Water plays a key role in the co-crystallization of active pharmaceutical ingredients

August 15 2012

Credit: AI-generated image (disclaimer)

There is much more to drug development than simply identifying a potent active pharmaceutical ingredient (API). Scientists must ensure that the API can tolerate the production process, remain stable during storage and distribution, and behave appropriately inside the patient's

body after administration. One emerging technique for improving the performance of APIs with non-ideal physicochemical properties is to co-crystallize them with a second compound that modulates their behavior. Srinivasulu Aitipamula and co-workers at the A*STAR Institute of Chemical and Engineering Sciences have now developed a novel route for preparing such co-crystals.

The researchers have discovered that adding water droplets can help to form co-crystals of caffeine, a compound known to act as a central nervous system stimulant and a muscle relaxant. Caffeine is inherently unstable to humidity — a property that can be improved by forming co-crystals with biocompatible compounds such as 4-hydroxybenzoic acid (4HBA). Computer models predict that co-crystals of caffeine and 4HBA in the ratio of 1:1 should form the most stable structure. To date, however, researchers have only been able to produce 2:1 and 1:2 co-crystals.

Aitipamula and his team have now successfully formed 1:1 co-crystals of caffeine and 4HBA, in the form of a monohydrate. By grinding together a 1:1 mixture of the two components along with two drops of water, a crystal structure was formed in which each pair of crystallization partners is partly held together by a water molecule.

According to Aitipamula, the key to water's ability to produce the 1:1 co-crystal is its capacity to both donate and accept hydrogen bonds — the intermolecular force that holds co-crystals components together. "In the case of the caffeine-4HBA co-crystal hydrate, unused hydrogen bond acceptors and donors are satisfied by forming hydrogen bonds with the water molecule," he says. Without water, the number of hydrogen bond donors and acceptors is unbalanced, resulting in the preferential formation of the 2:1 and 1:2 crystals instead.

The process also works for other APIs, as the researchers have found.

They have generated a 1:1 co-crystal hydrate of 4HBA with piracetam, a drug used to treat memory and balance problems. The results suggest that forming hydrates offers an alternative way to generate co-crystals with particular ratios of constituents, expanding the options for forming pharmaceutical materials.

The researchers are currently focused on developing new co-crystals for APIs and studying their physicochemical properties. “Our primary emphasis is to target APIs that pose problems in pre-formulation and dissolution,” Aitipamula says.

More information: Aitipamula, S., Chow, P. S. & Tan, R. B. H. Co-crystals of caffeine and piracetam with 4-hydroxybenzoic acid: Unravelling the hidden hydrates of 1:1 co-crystals. *CrystEngComm* 14, 2381–2385 (2012). dx.doi.org/10.1039/c2ce25080b

Provided by Agency for Science, Technology and Research (A*STAR), Singapore