INTRODUCTION

A co-crystal is a multi-component system in which all components are usually solid at room temperature in a stoichiometric ratio involving non-covalent interactions such as hydrogen bonds (most common interaction), VdVander Waals bonds, ionic bonds between components. Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Physicochemical properties of active pharmaceutical ingredients can be improved by employing crystal engineering technique. Co-crystallization with pharmaceutically acceptable GRAS (Generally Recognized As Safe) compounds do not affect the pharmacological activity of the API, but can improve physical properties, such as solubility, hygroscopicity, flowability, chemical stability, compaction behavior of nonionizable compounds (Gadade et al., 2016; Ross, Lamprou, Douroumis, 2016).

Co-crystal is a concept of supramolecular chemistry that is gaining the extensive interest of researchers from pharmaceutical and chemical sciences and of drug regulatory agencies. The approaches like hydrogen-bonding rules, solubility parameters, utility of Hansen solubility parameters, through the CSD database and thermodynamic characteristics can be utilized for the rational design of co-crystals and selection of coformers for the synthesis of multi-component co-crystals (Gadade et al., 2016; Mohammad, Alhalaweh, Velaga, 2011; Desiraju, 1995; Etter, 1990).

Posaconazole is a newly developed extended spectrum triazole with proven efficacy as antifungal...
treatment and used to treat invasive infections by Candida species and Aspergillus species in severely immunogenic patients (Schiller, Fung, 2007). It’s in vitro antifungal activity against zygomycetes species has been reported to be more pronounced compared to itraconazole (Connolly et al., 1999).

Solubility and dissolution are the key parameters for the therapeutic effect of a drug and to achieve the desired concentration of drug in systemic circulation for the pharmacological response. Posaconazole is a weakly dibasic drug that belongs to Class II of the Biopharmaceutical Classification System (BCS) (Amidon et al., 1995). Posaconazole is characterized by its low aqueous solubility of <1 μg/mL, high lipophilicity of Log P 4.6, and high molecular weight of 700.8 g/mol (Cristofoletti, Patel, Dressman, 2016; Schiller, Fung, 2007). Its large positive food effect and high solubility–pH dependence have resulted in low and erratic bioavailability (fraction absorbed <30%) in addition to daily doses of PSZ (300–600 mg) that are over 1000 times higher than what can be dissolved in a luminal volume of 250 mL. (Walravens et al., 2011; Amidon et al., 1982; Benet, Broccatelli, Oprea, 2011). It has variable bioavailability following oral administration, leading to inconsistent pharmacokinetics of this agent. Current oral formulations include a suspension and a delayed-release tablet. Given its broad and unique spectrum of activity, there is a need for crystal forms of posaconazole that can be formulated as suspensions or solid dosage forms with less variability as well as better solubility, dissolution, stability, and properties suitable for pharmaceutical processing. Posaconazole is structurally analogous to itraconazole. Several salts and cocrystals of azole drugs have been discovered. Recently co-crystals of posaconazole with 4-aminobenzoic acid (4AMB) have been generated by the reaction crystallization method and demonstrated a superior solubility compared to posaconazole (Kuminek et al., 2019). Generation of cocrystals of PSZ with 4-aminobenzoic acid (4AMB) using supercritical CO2 as an antisolvent in GAS (Gas Antisolvent) with acetonitrile, and as a solvent in CSS (Cocrystallization with supercritical solvent) methods are also reported (Long et al., 2020). However, there is no literature on solubility and dissolution rate enhancement of posaconazole with adipic acid as coformer by cocrystallization using solvent assisted grinding method.

Subsequently, there is a need to deliver posaconazole in formulation with increased solubility and improved dissolution profile. The development of co-crystals is a remarkable approach to increase its bioavailability by enhancing its rate and extent of dissolution (Lee, Zhang, Flanagan, 2011).

**MATERIAL AND METHODS**

**Material**

Posaconazole was obtained as a gift sample from Aurobindo Pharma-Hyderabad, adipic acid was procured from S.D. Fine Chemicals Limited, Mumbai. All other chemicals were of analytical grade.

**Preparation of co-crystals by solvent assisted grinding technique**

Posaconazole (1mmol) and coformer adipic acid (1mmol) were taken and mixed in a mortar pestle using ethanol (2-3 drops) as a solvent. The triturating process was carried out for 30-45 mins and co-crystals were stored in desiccators. The formation of new co-crystals was confirmed by melting point, FTIR, PXRD and DSC (Weyna et al., 2009).

**Determination of physical constant (melting point)**

The melting point of posaconazole and co-crystals were determined using open capillary tube method. The sample was filled and placed in the melting point apparatus (Cheney et al., 2011) (Biotech India Melting apparatus, Mumbai).

**Solid-state characterization**

**Fourier transform infrared spectroscopy (FTIR)**

Fourier Transform-Infrared Spectroscopy (FTIR) is an analytical technique used to identify organic and, in some cases, inorganic materials. The infrared absorption bands identify molecular components and structures. IR spectroscopy was conducted using FTIR
spectrophotometer (Shimadzu Corporation, Kyoto, Japan) with potassium bromide pellet method and background spectrum was collected under identical conditions. The spectrum was recorded in the wavelength region of 4000-400 cm⁻¹ (Mutalik et al., 2007).

**Powder x-ray diffraction (PXRD)**

The PXRD pattern of posaconazole and prepared co-crystals were studied to investigate the crystalline nature of posaconazole and co-crystals. The study was carried out using an x-ray diffractometer, Shimadzu module XRD 7000 (2θ=10-80 ºC, scan speed=2 deg/min) using Cu kα radiations. The tube operated at 40 kV (Tsutsumi et al., 2011).

**Differential scanning calorimetry (DSC)**

DSC method can be used as a screening tool for the detection of co-crystal formation in binary physical mixtures of drugs and co-former. Thermal analysis of posaconazole and prepared co-crystals were recorded on a DSC (Shimadzu DSC-60, Tokyo, Japan). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 10 ºC/min was employed with nitrogen purging. Powder sample (5-10 mg) was filled into an aluminium pan and was subjected to heating from 0-300 ºC, using an empty aluminium pan as a reference and analyzed. (Rahman et al., 2011).

**UV spectral interference of adipic acid with posaconazole**

Since the analysis of posaconazole was done in presence of adipic acid, it was necessary to identify the interference of adipic acid. For this purpose, posaconazole solution, adipic acid solution, the posaconazole-adipic acid solution was scanned in the range of 200-400 nm. (Nijhawan et al., 2014).

**Saturation Solubility Study**

Saturation solubility studies were performed in triplicate by adding an excess quantity of posaconazole-adipic acid co-crystals and pure drug in volumetric flasks containing 0.1 N hydrochloric acid. Volumetric flasks were agitated in an orbital shaker for 24 hours at 25 ºC at 100 RPM. The solutions were then filtered and amount of drug dissolved was analyzed spectrophotometrically.

**Dissolution studies**

Dissolution studies were carried out using USP dissolution test apparatus II in 900 ml of 0.1 N hydrochloric acid solution at 50 RPM, temperature was maintained at 37 ± 0.5 ºC. Posaconazole and posaconazole-adipic acid co-crystals containing the drug equivalent to 100 mg filled in hard gelatin capsules were added to the dissolution medium and samples were withdrawn at appropriate time intervals. The samples were filtered through a 0.45μm filter and analyzed spectrophotometrically at 255 nm (Shimadzu UV-2600 Tokyo, Japan) using 0.1 N hydrochloric acid as blank. The data obtained from dissolution studies were statistically validated, Further dissolution efficiency was calculated to compare dissolution performance of co-crystals with the pure drug by the following equation:

\[
\text{D.E.} = \frac{\int y \times dt}{y_{100} \times t} \times 100\%
\]

where y is the percentage of the dissolved product. D.E. is the area under the dissolution curve between time points \( t_1 \) and \( t_2 \), expressed as a percentage of the curve at maximum dissolution, \( y_{100} \) over the same time period (Costa, Sousa Lobo, 2001).

**Evaluation of micromeritic properties (Flowability)**

In order to achieve uniformity in tablet weight, the feed crystals must flow smoothly into the die cavity of the tablet machine. Therefore, it is essential to improve the flow properties of powders. For this purpose, angle of repose, Carr’s index and Hausner’s ratio were calculated for posaconazole and prepared co-crystals using the standard procedure reported in the pharmacopoeia. Angle of repose was determined by the fixed funnel method and Carr’s index, Hausner’s ratio
was calculated from bulk density and tapped density using the following equations.
Carr’s index = [(Tapped density - Bulk density)/Tapped density] x 100
Hausner’s ratio = Tapped density/ Bulk density

RESULTS AND DISCUSSION

The formation of co-crystal or salt is generally guided by a thumb rule of $\Delta pK_a (\Delta pK_a = pK_a \text{ (base)} - pK_a \text{ (acid)}$) value between active pharmaceutical ingredient (API) and coformer. The coformer is selected on basis of $\Delta pK_a$ values, where $\Delta pK_a$ is the difference between $pK_a$ of drug and coformer. If $\Delta pK_a<0$, a co-crystal will almost result and if $\Delta pK_a>3$, the result will most likely be a salt. The $pK_a$ and $\Delta pK_a$ value of posaconazole and adduct was found to be 4.6 and 0.19 respectively which infers the chances of co-crystal formation (Cheney et al., 2010).

Determination of physical constant (melting point)

Posaconazole showed an endothermic peak at 168.4°C. Co-crystals of posaconazole prepared with adipic acid have shown melting endothermic peak at 128.6°C i.e., lower than the melting point of pure drug and adipic acid (152 °C). This observation clearly indicated the formation of co-crystals of API with the coformer used. Within the survey 50 cocrystalline samples were analyzed; 26/50 (51%) co-crystals had melting points between those of the API and coformer, while 19/50 (39%) were lower than either the API or coformer, only 3/50 (6%) were higher, and 2/50 (4%) had the same melting point as either the API or coformer. These statistics clearly show that the melting point of an API can be altered through forming co-crystals, and the outcome will usually be a product having a melting point that is in between that of the API and coformer or lower than the API or coformer. The co-crystals are formed by physical interaction between API and coformer and generally H bonding is expected between polar functional group of API and coformer. This interaction results in alterations in molecular arrangement of co-crystal formed, hence giving new crystal form having altered physical properties such as melting point and/or solubility. Thus the strength of hydrogen bonding will definitely influence the melting point characteristic of co-crystal (Mulya et al., 2012 Schultheiss, Newman, 2009; Stanton, Bak, 2008).

Solid-state characterization

Fourier transform infrared spectroscopy (FTIR)

Fourier-transform IR (FTIR), the simultaneous study of the spectra of the co-crystals individual components and of their final mixture with polymer matrices, etc., is an important tool in detecting co-crystal formation and the elucidation of their structures. The co-crystals provide a different spectrum from that of the components due to the presence of hydrogen bonds, especially when carboxylic acid is used as a coformer and when a neutral hydrogen bond O–H ⋯ N is formed between an acid and a base (Karagianni, Malamatari, Kachrimanis, 2018). The IR spectrum for co-crystals of posaconazole with adipic acid is shown in Figure 1. The characteristic bands were identified and associated changes were recorded in Table I along with the literature data. The results revealed considerable changes in the IR bands of posaconazole indicating the formation of co-crystals of posaconazole with adipic acid.
Pharmaceutical co-crystals of posaconazole for improvement of physicochemical properties

**FIGURE 1** - FTIR spectral comparison of posaconazole, adipic acid and posaconazole-adipic acid co-crystals.

**TABLE I** - FTIR bands for characteristic changes of posaconazole and posaconazole-adipic acid co-crystal

| Drug            | Characteristic bands, cm\(^{-1}\)                                    | Inference                                      |
|-----------------|------------------------------------------------------------------------|------------------------------------------------|
| Posaconazole    | C=O – 1685.79, -CH (aliphatic) – 2964.59, C-H (deformation in aromatic rings) – 1548.84, C=N – 1510.26, OH – 3116.97, =C-H (stretching) – 3053.32 | Characteristic peaks have been observed         |
| Posaconazole-adipic acid | C=O – 1703.15, -CH (aliphatic) – 2966.52, C-H (deformation in aromatic rings) – 1548.84, C=N – 1510.26, OH – 3116.97, =C-H (stretching) – 3053.32 | C=O shift has been observed. Co-crystals might have formed. |
Powder X-Ray Diffraction Studies (PXRD)

PXRD is a powerful technique for determining the presence of polymorphs and crystal habit modifications in drug crystals. PXRD gives a unique fingerprint diffraction pattern characteristic of a particular solid form. If a co-crystal has been formed between two solid phases, the diffraction pattern of the prepared co-crystal must be clearly distinct from drug and coformer by the superimposition of PXRD pattern. The PXRD pattern of posaconazole is shown in Figure 2 which indicates the crystalline nature of the drug. Sharp intense peaks at 19.63°, 17.64°, 15.72° showed that sample is posaconazole. The pure adipic acid showed 2θ value for 100% intensity at 17.87°. The powder XRD pattern of co-crystal showed intense peaks at 17.67°, 19.37°, 9.77° indicating shifting in 2θ values. Prepared posaconazole-adipic acid co-crystals showed the presence of additional peaks, change in peak intensities that might be attributed to different crystal habits and arrangement of molecules indicating the formation of new crystal form which is again confirmed by DSC studies. Further, the relative intensities of their PXRD peaks were modified which might be attributed to the different crystal habits and arrangement of molecules, indicating the formation of new crystal form (Mulye et al., 2012; Garekani et al., 2001).

FIGURE 2 - PXRD pattern of posaconazole-adipic acid co-crystal and its individual components.
Differential scanning calorimetry (DSC)

DSC gives an accurate temperature for the onset of melting. DSC thermograms of posaconazole and co-crystals were shown in Figure 3. Posaconazole showed an endothermic peak at 168.48 °C corresponding to its melting point while the co-crystals showed a peak at 128.62 °C. The endothermic peak of co-crystals was found to be different the drug and co-crystal former, that confirms the formation of a new phase.

FIGURE 3 - DSC thermogram of posaconazole, posaconazole-adipic acid co-crystals and adipic acid.
Flowability studies

Micromeritic properties which are represented in terms of angle of repose, Carr’s index and Hausner’s ratio are reported in Table II. It has been found that posaconazole-adipic acid co-crystals had improved flowability compared to that of pure drug. The poor flow properties of pure posaconazole crystals might be attributed to their smaller particle size. On the other hand, the co-crystallization of posaconazole is resulted in an increase in the size of co-crystals and a significant alteration in their shape. This might be the reason for the improved flowability of co-crystals as compared to pure drug crystals (Patric, 2011; Buckton, 1998).

![Table II - Flow properties of posaconazole and posaconazole-adipic acid co-crystal](image)

| Name                           | Bulk density | Tapped density | Carr's index | Hausner's ratio | Angle of repose | Property       |
|--------------------------------|--------------|----------------|--------------|-----------------|-----------------|----------------|
| Posaconazole                   | 0.15±0.005   | 0.25±0.01      | 35±0.003     | 1.54±0.03       | -               | Very poor      |
| Posaconazole- adipic acid co-crystal | 0.36±0.005   | 0.47±0.01      | 17.55±0.2    | 1.27±0.02       | 31.22±1.2       | Fair           |

UV spectral interference of adipic acid with posaconazole

Based on the scans, it was observed that adipic acid did not show interference at the working concentration (255nm) as shown in Figure 4. Therefore, posaconazole was estimated at 255 nm for drug content and dissolution studies.

![FIGURE 4 - UV absorption spectrum of posaconazole, adipic acid and a mixture of posaconazole-adipic acid (10 µg/mL each) at 255 nm.](image)
Saturation Solubility Study

The co-crystals have shown enhancement in solubility as compared to pure drug alone. Solubility of the pure drug was found to be 0.0053 mg/mL while posaconazole-adipic acid co-crystals showed 0.0107 mg/mL solubility in 0.1 N HCl. Solubility of co-crystals was increased (2 folds) with adipic acidololds) with sodium acetate. These results agreed with the observations made with melting point studies indicating the successful interaction of posaconazole with coformers and formation of co-crystals. The existence of a correlation between the melting point of co-crystals and their solubility has been well documented. In the AMG517 study, the authors reported that after a correlation analysis of the solubility parameters, the highest interdependence was the Log of solubility (Log Smax) versus the melting point. A correlation plot of Log Smax versus co-crystal melting point of the nine AMG517 cocorystals showed a 55% correlation of the variability in Log Smax to variability in the melting point of the co-crystal, suggesting that higher melting point of a co-crystal contributes to its lower solubility (Stanton, Bak, 2009).

In vitro dissolution study

In vitro dissolution studies reveal that co-crystals showed enhancement in the dissolution rate. This can be observed from the comparative dissolution profile shown in Figure 5. The enhancement in the dissolution rate of posaconazole was 7.12 folds from adipic acid co-crystals within 30 mins. The release of pure drug was found to be 77% while posaconazole-adipic acid co-crystals showed complete drug release within 120 mins. From the dissolution study, it was revealed that the prepared co-crystal exhibited rapid and complete drug release as compared to posaconazole. The dissolution efficiency was expressed in terms of percentage and found to be 61.65% for posaconazole-adipic acid co-crystal compared to posaconazole (46.58 %) indicating dissolution efficiency has improved for co-crystal preparation (Yadav, Dabke, Shete, 2010). Similarity and Difference factors for co-crystal are calculated in comparison with pure drug. The values are found to be 35.1 and 39.2 for Similarity factor and Difference factor, respectively, indicating dissolution abilities of co-crystals are not similar to posaconazole (pure drug).

**FIGURE 5** - Dissolution-time profile of posaconazole and posaconazole-adipic acid co-crystal.
CONCLUSION

Through crystal engineering technique, multicomponent co-crystals of posaconazole were developed using adipic acid as a guest. Posaconazole-adipic acid co-crystal was successfully characterized by FTIR, DSC and PXRD. The co-crystals showed improved micromeritics properties and enhanced dissolution rate compared to pure drug. Based on the results, it can be concluded that pharmaceutical co-crystallization of posaconazole with adipic acid can be possible. It can be used as an alternative and effective approach for solid-state manipulation for improving physicochemical properties of posaconazole.

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