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AMORPHOUS SOLID DISPERSIONS AND SOLVATES OF ACORAMIDIS HCl

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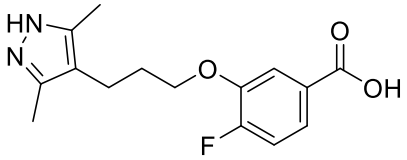
Abstract:

The present application relates to solid state forms of Acoramidis HCl and processes for preparation thereof.

Background:

The drug compound Acoramidis is chemically known as 3-(3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propoxy)-4-fluorobenzoicacid and has structure depicted by Formula I. This molecule is under development by Eidos Therapeutics for transthyretin stabilizer (cardiomyopathy).



Formula I

Crystalline solids normally require a significant amount of energy for dissolution due to their highly organized, lattice like structures. For example, the energy required for a drug molecule to escape from a crystal is more than from an amorphous or a non-crystalline form. It is known that the amorphous forms in a number of drugs exhibit different dissolution characteristics; and in some cases, different bioavailability patterns compared to the crystalline form. For some therapeutic indications, one bioavailability pattern may be favored over another. Therefore, it is desirable to have amorphous forms of drugs with high purity to meet the needs of regulatory agencies and also highly reproducible processes for their preparation.

In view of the above, it is therefore, desirable to have access to stable amorphous form of Acoramidis HCl. The amorphous form provided herein is at least stable under ordinary stability conditions with respect to purity, storage and is free flowing powder.

Amorphous solid dispersions of drugs are generally known to improve the stability and solubility of drug products. However, some of such amorphous solid dispersions are found to be unstable over time. Amorphous solid dispersions of drugs tend to convert to crystalline forms over time, which can lead to improper dosing due to differences of the solubility of crystalline drug material compared to amorphous drug material. The present invention, however provides stable amorphous solid dispersions of Acoramidis HCl with improved solubility. Moreover, the present invention provides amorphous solid dispersions of Acoramidis HCl which may be reproduced easily and is amenable for processing into a dosage form.

Examples

Example 1: Amorphous solid dispersion of Acoramidis HCl with Copovidone (1:1 w/w)

Acoramidis hydrochloride (200 mg) and Copovidone (200 mg) were dissolved in 20% methanol-DCM (15 mL). The solution obtained was filtered, concentrated under reduced pressure at 45 °C and dried under vacuum to obtain a sticky off-white solid (352 mg, purity: 99.46% by HPLC). 100 mg of this solid obtained was mixed with Syloid 244 FP (100 mg) and ground together to obtain a free flowing solid. Figure 1 is an illustrative X-ray powder diffraction pattern of this premix obtained.

Example 2: Amorphous solid dispersion of Acoramidis HCl with PVP K-30 (1:1 w/w)

Acoramidis hydrochloride (150 mg) and PVP K-30 (150 mg) were dissolved in 20% Methanol-DCM (15 mL). The solution obtained was filtered, concentrated under reduced pressure at 45 °C and dried under vacuum to obtain a sticky off-white solid (252 mg, purity: 99.50% by HPLC). 75 mg of this solid obtained was mixed with Syloid 244 FP (75 mg) and ground together to obtain a free flowing solid. Figure 2 is an illustrative X-ray powder diffraction pattern of this premix obtained.

Example 3: Amorphous solid dispersion of Acoramidis HCl with HPC (1:2 w/w)

Acoramidis hydrochloride (100 mg) and HPC (200 mg) were dissolved in 20% Methanol-DCM (30 mL). The solution obtained was filtered, concentrated under reduced pressure at 45 °C and dried under vacuum to obtain an off-white sticky fluffy solid (228 mg, purity: 99.35% by HPLC). 75 mg of this solid obtained was mixed with Syloid 244 FP (75 mg) and ground together to obtain a free flowing solid. Figure 3 is an illustrative X-ray powder diffraction pattern of this premix obtained.

Example 4: Amorphous solid dispersion of Acoramidis HCl with HPMC (1:2 w/w)

Acoramidis hydrochloride (100 mg) and HPMC (200 mg) were dissolved in 20% Methanol-DCM (20 mL). The solution obtained was filtered, concentrated under reduced pressure at 45 °C and dried under vacuum to obtain an off-white sticky fluffy solid (225 mg, purity: 99.37% by HPLC). 100 mg of this solid obtained was mixed with Syloid 244 FP (100 mg) and ground together to obtain a free flowing solid. Figure 4 is an illustrative X-ray powder diffraction pattern of this premix obtained.

Example 5: DMF solvate of Acoramidis HCl

Acoramidis hydrochloride (200 mg) was dissolved in DMF (10 mL) at RT. The solution was filtered and concentrated under reduced pressure at 70 °C. The solid obtained was under vacuum at 27 °C for 15-20 min to obtain the title compound. Details are given below.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.93-1.90 (m, 2H), 2.23 (s, 6H), 2.57 (t, J = 7.2 Hz, 2H), 2.73 (s, 2.46H, DMF), 2.89 (s, 2.52H, DMF), 4.07 (t, J = 6.4 Hz, 2H), 7.34 (dd, J = 10.8, 8.4 Hz, 1H), 7.56 (ddd, J = 8.4, 4.4, 2.0 Hz, 1H), 7.61 (dd, J = 8.4, 1.6 Hz, 1H), 7.95 (s, 0.76H, DMF)

Yield	Purity	Appearance	PXRD	TGDTA
188 mg	95.64% (by HPLC)	Off-white solid	Figure 5	Figure 6

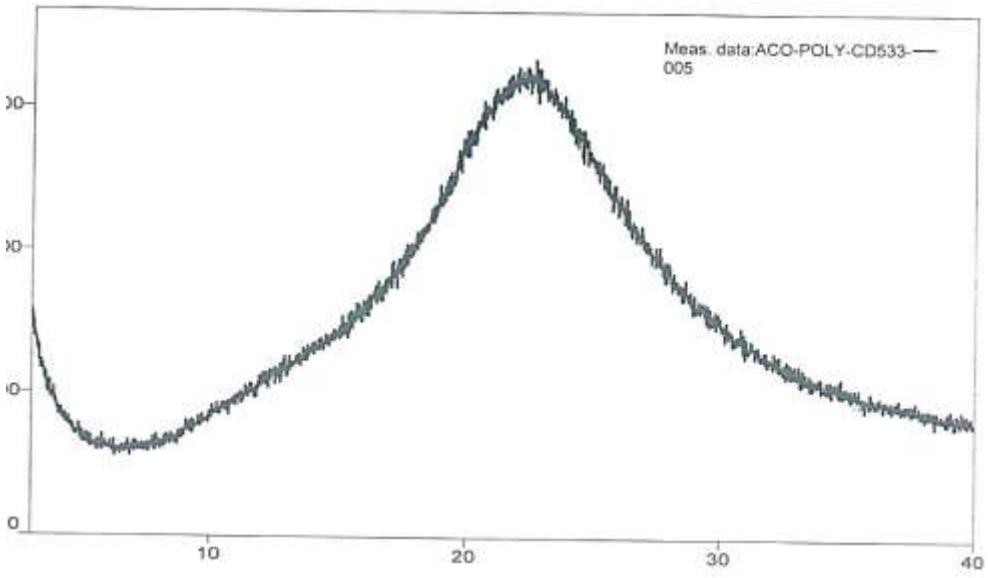


Figure 1: PXRD of Amorphous solid dispersion of Acoramidis HCl with Copovidone (1:1 w/w)

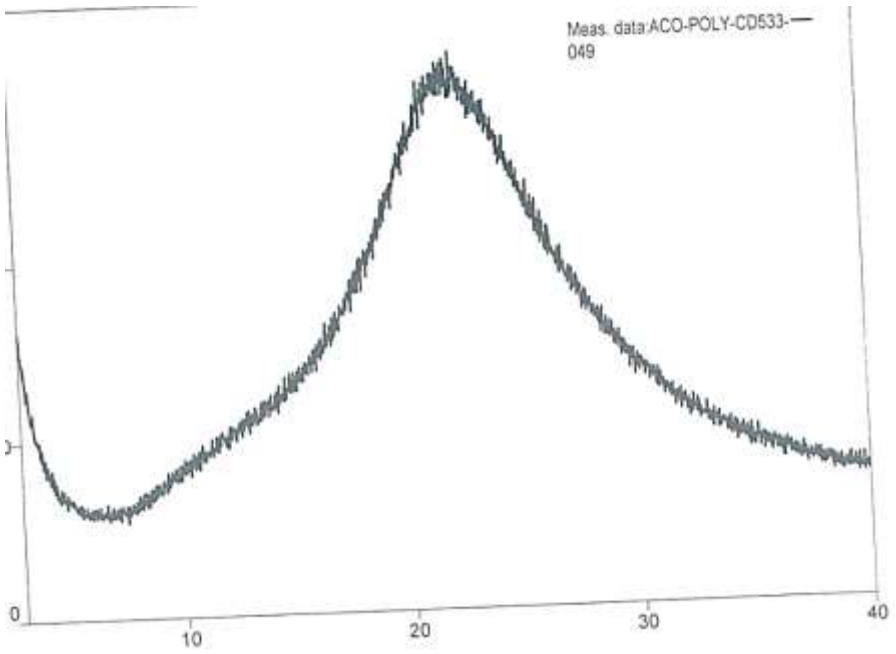


Figure 2: PXRD of Amorphous solid dispersion of Acoramidis HCl with PVP K-30 (1:1 w/w)

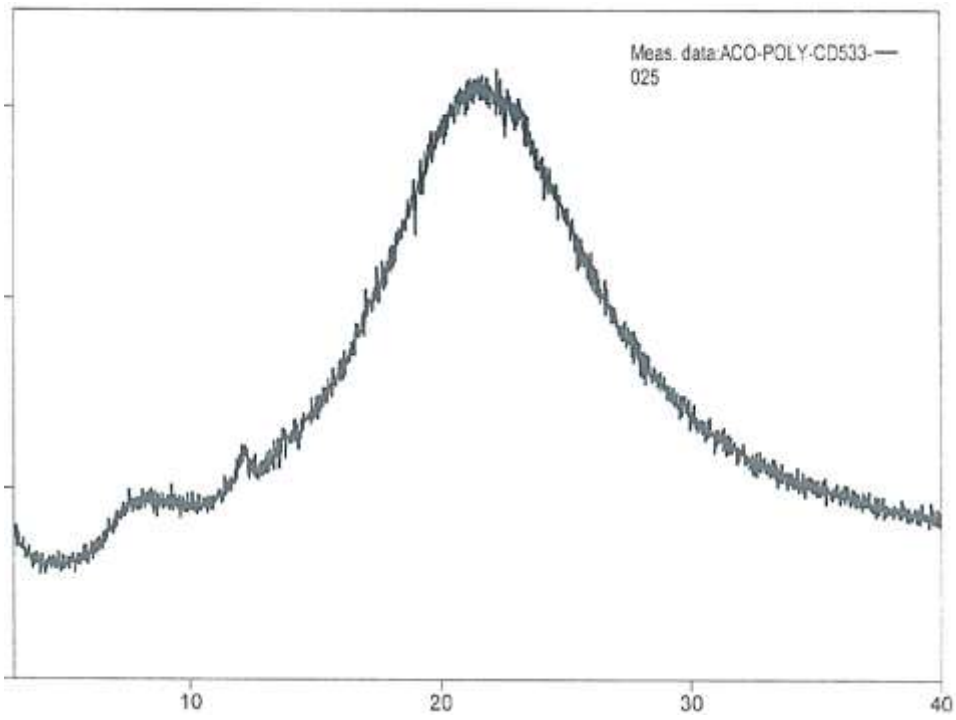


Figure 3: PXRD of Amorphous solid dispersion of Acoramidis HCl with HPC (1:2 w/w)

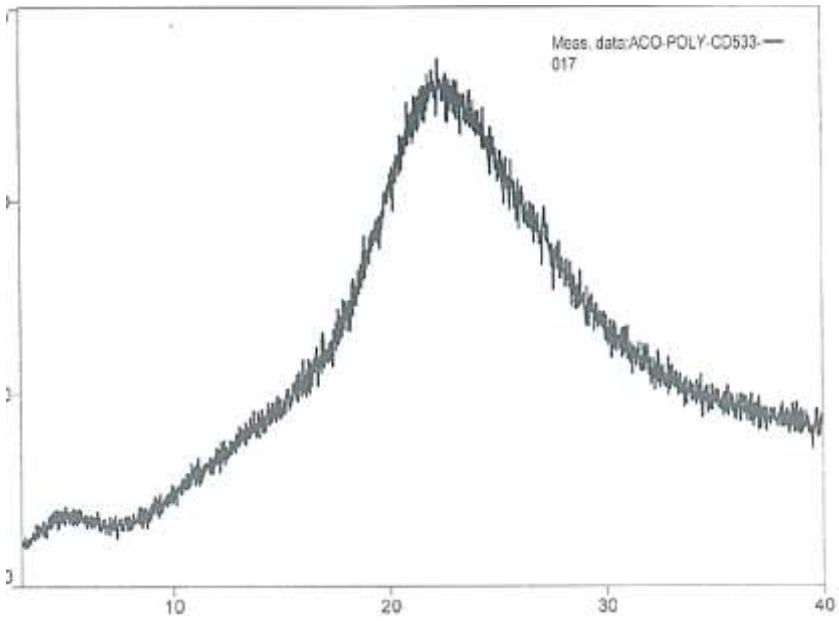


Figure 4: PXRD of Amorphous solid dispersion of Acoramidis HCl with HPMC (1:2 w/w)

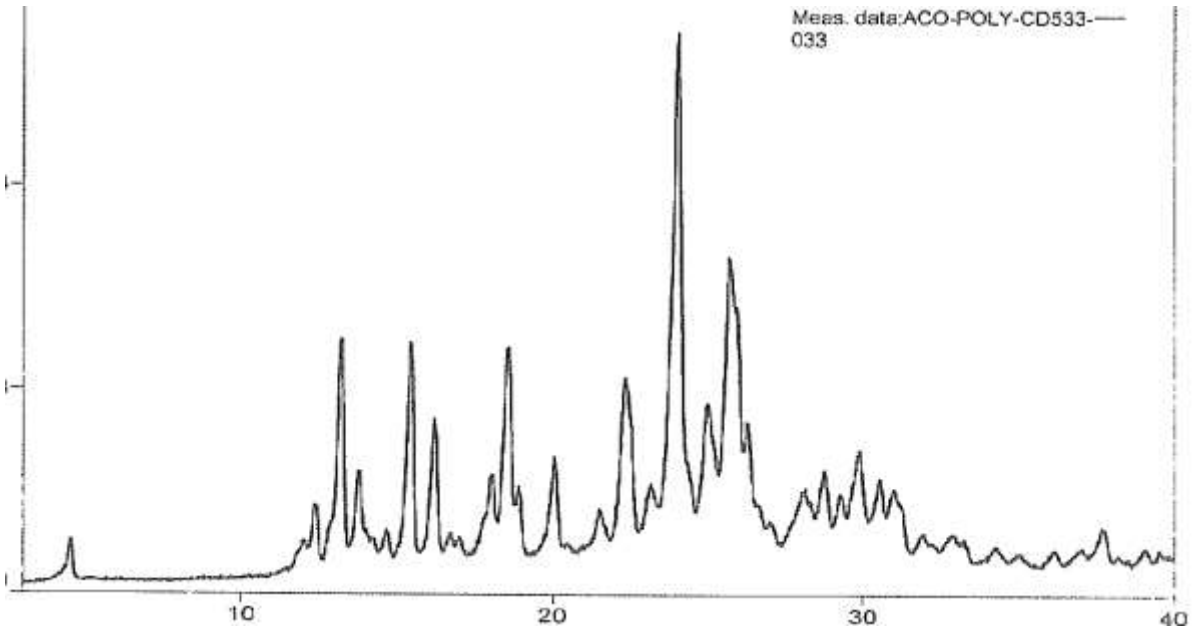


Figure 5: PXRD of DMF solvate of Acoramidis HCl

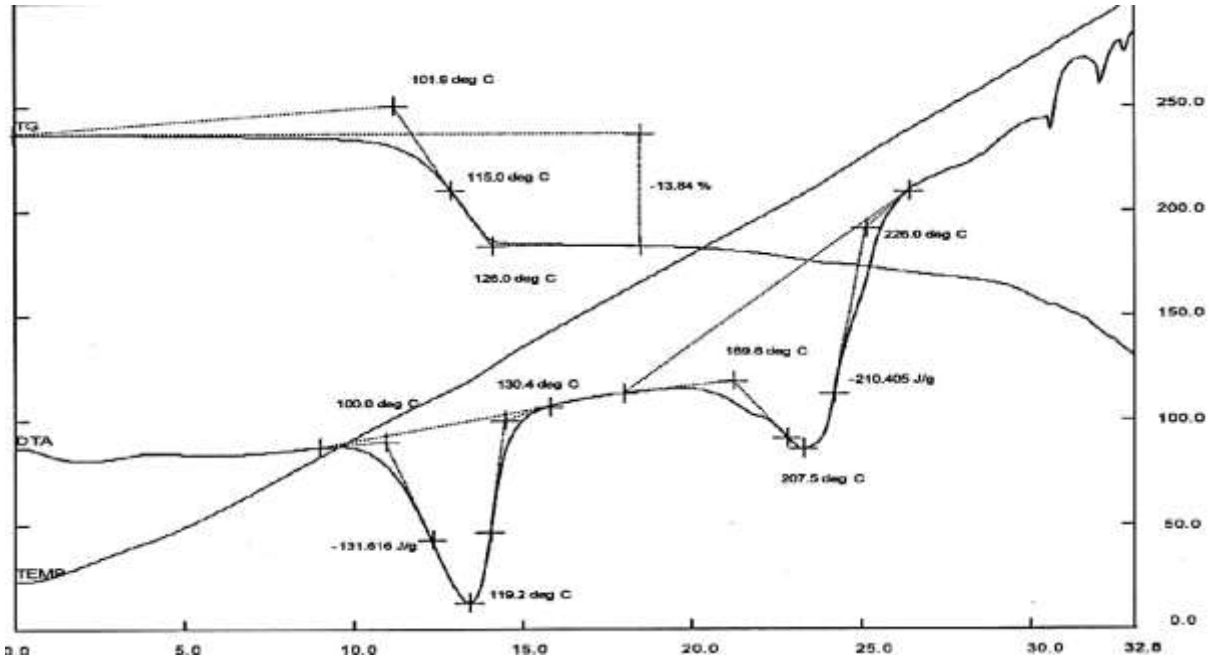


Figure 6: TGDTA of DMF solvate of Acoramidis HCl