Melting Point Phase Diagram of L-Proline and Diclofenac Co-crystal

Eleni Rodriguez
Florida State University Panama City

Abstract

Co-crystals are a vital part to pharmaceuticals, as they can be created to improve the properties of substances. The formation of co-crystals can make a drug have stronger efficiency, better bioavailability, or even generate a new form of the same drug that could make it more easily absorbed. There is a wide range of benefits from their developments. L-Proline and diclofenac's co-crystal directly improves the low solubility of diclofenac, a commonly used non-steroidal anti-inflammatory drug (NSAID), allowing for greater absorption into the body when taken. Although this co-crystal is known, a melting point phase diagram for it has yet to be determined and analyzed to observe its correlation to preexisting differential scanning calorimetry (DSC) data. Various mole fractions of L-Proline and diclofenac are prepared in methanol and left to crystallize, and then the melting points of these crystals will be taken to determine and present a melting point phase diagram. This will allow for a visual representation of the co-crystal's unique properties at different ratios.

Introduction

Co-crystals are a class of crystalline materials made of two or more substances that can help enhance and alter the effects of pharmaceutical drugs. In this case, diclofenac has a high permeability but very low solubility, making the bioavailability less in the body when taken. Diclofenac is a commonly used NSAID, and therefore mixing it with L-Proline, an amino acid, allows the mixture of the two to create a version of diclofenac that contains higher efficiency. This way, taking diclofenac can lead to better results and less of it will be required as its potency will be stronger. Knowing the melting point phase diagram could allow for better predictions and understanding of its behavior, assessing purity, and taking note of how pressure may be affecting phase transitions. Furthermore, this co-crystal when melted degrades the product and breaks it down, which changes it completely from what it was previously. Knowing its range can also prevent the accidental formation of new compounds when this crystallization is heated up to more than desired.

Hypotheses

- If the co-crystal is accurate to information based on previous literatures, then it should be found at a 0.5/0.5 ratio of L-Proline and diclofenac and contain the smallest melting point range that is around 154.8°C.

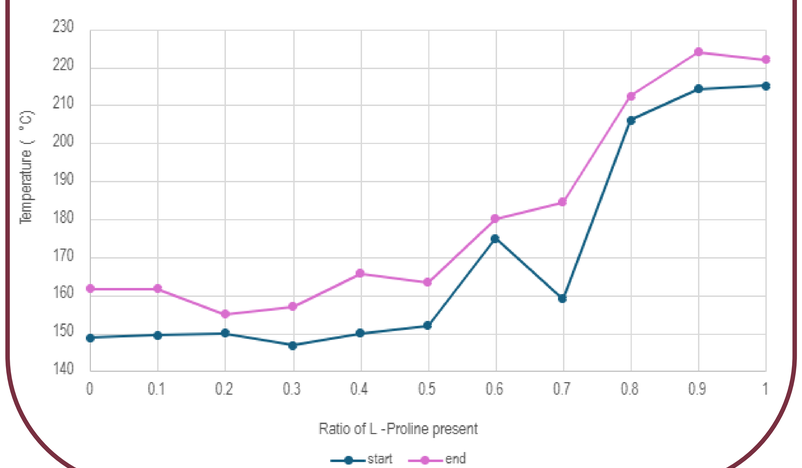
Methods

- Prepare two solutions (one with L-Proline and the other diclofenac) with methanol that each contain the same level of molarity, in this case, 0.0694 M.
- Specific ratios of the two were put into miniature test tubes. In increments of 0.1mL, these ratios were created using drops, with 20 drops of the solutions being considered to equal 1mL.
- Then, these were allowed to evaporate over at least a weekend.
- The crystals were scraped out the tubes and put into melting point capillaries and then the melting points of all were found. At the first drop spotted, the temperature was written in the 'start' location and when it appeared to be fully liquid, the temperature in the 'end' was written.

Results

All the mixtures caramelized, and in the ratio of 0.7 L-Proline and 0.3 diclofenac, the liquid clumped up into a ball. Even so, all of it never fully dripped to the center, and it seems that much of the L-Proline stuck around the sides of the capillary tube leaving a gooey textured liquid on the side that never came downward.

The 0.5 to 0.5 ratio crystals (picture to the right) were a lighter brown when they melted in comparison to the other results as well. Below is the melting point phase diagram of the ratio mixtures.



Discussion

The desired melting point range for the co-crystal at around 154.8°C is seen at the 0.5 ratio of L-Proline and diclofenac. However, in some other samples, it is evident that the melting point range is smaller than what we should expect. This is especially present in the ratios with 0.2 L-Proline and 0.8 L-Proline, which could be the nature of these mixtures or an error attributable to the varying amount of co-crystal that these ratios produced. In these ratios, the amount of co-crystal formation was less than in other ratios. Since the amount of product that could be placed in the melting point capillary tube was less than the others that yielded far more product, it could have led to a smaller range in melting point since it could melt faster. Furthermore, it was rather difficult to see when the first drops occurred from how brown the substances got, leading to potential inaccuracies when collecting the data.

Conclusions

- The melting point diagram of the co-crystal of diclofenac and L-Proline is found, however, doing another run of the melting points and attempting to use closer yields of the crystals when taking melting points would help with any potential discrepancies that were perceived. Furthermore, due to how difficult it is to tell when the first drop of liquid forms because the crystals pack together in heat and begin to brown, it is possible that slight disparities in data could be recorded. We can also observe that as the ratio of L-Proline increases, so does the melting point range. This makes sense as L-Proline has a higher melting point than diclofenac. The main co-crystal (0.5 ratio of both) was seen, ensuring that the ranges are at least on par with what would be expected.

References

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