Benperidol, 1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one, is an antipsychotic, used for the treatment of schizophrenia and to control antisocial hypersexual behavior. It is known to exist in three polymorphic forms I – III, a dihydrate DH, and an ethanol solvate SEt. These phases have been characterized by PXRD peak positions and melting points, as well as by the IR spectra. Crystal structure, however, has been reported only for polymorph I, which crystallizes in R–3 space group with Z=18. A recent study of the similar molecule droperidol shows that it exists as four polymorphs and eleven solvates. Moreover, benperidol has three strong hydrogen bond acceptors and only one hydrogen bond donor, suggesting it could be a promiscuous solvate former as well.

We tried to explore, understand, and rationalize the benperidol solvate formation, stability, and phase transformations. Benperidol was crystallized from solvents belonging to different solvent classes, the obtained solvates were characterized, and their crystal structures, as well as solvent and benperidol properties were used to rationalize their formation.

Crystallization of benperidol produced nine new solvates containing methanol, acetonitrile, ethyl acetate, nitromethane, 1,4-dioxane, water, benzyl alcohol, carbon tetrachloride, and chloroform, while the desolvation of benperidol solvates produced two new polymorphs IV and V. It was determined that benperidol forms two sets of isostructural solvates: type 1 (with methanol and ethanol) and type 2 (with acetonitrile, nitromethane, and ethyl acetate).

Desolvation studies of benperidol solvates showed that the stability of solvates can be associated with the intermolecular interactions in the crystal structure, while the structures of desolvation products were determined through an interplay of structural similarity and thermodynamic stability of the resulting polymorphs, and each of these factors could become dominant due to sample preparation procedures or experimental conditions.

The inability of benperidol molecules to pack efficiently without solvent was found to be the main reason for solvate formation, whereas the presence of specific functional groups in benperidol molecule enabled the formation of a wide range of stable solvate structures containing various solvent molecules. By using both sets of isostructural solvates it was proved that both the possible interactions and the size and shape of the solvent molecules were important factors in solvate formation. The formation of both benperidol hydrates, however, was driven by the compensation for hydrogen bond donor deficiency.