CHARACTERIZATION AND SOLUBILITY STUDIES OF PHARMACEUTICAL COCRYSTALS OF PALIPERIDONE

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Abstract:
Paliperidone is Chemically, (±)-3-[2-[4-(6-fluoro-1,2benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2- a]pyrimidin-4-one (Fig. 1). It is a psychotropic agent belongs to the chemical class of benzisoxazole derivatives, indicated for the treatment of schizophrenia. Paliperidone is the major active metabolite of risperidone. The mechanism of action of Paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism. It has poor bioavailability (28%).The hydrogen bond interactions between Paliperidone (P) and pharmaceutical coformers involving (-OH) from donar (Paliperidone) and two O atoms from acceptor (conformers).Liquid-assisted grinding method was successfully employed. These cocrystals were characterized basing on their unique thermal [differential scanning calorimetry (DSC) and spectroscopic [fourier transform infrared spectroscopy (FTIR)] profiles. They were further confirmed by power X-ray diffraction (PXRD) studies and characteristic vibrational modes in Raman spectra. The conformers prepared using benzoic acid, cinnamic acid and salicylic acid exhibited markedly high solubility compared to the pure Paliperidone (P).
Keywords: crystal form, physicochemical property

Introduction:

The major challenge to the design of oral dosage forms lies with their poor bioavailability. The most common causes of low oral bioavailability are poor solubility and low permeability of active pharmaceutical ingredient (API). Multiple approaches have been adopted to improve the solubility of poorly water soluble APIs including micronization, complexation with cyclodextrins, cosolvency, solid dispersions, salt forms, nanoparticles and surfactants, etc. Cocrystals are a class of multicomponent molecular crystals demonstrated to enhance the solubility, bioavailability and/or stability of API, which has been proposed as a unique crystal engineering approach to alter the physicochemical properties of compounds.

The present work was oriented towards improving solubility of Paliperidone by preparing cocrystals using liquid-assisted grinding technique (LAG) with the help of conformers such as benzoic acid, cinnamic acid and salicylic acid. The improvement in solubility is confirmed by characterizing prepared cocrystals by using several techniques such as thermal [differential scanning calorimetry (DSC) and spectroscopic [fourier transform infrared spectroscopy (FTIR)], power X-ray diffraction (PXRD) studies and dissolution test.