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Research Article

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-4H-pyrido[1,2- a]pyrimidin-4-one. 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). They were further confirmed by SEM studies. The conformers prepared using benzoic acid, cinnamic acid and salicylic acid exhibited markedly high solubility compared to the pure Paliperidone (P)..

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 ingredients (API). To increase the solubility of poorly water-soluble APIs, a variety of techniques have been used, including micronization[1], complexation with cyclodextrins[2], cosolvency[3-4], solid dispersions[5], salt forms[6], nanoparticles[7] and surfactants[8], etc. Cocrystals have been presented as a novel crystal engineering strategy to change the physicochemical properties of compounds. They are a family of multicomponent molecular crystals that have been shown to improve the solubility, bioavailability, and/or stability of API.

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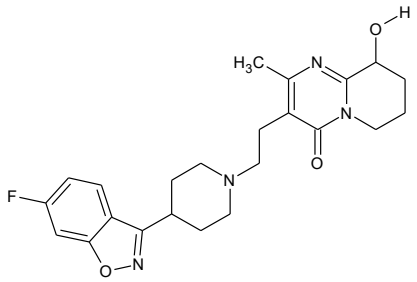
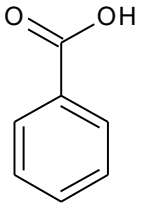
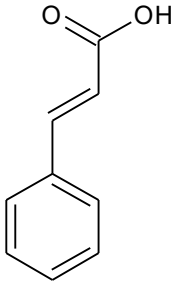


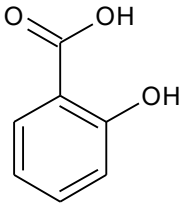
Figure1: Structures of Paliperidone



Benzoic acid



Cinnamic acid



Salicylic acid

The goal of the current work was to make Paliperidone more soluble by creating cocrystals utilizing the liquid-assisted grinding technique (LAG) and conformers such benzoic acid, cinnamic acid, and salicylic acid. Characterizing the produced cocrystals using a variety of methods, including thermal [differential scanning calorimetry (DSC) and power X-ray diffraction (PXRD), SEM examinations and saturation solubility studies confirms the improvement in solubility.

Experimental Section:

MATERIALS AND METHODS

Paliperidone was a gift sample from Vasuda Pharma Chem Ltd, HYD. The three acids—benzoic, cinnamic, and salicylic—were bought from SD Fine Chemicals in Mumbai, India. The supplier of the ethanol was HiMedia in Mumbai, India.

Preparation of cocrystals

LAG method was used to create cocrystals. Methanol was added dropwise as a solvent during grinding while equimolar amounts of the API and conformers (benzoic acid, salicylic acid, and cinnamic acid) were placed in a mortar and pestle at room temperature. The resulting material evaporated and dried.

Differential scanning calorimetric (DSC) Studies

When comparing the amount of heat needed to raise the temperature of a sample and a reference as a function of temperature, DSC is a thermo analytical technique that is used to measure the difference. DSC spectra are captured using Perkin Elmer DSC4000 equipment. The samples were crimped using non-hermetic aluminium pans, which were heated at a rate of 20° per minute and scanned from 50 to 250.

Powder X-ray diffraction (XRD) studies

The XRD spectra of the synthesised cocrystals were examined. The spectra aid in structural characterization and provide information on the crystal structure, chemical make-up, and physical characteristics of the substance. PXRD is an effective method for detecting changes in the crystal lattice, making it useful for researching polymorphism, medicinal salts, and co-crystalline phases. The samples were exposed to a copper tube with a 40KV voltage, and the spectra were recorded using a 30mA current. With a step size of 0.6 seconds and a scan range of 10° to 80°.

Solubility studies

Using the 24-hour shake flask method, the saturation solubility studies of paliperidone and its cocrystals were determined. In this investigation, extra amount of drug and cocrystals was addedd into vials with 10 ml of water. This was shaken with a mechanical shaker at room temperature for 24 hours. After filtering the mixture, a spectrophotometric analysis at 280 nm was performed to determine how much amount of drug and cocrystals had been dissolved.

Intrinsic Dissolution studies:

The intrinsic characteristics of a drug are measured as a function of the drug as a function of the dissolution media, such as pH, ionic strength, and

counter ions. Intrinsic dissolution assesses the rate of dissolution of a pure substance from constant surface area, which is independent of formulation effects. The effectiveness of APIs in vivo can be determined by looking at their intrinsic dissolution rate. Utilising the paddle method, the dissolving rate investigations were carried out in 900 ml of buffer (0.1NHCl) at 50 rpm and 37.5ºC in a dissolution equipment (Electrolab dissolving Tester (USP), TDT-06L).The dissolution medium (0.1NHCl) was combined with 100 mg of the drug or its equivalent in cocrystals, and samples were taken at regular intervals for four hours. The amount of fresh media was added to maintain the sink conditions.

SEM analysis

Paliperidone-Benzoic acid, Paliperidone-Cinnamic acid, and Paliperidone-Salicylic acid surface morphology was studied by SEM. It is clear that paliperidone has crystallised because it has typical crystalline structures in the compounds paliperidone-benzoic acid, paliperidone-cinnamic acid, and paliperidone-salicylic acid.

Results and Discussion:

The possible carboxylic-phenolic interactions with the Paliperidone and coformers were shown in Figure 2.

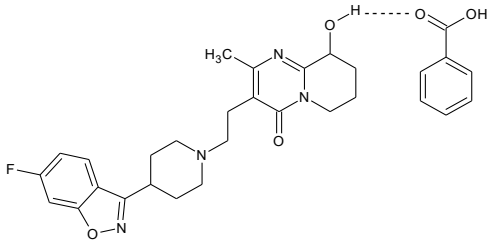


Figure 2 A: Hydrogen bond interactions of Paliperidone-Benzoic acid

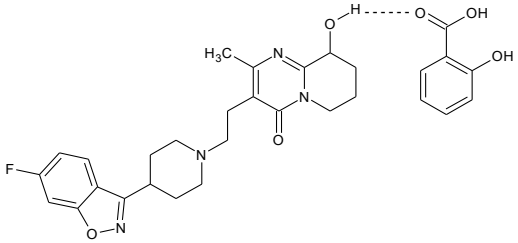


Figure 2 B: Hydrogen bond interactions of Paliperidone-Salicylic acid

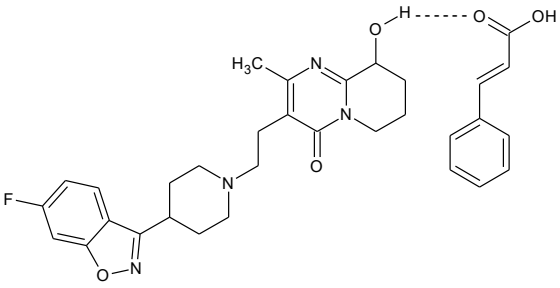


Figure 2 C: Hydrogen bond interactions of Paliperidone-Cinnamic acid

Characterization:

DSC studies:

The pattern and intensity of the DSC thermograms of the pure drug and the synthesised cocrystals were compared. The melting point of pure paliperidone was shown by a single sharp endothermic peak in the DSC data at 184.34 ºC. Paliperidone and benzoic acid cocrystal's DSC thermogram showed a single abrupt endothermic peak at 167.35ºC, which corresponds to the melting temperature and shows cocrystal formation rather than physical mixing. Paliperidone-cinnamic acid DSC data showed a single, abrupt endothermic peak at 152.53ºC, indicating the development of cocrystals. Paliperidone-Salicylic acid's DSC thermogram showed a single, abrupt endothermic peak at 172.56ºC, which is also the melting point of the co crystals that were generated. The fact that the cocrystals created had lower melting points than Paliperidone suggests that the cocrystals of Paliperidone with Benzoic acid, Cinnamic acid, and salicylic acid had higher cohesive energies.

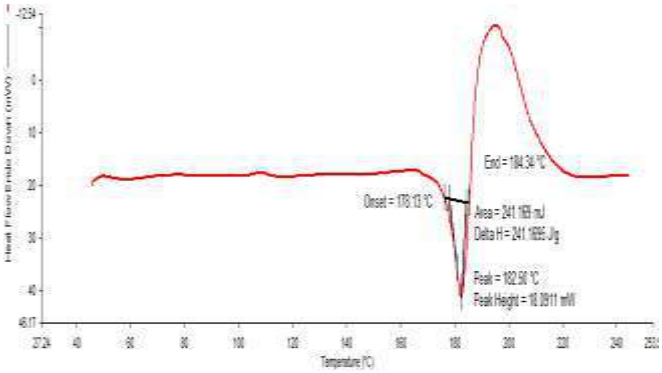


Figure 3A: DSC thermogram of pure drug Paliperidone

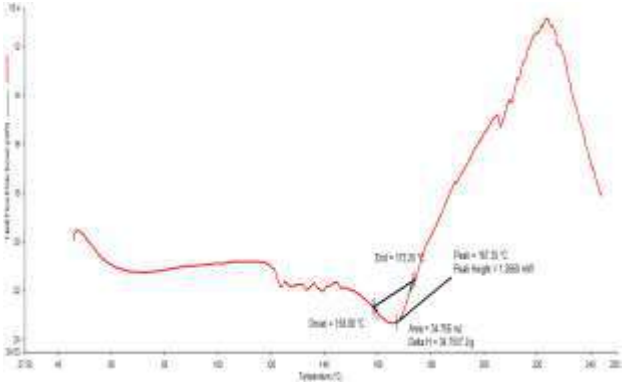


Figure 3B: DSC thermogram of Benzoic acid +Paliperidone

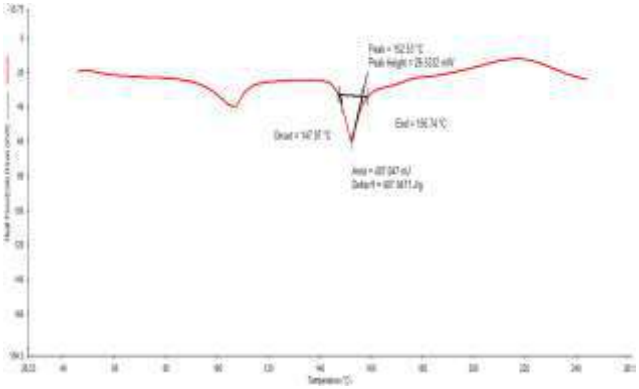


Figure 3C: DSC thermogram of Cinnamic acid +Paliperidone

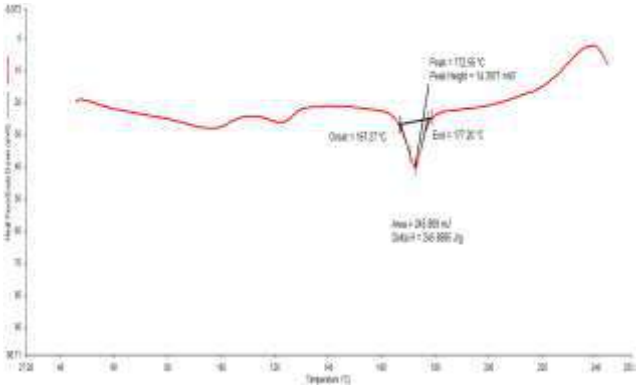


Figure 3D: DSC thermogram of Salicylic acid +Paliperidone

Solubility studies:

The produced cocrystals and the pure medication were studied for saturation solubility in aqueous media by shaking the samples on a mechanical shaker for 24 hours at room temperature. The samples were then analysed by UV spectrophotometer at 280 nm. The table 1 and Figure 4 depicted that the pure Paliperidone showed 0.25mg/ml whereas Paliperidone-Benzoic acid cocrystal showed 1.022 mg/ml; Paliperidone-Cinnamic acid cocrystal showed 1.085 mg/ml and Paliperidone-Salicylic acid cocrystal showed 2.023 mg/ml. The findings suggested that cocrystals produced with Salicylic acid had a significantly higher solubility in aqueous media than pure API (Paliperidone) and about a 60-fold increase in solubility.

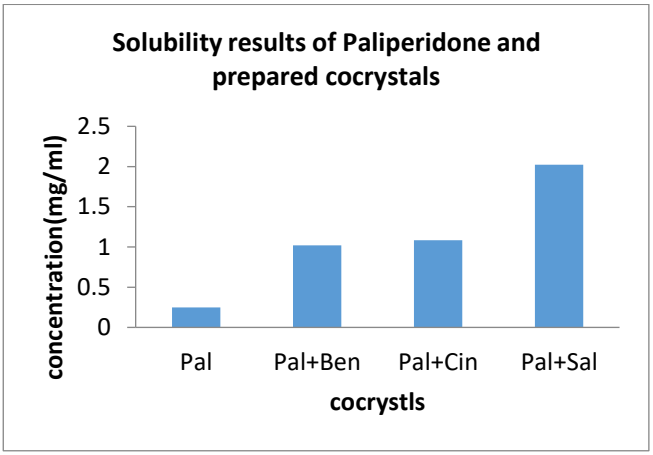


Figure 4: Solubility results of Paliperidone and prepared cocrystals

Table 1: Solubility profile of Paliperidone and cocrystals

S. No.	Samples	Solubility (mg/ mL)
1	Pal	0.25
2	Pal+Ben	1.022
3	Pal+Cin	1.085
4	Pal+Sal	2.023

SEM analysis:

Paliperidone-Benzoic acid, Paliperidone-Cinnamic acid, and Paliperidone-Salicylic acid surface morphology were studied by SEM and the images are displayed.

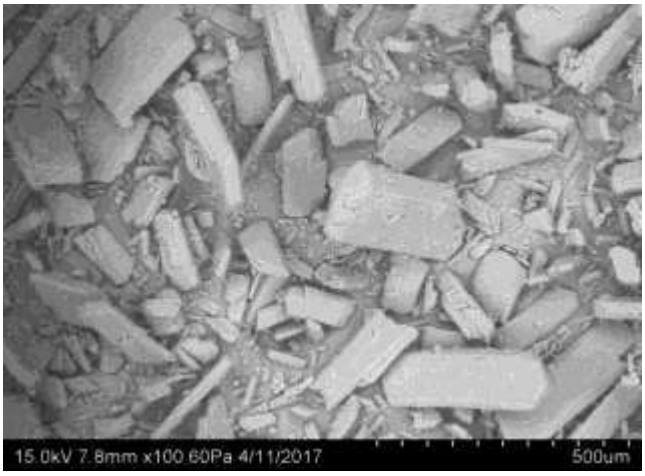


Figure 5A: Sem picture of paliperidone A

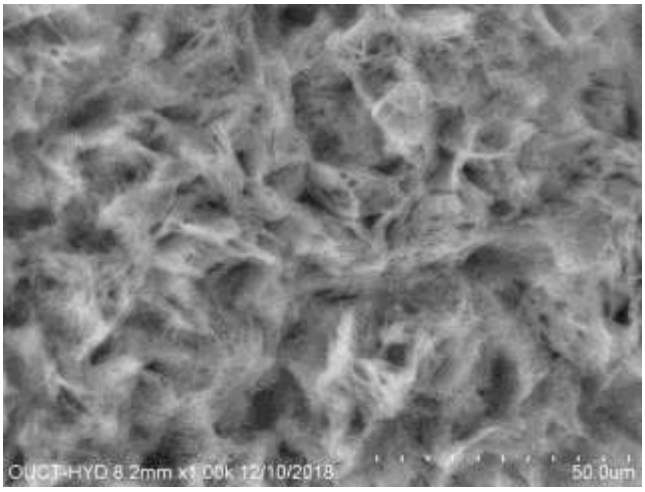


Figure 5B: Sem picture of Paliperidone-Benzoic acid

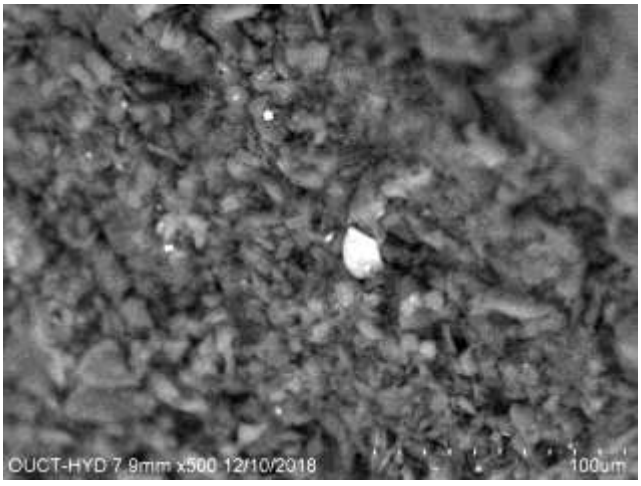


Figure 5C: Sem picture of Paliperidone-Cinnamic acid

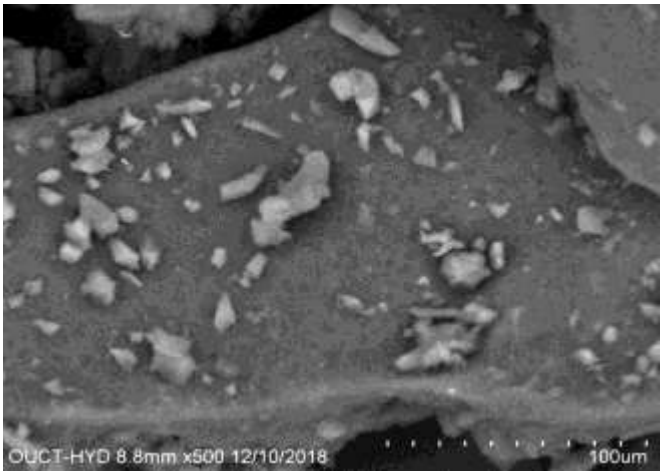


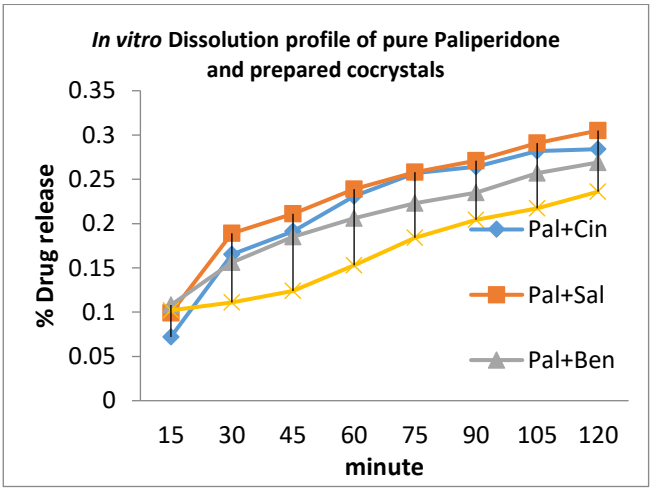
Figure 5D: Sem picture of Paliperidone-Salicylic acid

Dissolution test:

Paliperidone-Salicylc acid showed highest cumulative % drug release 37% within 15min, when compared with pure drug showed 28% at 15min. This study clearly showed that the design of cocrystals of paliperidone increased dissolution over pure drug.

Paliperidone-Salicylc acid reached 90% drug release within one hour, when compared with pure drug showed 81% at 1 hour because in liquid solid compacts the drug was present in solubilized state. So, drug surface available for dissolution got tremendously increased.

***In vitro* Dissolution profile of pure Paliperidone and prepared cocrystals**



DISCUSSION

To increase the solubility of the Paliperidone drug, a number of approaches are available that can be utilised singly or in tandem. Paliperidone's cocrystals were made using coformers like benzoic acid, cinnamic acid, and salicylic acid to further increase the drug's solubility. Using the LAG approach, three brand-new paliperidone cocrystals with coformers were created. DSC and SEM examinations were used to completely characterise each one. These findings make it clear that carboxylic-phenolic hydrogen bonds serve as the foundation for most intermolecular interactions. We will be able to test and synthesise advanced Paliperidone cocrystals with the use of the study's findings. DSC thermograms that showed a single abrupt melting endotherm at a site distinct from that of paliperidone and coformers suggested the formation of a novel crystalline phase. Before the genuine melting, there was a large desolvation endotherm, which suggested that solvated cocrystals had formed. Salicylic acid is the preferred coformer for the preparation of cocrystals of paliperidone, as evidenced by the fact that the paliperidone-Salicylic acid crystals had a significantly higher solubility than the other two crystals (2.03 mg/ml). Additionally, intrinsic dissolution studies in 0.1NHCl revealed that the cocrystallization method significantly increased the drug's bioavailability.

CONCLUSION

The drug paliperidone is prescribed to treat schizophrenia. It has a low (28%) bioavailability. Paliperidone (P) and pharmaceutical coformers engage via hydrogen bonds that include two O atoms from the acceptor (conformers) and (-OH) from the donor (Paliperidone).These cocrystals were successfully created using the liquid-assisted grinding process. The distinct thermal properties of these cocrystals were identified using differential scanning calorimetry (DSC).They were further supported by tests using SEM. Comparing these cocrystals to pure Paliperidone (P), they showed noticeably higher solubility (30–50 times higher). Additionally, they were assessed for their *in-vitro* dissolution studies, where all of the cocrystals displayed noticeably high dissolution profiles (50%) and indicated that they were in favour of enhancing Paliperidone's oral bioavailability**.**

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