Poster Presentation

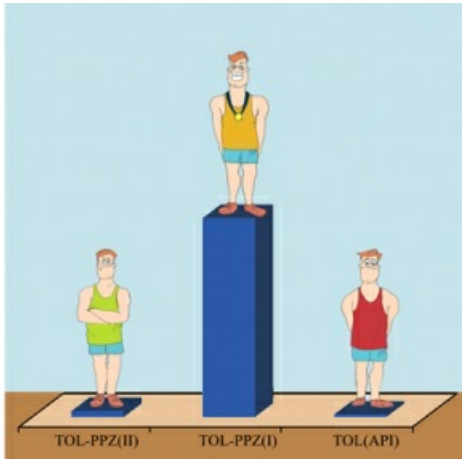
MS003.P11

Solubility enhancements through drug–coformer interactions for antidiabetic drugs

Ali Samie[1], Gautam Radhakrishna Desiraju[2]
[1]*Department Of Chemistry, Ferdowsi University Of Mashhad, Mashhad 917751436, I.R., Mashhad, Iran, Islamic Rep.,* [2]*Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 56001, India., Bangalore, India*
E-mail: alisamie.chemistry@gmail.com

Pharmaceutical cocrystals are well-investigated compounds in which properties of active pharmaceutical ingredients (APIs). Drugs are generally classified into the four categories in the Biopharmaceutics Classification System (BCS): class I (high solubility, high permeability), class II (low solubility, high permeability), class III (high solubility, low permeability), and class IV (low solubility, low permeability). Poor solubility and/or permeability of APIs are the main factors to restrict the bioavailability of APIs during drug discovery and development. Many approaches have been employed to improve the solubility and permeability of APIs. Gliclazide (GCZ), Tolbutamide (TOL) and Glipizide (GPZ) are BCS class II antidiabetic drugs with poor aqueous solubility. Multicomponent solid forms, salts and cocrystals of GCZ were obtained upon liquid assisted grinding (LAG) with coformers of catechol (CAT), resorcinol (RES), p-toluenesulfonic acid (PTSA) and piperazine (PPZ). Solubility of TOL and GPZ have been modified by salt formation with PPZ. The multicomponent solids were characterized by single crystal X-ray diffraction (SCXRD), powder X-ray diffraction (PXRD), fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) and further subjected to solubility studies. The cocrystals/salts, in all cases, showed improvements in the solubility and dissolution rates compared to the parent APIs. GCZ –PPZ, TOL–PPZ (I) and GPZ–PPZ showed 6.6, 80 and 89.4 fold enhancements respectively in the solubility. The reasons for the improved solubility of the cocrystals/salts in terms of drug-coformer interactions are discussed. While salt formation can enhance solubility by 100-1000 times, cocrystal formation can increase it typically 4–160 fold. It is to be noted that the solution crystallization of these drugs is tedious and often results in poor crystals that were obtained slowly, after many months. This could be due to the entropic reason arising from the molecular flexibility which prolongs the crystallization process. In the case of TOL-PPZ (I) the DSC peak is split into two peaks. We conclude that this observation may have to do with the presence of two TOL polymorphs in the mortar which might lead to two different polymorphic salts when ground with PPZ.

[1] Desiraju, G. R. et al. (2011), Crystal Engineering: A Textbook, World Scientific, 148-149.
[2] Rastogi, R. P. & Singh, N. B. (1966), J.Phys.Chem., 70, 3315-3324.
[3] Fischer, F. et al. (2016), Cryst. Growth Des., 16, 1701–1707.



Keywords: antidiabetic drugs, BCS class II, solubility enhancement