Poor aqueous solubility is a major challenge for the drug development process, and many strategies have been developed to combat this problem. Cocrystals have gathered much interest in the recent years, due to their ability to enhance drug solubilities by orders of magnitude. However, highly soluble cocrystals tend to undergo rapid solution mediated transformation back to less soluble drug form during dissolution, leading to little or no dissolution advantage. Whereas cocrystals with more modest solubility enhancements over drug might exhibit slower conversion leading to improved dissolution behavior. Therefore, cocrystal dissolution results can be misleading, and they are only useful in tandem with the knowledge of cocrystal thermodynamic solubility and solution phase dependence. Cocrystal solubility is highly dependent on solution conditions, such as pH, and this dependence can differ from its parent drug’s due to coformer’s physicochemical properties. A weakly basic drug, ketoconazole (KTZ), and its cocrystals with adipic (ADP), fumaric (FUM), and succinic acid (SUC) were used in this study to demonstrate how solution pH can impact their solubility, thermodynamic stability, and dissolution behavior. By altering solution pH, the three cocrystals can exhibit higher, lower, and equal solubility to that of the parent drug, further illustrates the importance of solution condition considerations. KTZ cocrystal dissolution behavior in pH 6.5 and pH 5.0 aqueous buffer media were also examined, and in most cases, the cocrystals were able to generate supersaturation with respect to drug solubility. However, KTZ-FUM, with over 3,000 fold higher solubility than the drug in pH 6.5 buffer, failed to demonstrate superior dissolution behavior due to rapid cocrystal to drug conversion. Therefore, in order to maximize dissolution advantage, it is important to balance solubility enhancements and conversion kinetics. Knowledge of cocrystal solubility and thermodynamic stability is crucial for rational design of dissolution experiments and accurate interpretation of those results, without which, the true potential of these cocrystals may be overlooked.

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