cocrystal, disappearing polymorphs, proton transfer, bioavailability, gastrointestinal permeability, polymorph, crystal engineering, coformer, heteromolecular synthon, hirshfeld plot

INTRODUCTION

A brief introduction to polymorphs, solvates and hydrates

Polymorphism is the property of chemical and biological compounds to form multiple crystalline structures. It is theorized that almost any substance can exist in 2 or more crystalline forms. Polymorphism is very prevalent in pharmaceutical drug substances and drug products. Polymorphism was first observed in 1821 by the German chemist Mitscherlish.

Polymorphs can be classified based on their structure and composition. The crystalline structures are formed when molecules of the substance form regular crystalline unit cells which are repeated to form larger structures. Two different crystalline forms have different spatial arrangements of the same molecule. Their properties like melting point, solubility etc. are

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very well defined. The crystalline forms are usually very stable in comparison with amorphous forms. The majority of drug substances used in the pharmaceutical industry exhibit polymorphism.

Amorphous forms (also called non-crystalline forms) have random spatial arrangement of molecules. The degree of disorder is very high, and no discernible repetitive structure is observed. Generally, in comparison with crystalline polymorphs, amorphous solids have a faster dissolution rate, and are less stable.

Crystalline forms that have solvents (usually from processing) incorporated into their structure are called solvates. The proportion of the solvents in the crystal structure is not fixed, but varies according to process conditions. If the solvent is water, it is called a hydrate. Hydrates are the most common solvates among pharmaceutical drug substances. Hydrates are thermodynamically more stable than the anhydrous form, and therefore less soluble and slower to dissolve. The hydrates lose their water upon heating.

Cocrystals are crystalline materials formed by two or more crystalline materials in the same crystalline lattice. These molecules are bonded to each other through non- covalent bonding. However, they do have a defined stoichiometry. Cocrystals are designed through crystal engineering for better solubility and stability.

Several properties of the molecule are impacted by polymorphism. These include rate of dissolution, rate of reaction, stability, melting point, solubility, heat capacity, refractive index, molar volume, hardness, compatibility, flow properties (and therefore blending), surface free energy and interfacial tension. A consequence of these differences in properties is that polymorphism can affect the safety and efficacy of the drug product. Thus identification, quantitation and characterization of the polymorphism of the drug substance is required by regulatory agencies early in development.

Among the different effects of polymorphs on pharmaceuticals, bioavailability, solubility, stability and safety (toxicity) rank high. These properties must be studied carefully and evaluated at pre- clinical stage to avoid surprises later in development. These have been recognized as key elements in pharmaceuticals by regulatory agents around the world.

The US FDA, European EMA and International Council for Harmonization (ICH) have laid down guidelines that drug developers are expected to follow. The US FDA published guidelines on ANDAs: Pharmaceutical Solid Polymorphism, Chemistry, Manufacturing and Control, in 2007. The guideline defines polymorphs and polymorphism, characterization of polymorphs, importance of polymorphism on drug substance and drug product, and setting limits on polymorph components. There is a decision tree to follow as well. The FDA has also published a regulatory guideline on cocrystals in 2018 entitled "Regulatory Classification of Cocrystals". This guidance is applicable to ANDAs and NDAs. The EMA guideline "Reflection Paper on Use of Cocrystals of Active Drug Substances in Medicinal Products' was published in 2016. The guideline describes analytical methods that may be used to characterize polymorphs. The ICH guideline includes a decision tree in Q6A- Test procedures and Acceptance Criteria for Drug Substances and Drug Products, published in 1999.

An introduction to cocrystals

Significant compositional and functional overlap exists between multicomponent solid forms such as salts, polymorphs, cocrystals, solvates, hydrates, molecular or inclusion complexes, solid solutions, and so on. Furthermore, these categorizations can exist as amorphous or crystalline states, involve (varying degrees of) proton transfer, ion pairs, hydrophobic bonds and can exist in combination with each other in the same crystal lattice (1). These chimera; of necessity; hence resist assignment of mutually exclusive nomenclature. The FDA and EMA have therefore drafted different, yet broad, definitional guidelines on cocrystal nomenclature. This current permissive regulatory landscape can be leveraged to tune API characteristics, both in the solid state and in situ and to significantly increase bioavailability of BCS class II or IV compounds, by deftly manipulating

select diverse parts of this chimera. For example, escitalopram oxalate, Lexapro®, exists in a crystal form that is composed of protonated escitalopram cations, water molecules, oxalate dianions, and diprotonated (neutral) oxalic acid molecules in the same crystal (2). The significant leeway that exists in designing cocrystal formulations serves to further accentuate their intrinsic advantages to maximize bioavailability and clinical efficacy.

The crystal engineering of pharmaceutical cocrystals involves the selection of the coformer based on supramolecular synthon architectural constraints, the desired extent of proton transfer and the suppression of interconversion of the metastable API to its least-free-energy and least-soluble polymorph in GI fluids. Various empirical and semi-empirical methods have been developed to predict the solubility and permeability of the API formulated as a cocrystal with a coformer. Cocrystal formulations are yet another tool in the pharmaceutical formulator's toolkit to increase the solubility of sparingly soluble APIs'.

Coformer attributes for maximum GI permeation and bioavailability

The cocrystal properties of dissolution, the extent of supersaturation, and permeability are influenced to a large extent by the coformer. This is because the stability of the hetero supramolecular synthon due to the intermolecular attractions between the API and coformer, the enthalpic and entropic contributions to the thermodynamic favorability of the cocrystal *vis-a-vis* the API and the coformer, and the crystal habit and packing are determined by the choice of coformer. Many crystal engineering approaches are available (3), that when employed judiciously, can predict; at least semi - *a priori*; cocrytal formation ability with any coformer with a given degree of certainty. Models and algorithms to predict cocrystal formation include; the concept of supramolecular synthons (4) (predictable structural units connecting molecules in a crystal structure based on intermolecular interactions of hydrogen and halogen bonds (5)) molecular complementarity (6) (usually using the Cambridge Structural Database), molecular electrostatic potential maps (7), Hansen solubility parameter (8), free energy of mixing, and machine learning (9, 10, 11).

The excess free enthalpy, ΔH_{ex}, of mixing has been used to predict cocrystal formation from coformers (12). ΔH_{ex} was found to be a more accurate descriptor when compared with hydrogen bonding interactions and seemed particularly amenable to high throughput computational screening and coformer ranking. A cocrystal is enthalpically favored over the pure (supercooled) liquid states of the individual components (API and coformer) when $H_{ex} < 0$. To prevent solvate formation with the crystallization solvent, the opposite holds true, viz. the greater the ΔH_{ex}, the lesser the probability of competing solvate formation (13). These considerations obviously do not apply when the method of cocrystal formation does not use any crystallization solvents, such as mechnochemical grinding, ultrasound, solid-state shear milling or crystallization from melts. Knowledge based models and empirical data suggest that molecular size and polarity strongly affect cocrystallization, whereas hydrogen bonding capability does not. Therefore, in many cases, ΔH_{ex} is more effective than H-bonding calculations using the Hansen solubility parameter to predict cocrystal formation. It does not appear though that such rational solvent selection models are being used in current cocrystal research. Table 1 lists pertinent coformer attributes that influence cocrystal formation.

The rate of dissolution (supersaturation) into gastric fluid must be equal to or less than the rate of conversion of the amorphous or more soluble polymorph to the least soluble crystalline state of the API. This increases the time window for permeation from the GI tract into the systemic circulation. The goal should hence be to not necessarily decrease the time to C_{max} at the expense of the AUC. Modest increase in time to C_{max} may lead to a significant increase in bioavailability (AUC). This should result in improvement in dosing/posology of these APIs', many of which are meant for prophylactic or lifetime use, where time to C_{max} takes less precedence over AUC increase.

It may be necessary to consider the relative Hirshfeld surface areas of coformer, API and cocrystal to predict

Table 1 Attributes influencing cocrystal formation

ATTRIBUTE STUDIED	ADVANTAGEOUS	DISADVANTAGEOUS
Hirshfeld surface area percent contribution (Coformer to API ratio)	> 1	< 1
Excess enthalpy of mixing, kJ.mol^{-1} (Cocrystal – pure solids)	< -0.18	> -0.18
Aqueous solubility of coformer	Not excessively high	High
Free energy of formation kJ.mol^{-1} (Cocrystal – pure solids)	$-11 < \Delta G_f < -5$	$\Delta G_f < -11$ or > -5
Heteromolecular synthon complementarity (between API and coformer)	High	Low
Miscibility, Hansen Parameter, (API - Coformer)	low	High
Excess enthalpy of mixing (Cocrystal-crystallization solvent)	High	Low

relative diffusivities also percentage interactions in Hirshfeld plot was found to be approximately proportional to bioavailability (solubility x permeability) of the cocrystal (14). In another study that investigated variable stoichiometry cocrystals of theophylline with aminobenzoic acids (15), the percent N-H intermolecular interactions between API and coformer obtained from Hirshfeld plots were strongly correlated to the product of the cocrystal solubility and permeability.

On the other hand, cocrystal formation of ambrisantan with L-aspartic acid and glycylglycine demonstrated a linear correlation ($R^2 > 0.96$) of percent O-H bonds between API and coformer to the product of the intrinsic dissolution rate (IDR) and API plasma concentration at 1 hour (16). Although no correlation between Hershfeld plot contributions and bioavailability was evident in yet another study using ethenzamide cocrystals (17), an inverse correlation between cocrystal solubility and API flux was present ($R^2 > 0.87$). While the inverse correlation between solubility and permeability generally holds true, there appears to be a more complex relationship between API-coformer intermolecular bond contributions from donor-acceptor atoms and bioavailability. The bioavailability of some API-coformer cocrystals can be predicted from certain Hershfeld type-of-atom contributions, but not from others. More research is needed to determine why this is so.

Tuning cocrystal solid state properties and bioavailability with complexation induced coformer pK_a shifts and the addition of stoichiometric excess of coformer to the APIsalt.

Since the Salt ↔ cocrystal proton transfer is now increasingly recognized to be a continuum state (18), rather than a binary one, a question to be asked is, can the supraheteromolecular synthon in cocrystals be modified so that it does not exhibit proton transfer while in the cocrystal state, but does so when dissolved in GI fluids? In other words, can a heterosupramolecular synthon be designed such that intermolecular hydrogen bonds between the (acidic) coformer and (basic) API cause an upward pK_a shift of the acidic coformer so as to induce cocrystal (as opposed to salt) formation. The decomplexation of the coformer and API in the gastric fluid would decrease the pK_a of the coformer so that the API can then form a salt with the coformer *in situ* (Figure 1). In other words, can the structure of the coformer be such that the pK_a difference is < 3 but is yet at the threshold where a cocrystal is formed during processing and tableting, which, subsequently transforms *in vivo* into a salt after disintegration of the tablet and when contacted by GI fluids? Complexation induced pK_a shifts are well documented in the literature (19, 20), with the largest supramolecular shift of 4 units being reported for thiabendazole complexed with cucurbit[7]uril (21). Such a phenomenon would be advantageous from a formulation standpoint if the salt is unstable or not amenable to further processing; or if the cocrystal defies attempts to increase API availability over the salt form. IP also undoubtedly

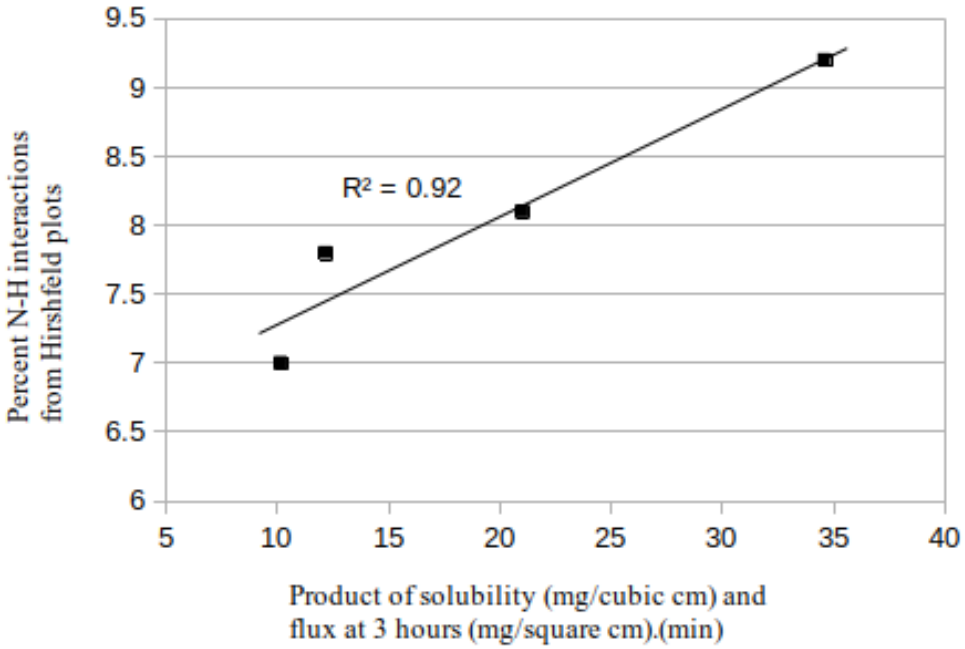

Figure 1 Calculated using data published in Reference 15.

would play a role.

As a corollary, it is interesting to note is that the salt of an API with an acid can be formulated as a cocrystal with additional undissociated or unionized acid. This is the case with the approved product Odomzo® (Sonidegib), which is officially listed as the diphosphate salt in the patient package insert but was actually found to be the dihydrogenphosphate salt cocrystallized with an un-ionized molecule of phosphoric acid (22). Along similar lines, Peresypkin et.al. presented the case of a monohydrochloride salt of an API in complex with HCl (23). The complex exhibited significantly greater stability when compared with the anhydrous monohydrochloride salt or the free base. The literature does not yet seem to have connected this important discovery with a deliberate method to improve salt properties; i.e., by transforming salts into cocrystals by addition of excess acid (for basic APIs) (Figure 2). For instance, 2 equivalents of acid added to the free base (with one measurable and protonable pKa) – and then crystalized - may result in a mono-protonated base cocrystalized with the unionized acid in a 1:1 molar ratio. If the acid form of the API is unstable, toxic or has an unfavorable ADME profile, its cocrystal with additional stoichiometric acid equivalents may be investigated for improvements. This approach has the potential to save effort, time and money in the drug development process.

Inclusion of crystallization inhibitors and solubilization enhancers in cocrystal formulations

A significant amount of research in the field of cocrystals is focussed on increasing and sustaining the released (higher free energy) form of the API (from the cocrystal) in solution in the GI fluid so that its permeability can be increased (the so-called spring and parachute effect (24)); with much attention being given to crystalization inhibitors (25) and/or solubilization enhancers. Such excipients include polymers and amphoteric molecules and/or surfactants. In our opinion and of others (26), this trajectory arm of current research into cocrystals needs realignment. This is because these approaches work equally well with amorphous solid dispersions, lipid-based drug delivery systems, complexation with cyclodextrins, nanoparticles, and microemulsions; hence if found to be advantageous with a particular API; there would be

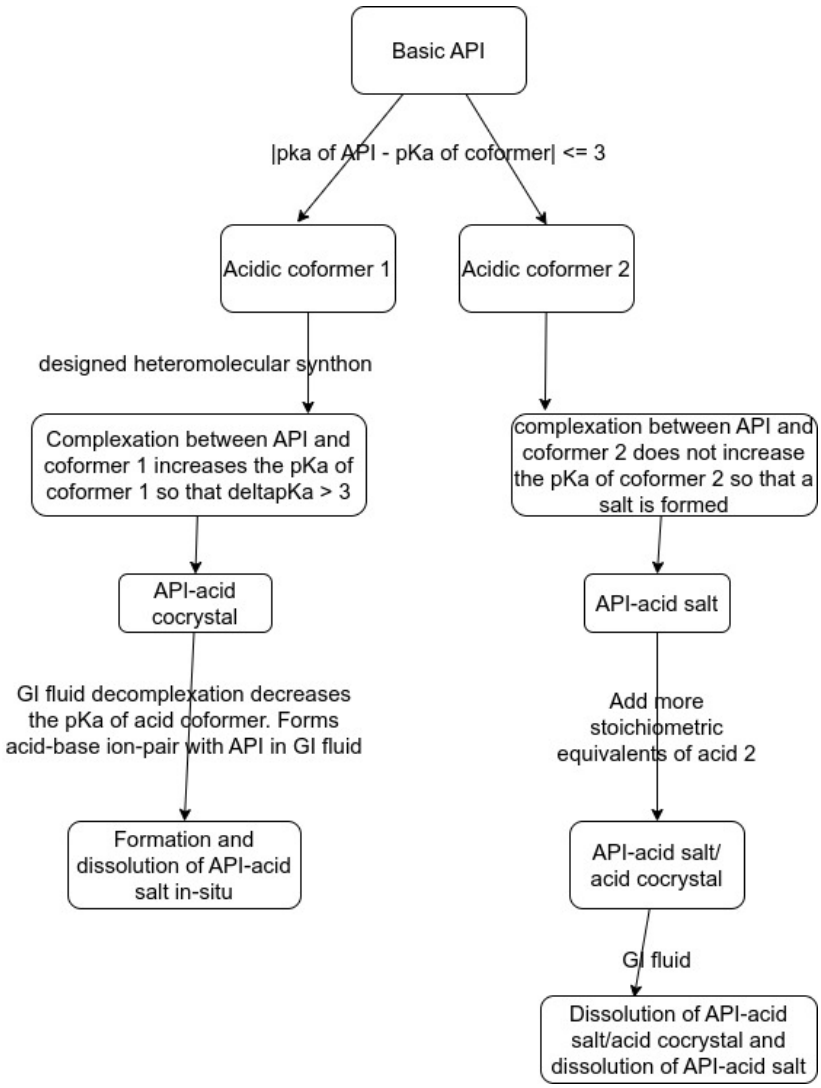

Figure 2 Two approaches to the formation of cocrystal with [API_{salt} + nonionized $acid_{coformer}$] and [API + pKa shifted $acid_{coformer}$]

no preponderant compelling necessity of exploring only cocrystal formulations, because a similar effect could just as well be obtained by the aforementioned legacy drug delivery systems. For example, a quote from a manuscript states "...The above expression clearly suggests a way of fine-tuning cocrystal supersaturation by changing drug solubilization, through addition of polymers, surfactants, lipids or additives that preferentially solubilize drug over coformer.", begs the question: why then is a cocrystal formulation needed in the first place? Granted that cocrystals fill a gap with regard to unfavorable or non-existant ionization constant API profiles and stability over amorphous solid dispersions; research into cocrystals needs to focus more on the properties of the coformer and the stability of the resultant cocrystal heteromolecular synthon, such that stabilization and/or solubility or permeability increasing mechanisms after release into the GI fluid are intrinsic to the API-coformer cocrystal, such as ion pairing or hydrophobic (non-micellar) molecular interactions between coformer and API in GI fluid (27). Table 2 presents the properties of a coformer that are pertinent to achieving an optimum level of supersaturation in the GI fluids. Choosing a coformer that endows a cocrystal with a so-called 'solubility advantage' (28) (that subsequently leads to precipitation of the higher free energy component on the cocrystal surface); and then negating that advantage

Table 2 Attributes influencing optimum GI saturation Solubility enhancement*, *viz.*, rate of dissolution (supersaturation) in GI fluids is ≤ than rate of formation of least free energy crystalline solid, so as to allow a greater permeability time window

ATTRIBUTE STUDIED	ADVANTAGEOUS	DISADVANTAGEOUS
Hirshfeld surface area percent contribution (ratio of Coformer to API)	>1	<1
Excess enthalpy of mixing (Cocrystal – Pure solids)	Negative	Positive
Lipophillicity index (API - coformer)	Low	High
Aqueous solubility of coformer	Moderately high	High
Free energy of formation, ΔGf, kJ.mol^{-1} (CoCrystal – Pure solids)	Moderately low, $-8 < \Delta G_f < 0$	Very low or very high, $\Delta G_f < -8$ or >0
Heteromolecular synthon complementarity (between API and coformer)	High	Low
Miscibility, Hansen Parameter, (API - Coformer)	low	High
Excess enthalpy of mixing (Cocrystal-crystallization solvent)	High	Low
Ion pairing or Hydrophobic (non-micellar) molecular interactions between coformer and API in GI fluid	High	Low

*This also equates to an optimum GI Permeability enhancement. *viz.* Rate of permeation of high energy solid is ≥ the rate of dissolution (supersaturation) in GI fluids. This may equate to a greater time to C_{max} but a greater AUC.

with 'rational additives selection' (29), or addition of excess conformer (30), defeats the purpose of the coformer. It signals a lack of knowledge to enable a priori prediction of the lattice, solvation barrier and solubilization free energies (31) as well as a knowledge deficit about the approximately inverse correlation between supersaturation solubility and permeability (32), in the complexed or micellar solubilized state with crystalization inhibiting polymers or surfactants respectively. A coformer should cause a moderate increase in the apparent solubility of the API such that its (resultant relatively low) supersaturation level in the GI tract prevents fast kinetic transformation to the most stable crystalline form, thereby increasing permeability.

Disappearing polymorphs

In this context, the mechanisms that favored the slow interconversion of metastable to stable polymorphs; the so-called 'disappearing polymorphs'; that plagued formulations of ritonavir (33) (Norvir®), ranitidine hydrochloride (34) (Zantac®) and rotigotine (35) (Neupro®), could be purposely engineered into cocrystal formulations. One possible mechanism was the slow interconversion from dimerized metastable polymorphs (36) due to the lesser number of API low energy rotatable bonds or steric hindrance for rotating those bonds provided by the H-bonded dimer (37). Concurrently, the decrease in the free energy due to dimerization, ΔG_d, for these 'disappearing polymorphs' was calculated to be high (Figure 3). Similarly, the disappearing polymorph II for the urea-barbituric acid (UBA) cocrystal (38) involved an anlysis of H-bond propensity calculations (39). The H-bonds involved in the urea dimer formation had the highest individual score among all the H-bonds observed in UBA polymorphs. These interactions occured in the polymorph I and polymorph III forms but were absent in polymorph II, in which all moderate H-bonds were found to be of heteromolecular origin. Hence, the formation of polymorph II is kinetically hindered if urea molecules preorganize in solution into H-bonded aggregate dimers. The problem of 'disappearing polymorphs' remains largely insoluble, in part due to an inability to unravel interconversion mechanisms (40). Progress in this area is much needed so that these mechanisms can be utilized to increase the persistence of cocrystal formulated metastable API polymorphs in the GI fluid.

Neural networks and machine learning algorithms to identify coformers, heterosynthon structures and/or API-coformer molecular descriptors that increase API bioavailability

Coformers with relatively lower aqueous solubility, those that tend to form moderately stable supra heterosynthons with the API (41), with a ΔG_f (42) of ~ -8 kJ.mol^{-1}, form stable ion-paired or H-bonded dimers with the API in solution (43), present a larger surface area contribution of the relevant H-bonding groups than the API in Hirshfeld plots, provide a negative cocrystal ΔH_{mix} relative to the API and coformer are suited for this purpose. Choosing a coformer, crystallization solvent or method to form a cocrystal still remain either empirical or heuristic attributes with negligible first-principles predictability (44) of subsequent dissolution, solubility and permeability (although, see below). Interestingly, current binary classifier machine learning algorithms are written to predict cocrystal formation; however; to the best of our knowledge; as of the time of writing of this manuscript, there exist no algorithms where the cost-function represents the desired dissolution and permeability of the cocrystal so that the weights of molecular descriptors may then be adjusted in feed-back loops based on the minimization of this cost-function. In our opinion, this yawning gap in knowledge needs exploitation so that API and coformer can be paired from a bioavailability – rather than from a formulation – standpoint, of fit-for-purpose (Figure 4).

Other approaches to improve cocrystal bioavailability

Biomimetic strategy

Plants use secondary metabolites, precursors of organelles or products of metabolism to keep aromatic free bases in solution. Chlorogenic acids (45) or acidic compounds that are the precursors for the formation of lignocelluloses are ubiquitously used in plants for this purpose. Such acids are caffeic acid, ferulic acid, syringic acid, galacturonic acid, coumaric acid, shikimic acid, and quinic acid (among others). Not much research has been done into using these acids as coformers. Even though many of them do not have GRAS status, they are routinely consumed or formed in the body and are more likely to meet with favorable regulatory review. A biomimetic strategy such as the one mentioned may prove enriching in the search for suitable coformers (46).

Amphiphilic compounds as coformers

Amphiphilic compounds and surfactants have found extensive use as crystal inhibitors, rather than as coformers. Attempts have been made to increase the solubility of sparingly soluble APIs' by complexation with amphiphilic compounds (47), and by incorporation into the crystal lattice (48). However, whether or not, such complexes actually exist; or can exist, as cocrystals, has not yet been investigated. As a first approximation - assuming that a cocrystal can be formed between the API and the amphiphilic coformer - for this approach to be successful, the free energy cost of amphiphilic micelle formation must not exceed the free energy cost for hydrophobic or ion-pairing with API upon dissolution of the cocrystal in the GI fluid (Table 2). It follows that the amphiphilic coformer must therefore have a sufficiently high critical micelle concentration.

CONCLUSION

The adoption of cocrystals into pharmaceutical formulations is expected to propel this, as yet, moribund field into clinical and monetary prominance. The increase in resources and research that will inevitably follow is expected to address long standing problems in crystal engineering such as ab initio predictions of heterosynthon structure, identification of molecular descriptors to enable bioavailability enhancing coformer selection, prediction of supersaturation levels and polymorphic transition of the API in GI fluids, a priori prediction of the cocrystal lattice, solvation barrier and solubilization free energies, on-demand/environment, formulation enabled, proton transfer between API and coformer and the development of neural networks or AI, trained on empirical data to predict ideal API-coformer pairs without the need to explicitly understand mechanisms. It is ironic that failure mechanisms that result in the delayed appearance of a less-soluble polymorph in pharmaceutical formulations (disappearing polymorphs) could (and should) be

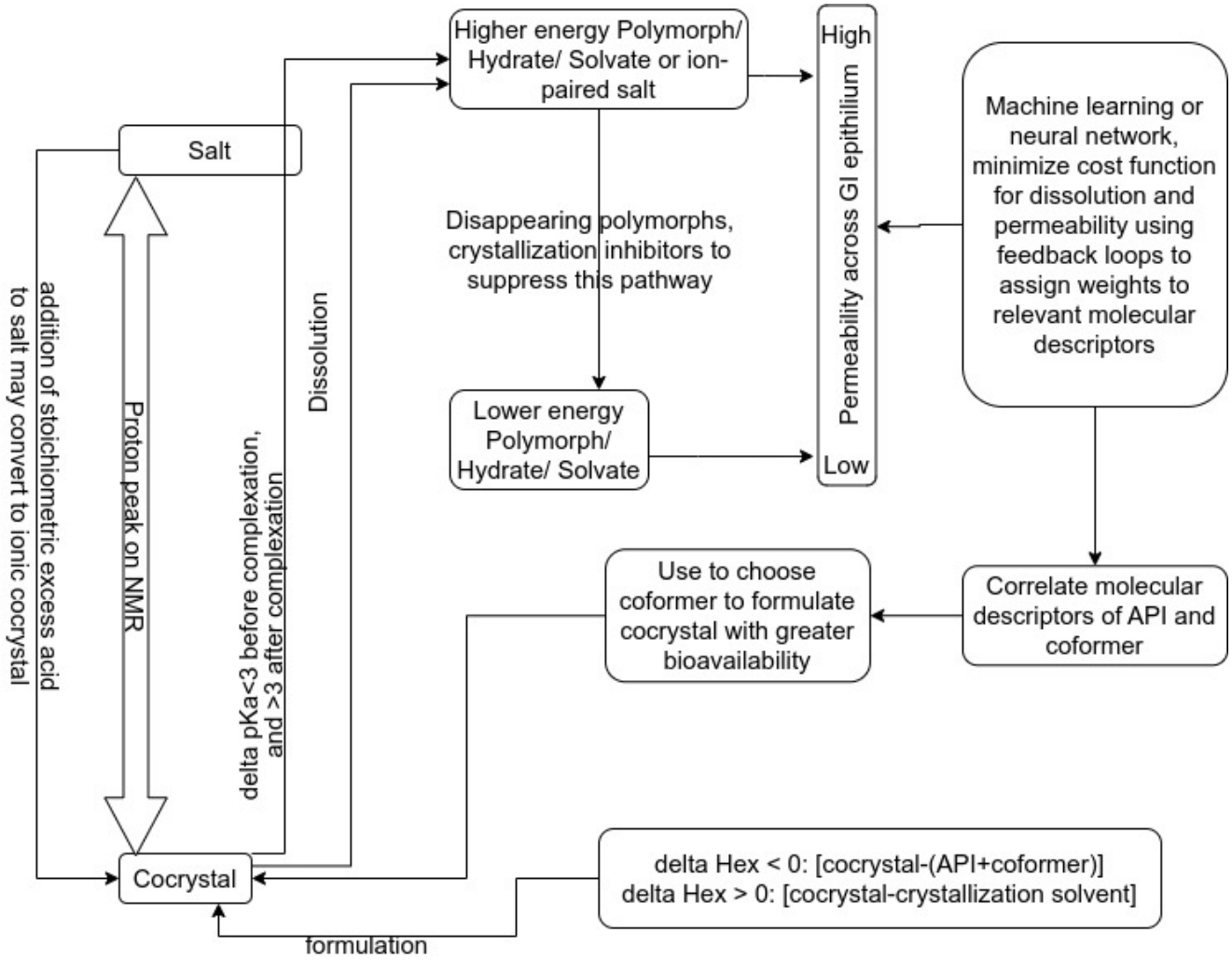

Figure 4 Incorporation of coformer selection approaches to yield greater bioavailability.

gainfully utilized to facilitate the delayed appearance in vivo of less-soluble polymorph(s) in cocrystal formulations. The bioavailability increase afforded by cocrystal formulations has the potential to enable greater patient compliance due to favorable posology, introduce more efficacious drugs into the therapeutic armamentarium, enable line-extensions and expand intellectual property portfolios, reduce the cost-of-goods; and hence of medicines, and add one more valuable tool in the repertoire of the pharmaceutical formulation scientist.

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