A fresh look at cocrystal formulations.

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Editorial

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Insoluble, non-ionizable and sub-micellizable or sub-complexable APIs' have another avenue toward therapeutic usefulness: cocrystal formation. When combined with a suitable coformer, the molecules of API and coformer can be made to exist in the same crystalline lattice; such that a transient API solubility advantage is obtained upon dissolution in GI fluids. This solubility advantage can transport the API past the GI epithelium into the blood. Considerable *a priori* knowledge of crystal engineering is required to achieve this ideal situation enumerated above, such as supramolecular synthon architecture, thermodynamic free energies, molecular complementarity and electrostatic potentials. Since the utilizability of the cocrystal phenomenon for APIs' previously considered unformulatable is so high, empirical science continues to be the driver in formulation of APIs' using this technology; with first-principles understandably taking a back seat.

Research into this field has hence been extrapolated from legacy BCS class II or IV API methodology with a preponderant objective to increase their solubility in the GI tract upon dissolution. To this end, formulatiors have added non-coformer substances such as surfactants, disintegrants and polymers in the oral dosage form containing the API-coformer cocrystal, to increase the supersaturation solubility of the latter in the GI tract. In this issue of the Journal of Excipients and Food chemicals, we emphasize the need to gravitate away from this research trajectory, since it ignores the inherent advantages of formulating an API into a cocrystal in the first place.

We discuss several other empirical, non-obvious, and therefore, under-researched, aspects of cocrystal formulations which maximize the cocrystal advantage to increase the solubility and permeability of the API. For example, we put forward the hypothesis that adding excess acid (to a basic API salt) or excess base (to an acidic API salt) - in excess of the stoichiometric amount required to form the salt of the API - may form a salt-acid or a salt-base cocrystal when the solution is crystalized. While such cocrystals are known to exist in marketed drug products, the idea that a *deliberate* addition of excess (complementary) acid or base to *any* API-salt may yield a cocrystal upon crystallization has not – to our knowledge – been proposed. Such a method may be particularly useful when the salt of the API is not stable in its solid state, or is hygroscopic or changes polymorphic structure to a less ideal one upon certain storage conditions or when mixed with excipients.

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Going further, we propose that coformers may be selected such that the process of complexation with the API decreases the | conformer (pk_a) – API (pk_a) |. This enables a cocrystal to be formed, when formulated as an oral solid dosage form. Conversely, upon administration, when dissolution occurs in the GI fluids, decomplexation of the coformer with the API increases the | conformer (pk_a) – API (pk_a)|. This enables *in situ* salt formation in the GI fluid, thereby increasing the supersaturation solubility and permeability of the API across the GI epithelium.

We propose that the mechanisms that favoured the slow interconversion of metastable to stable polymorphs; the so-called 'disappearing polymorphs'; that plagued formulations of ritonavir (Norvir®), ranitidine hydrochloride (Zantac®) and rotigotine (Neupro®) be purposely engineered into cocrystal formulations by judicious choice of coformer. Such an approach will increase the time that the high-energy API polymorph takes to convert into the lesser soluble polymorphic form in the GI tract; again, increasing its permeation across the GI epithelium. We draw attention to the fact that the problem of 'disappearing polymorphs' remains largely insoluble; in part due to an inability to unravel interconversion mechanisms. Progress in this area is much needed so that these mechanisms can be then beneficially utilized to increase the persistence of cocrystal formulated metastable API polymorphs in the GI fluid.

We echo a, hitherto largely ignored, proposal from the literature of using chlorogenic acids as coformers in API cocrystal formulations. These acids are precursors for the formation of lignocelluloses in plants. Even though many of them do not have GRAS status, they are routinely consumed as plant products and are hence more likely to meet with a favourable regulatory review.

Lastly, we describe the importance of AI or neural networks as an epitome of empirical methodology so that API and coformer can be paired to impart the maximum bioavailability of the API in the GI tract. Current binary classifier machine algorithms are written to predict whether the coformer is capable of forming a cocrystal with the API, i.e., to predict cocrystal formation. However, we could find no algorithms where the cost-function represents the desired dissolution and permeability of the cocrystal such that the weights of the molecular descriptors may be adjusted in feed-back loops based on the minimization of this cost-function; i.e., predict API bioavailability from cocrystal formulation. This may be due to the fact that insufficient data is available for the algorithm to train on; which leads to the question of standardization of measurement of solubility and permeability from cocrystal formulations. Industry-wide standardization of permeability, dissolution and solubility measurement protocols of cocrystal formulations will enable data to be used from any published manuscript to train AI algorithms and predict ideal API-coformer pairs without the need to explicitly understand mechanisms.

Using solubilization methodologies and approaches from legacy complexed or micellized APIs' are likely to be insufficient, unsuitable and maladaptive for cocrystal formulations, even to the extent that inherent cocrystal solubility advantages may be overlooked. We have suggested concepts in the manuscript accompanying this editorial that will hopefully enable re-examination of cocrystal formulations from a first-principles perspective, so as to capture their full potential for bioavailability enhancement.