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Crystal forms of linezolid

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ABSTRACT

Three crystal modifications (polymorphs) of Linezolid designated as Form A1, Form B1 and Form C1 have been obtained through recrystallization using organic solvents under different conditions. Thus obtained crystal forms of Linezolid were characterized by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and thermo gravimetric analysis (TGA) and the data acquired proved the crystal forms to be different than the prior art forms.

Keywords: Linezolid, Crystal form, Polymorphism, PXRD

INTRODUCTION

It has been known since the middle of 18th century that many substances could be obtained in more than one crystalline form [1] but the subject of drug polymorphism has received extensive academic and industrial attention since the early pionering reports of Aguiar and colleagues at Parke-Davis, in which effect of polymorphism on dissolution and bioavailability were highlighted for chloramphenicol palmitate [2,3]. It is the wellknown fact that nature of structure adopted by a given compound on crystallization would have a profound effect on the solidstate properties of the system. It was found that various polymorphs could exhibit different solubilities and dissolution rates and these differences sometimes lead to the existence of non-equivalent bioavailabilities for different forms. Polymorphism in crystalline solid is defined as materials with the same chemical composition different lattice structures and/or different molecular composition [4,5,6,7]. Pseudopolymorphism is a term that refers to crystalline forms with solvent molecules as an integral part of the structure. [8,9] Knowledge of crystal structure has also been applied to further understand chemical stability and dehydration or solvent loss [9].

There is a renewed interest in polymorph;this is partly due to increased economic pressure faced by pharmaceutical companies and the greater awareness of the effect that polymorphs may have on the bioavailability, manufacturability and stability of the product. This is also reflected in regulatory recommendations with regard to polymorphism appearing in both 'new drug application' (NDA) and 'abbreviated new drug application' (ANDA) particularly those for solid dosage form [10,11,12].

Once the diversity of solid state form is known, a decision can be made as to which crystal form should be selected for further development during preclinical & clinical testing. This decision must ultimately be based upon the physico-chemical attributes of various crystal forms including their solubility and physical and chemical stability.

Linezolid is a synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. A member of the oxazolidinone class of drugs, Linezolid is active against

most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) [13]. The main indications of Linezolid are infections of the skin and soft tissues and pneumonia (particularly hospital-acquired pneumonia), although off-label use for a variety of other infections is becoming popular.

Discovered in the 1990s and first approved for use in 2000, Linezolid was the first commercially available 1,3-oxazolidinone antibiotic. As of 2009, it is the only marketed oxazolidinone, although others are in development. As a protein synthesis inhibitor, it stops the growth of bacteria by disrupting their production of proteins. Although many antibiotics work this way, the exact mechanism of action of Linezolid appears to be unique in that it blocks the initiation of protein production, and not one of the later steps. [14]. Bacterial resistance to Linezolid has remained very low since it was first detected in 1999, although it may be increasing.

When administered for short periods, Linezolid is a relatively safe drug; it can be used in patients of all ages and in people with liver disease or poor kidney function. Common adverse effects of short-term use include headache, diarrhea, and nausea. Long-term use, however, has been associated with serious adverse effects; Linezolid can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks. If used for longer periods still, it may cause peripheral neuropathy (which can be irreversible), optic nerve damage, and lactic acidosis (a buildup of lactic acid in the body), all most likely due to mitochondrial toxicity.

Linezolid, chemically N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide having CAS Registry Number: 165800-03-3 is an antibacterial agent. Linezolid is an oxazolidinone, having the empirical formula $C_{16}H_{20}FN_3O_4$ and the structure as shown in Fig. 1.

Linezolid was first disclosed by Upjohn Company [15]. Various solid state forms of Linezolid have been disclosed in the prior art: crystalline Form I [16], Form II [17], Form III [18] and many others [19, 20], amorphous form [21], hydrated forms [22, 23] and co-crystals [24].

MATERIALS AND METHODS

Materials

Linezolid was provided by Parth Laboratories Pvt. Ltd. Other chemicals and solvents were of analytical reagent or special grade.

Preparation of polymorphic forms

Form A1

1g of Linezolid was slurried in 10 mL of methanol. The mixture was stirred at room temperature for a slurry time of 20 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with methanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form A1.

Form B1

1g of Linezolid was slurried in 10 mL of propanol. The mixture was stirred at room temperature for a slurry time of 28 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with propanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form B1.

Form C1

1g of Linezolid was slurried in 10 mL of ethanol. The mixture was stirred at room temperature for a slurry time of 18 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with ethanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form C1.

Methods

Powder X-ray diffraction

Powder X-ray diffraction (PXRD) patterns under ambient conditions were collected on Rigaku DMAX-IIIA diffractometer using graphite monochromatized CuKα radiation (λ=1.54178 Å). The measurement conditions were isothermal; target, Cu; voltage, 30kV, current, 10mA.

Thermal Analysis

The DSC thermogram was obtained using a Shimadzu DSC-50 instrument. The temperature range of scans was 30-350°C at a rate of 10°C/min. The weight of the sample was 2-5 mg. The sample was purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 µl aluminum crucibles having lids with three small holes were used. The TGA thermogram for Linezolid forms was performed on TGA-50 instrument (Shimadzu) using alumina pan and a sample weight 7-15 mg.

RESULTS AND DISCUSSION

X-ray powder diffraction patterns of three Linezolid crystal forms Form A1, Form B1 and Form C1 are illustrated in Fig. 2 and they showed differences. DSC curve of Linezolid Form A1 is illustrated in Fig. 3. DSC curves of Linezolid Form B1 and Form C1 are illustrated in Fig. 4. TGA curves of Linezolid Form A1, Form B1 and Form C1 are illustrated in Fig. 5. The DSC, TGA and PXRD results confirmed the existence of three crystal forms of Linezolid.

Fig. 1 Structure of Linezolid

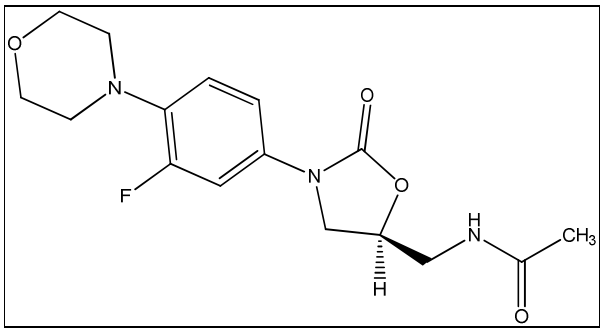


Fig. 2 X-ray powder diffraction patterns of three Linezolid forms

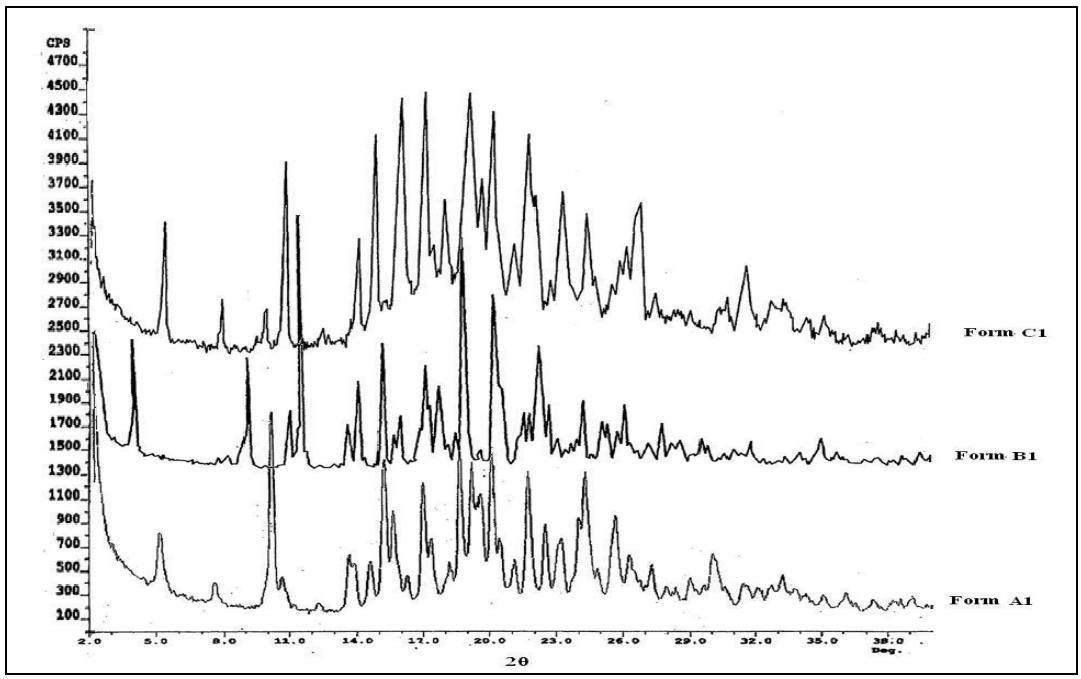


Fig. 3 DSC curve of Linezolid A1 form

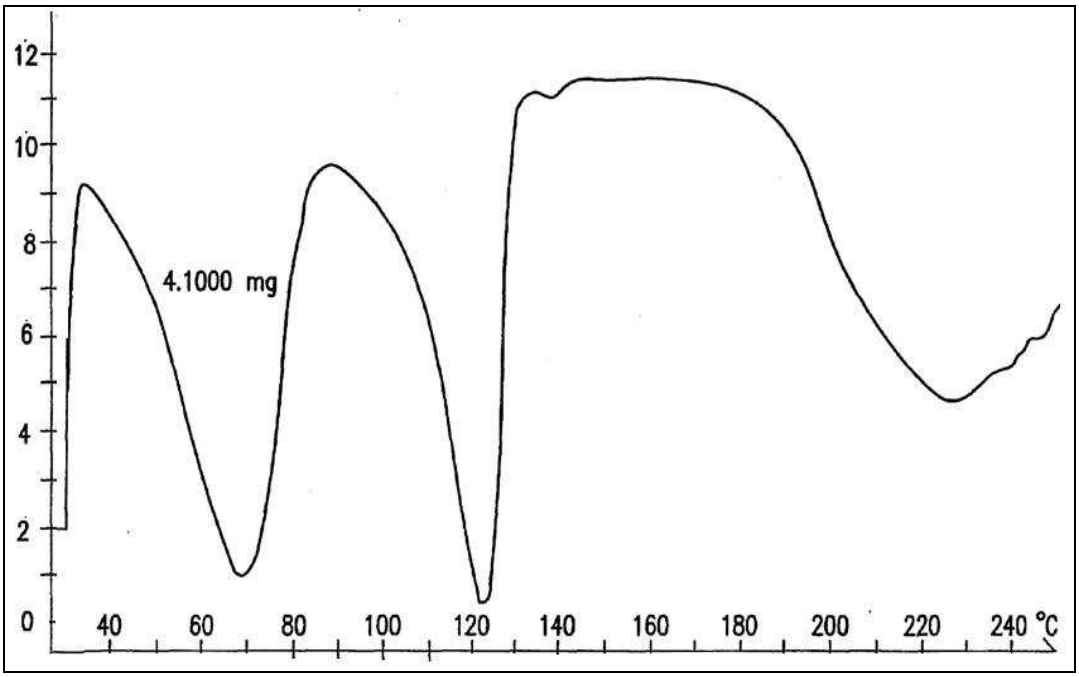


Fig. 4 DSC curves of Linezolid B1 and C1 forms

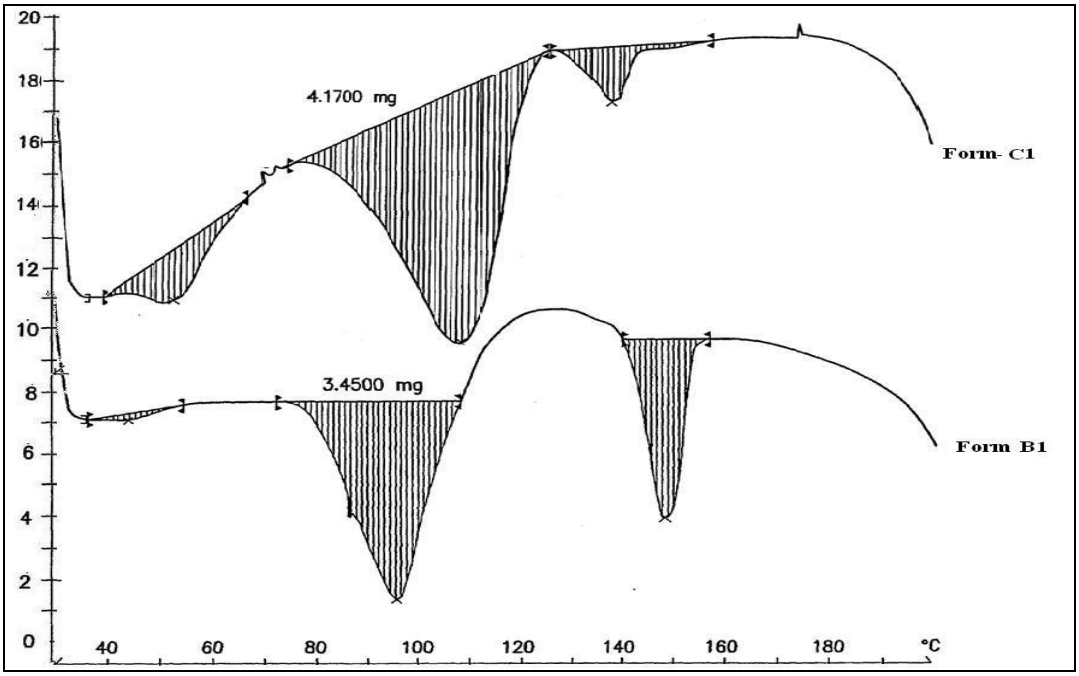
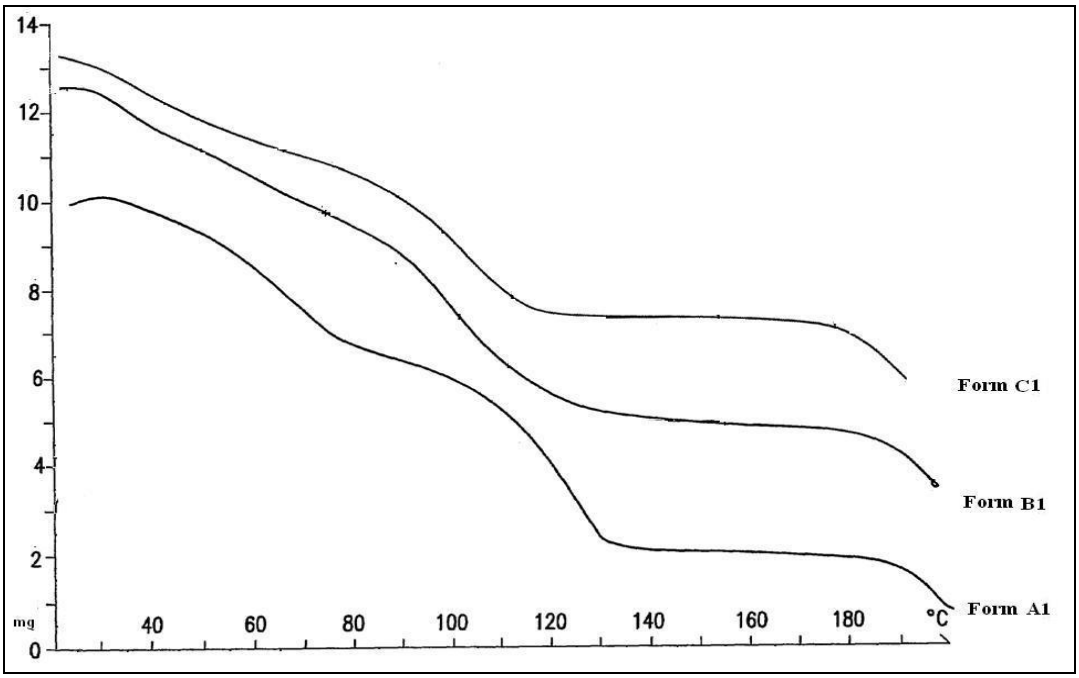


Fig. 5 TGA curves of three Linezolid forms



CONCLUSION

Three crystal forms of Linezolid were prepared by recrystallization from different solvents. The crystal forms were characterized by DSC, PXRD and TGA. X-ray diffraction patterns of three Linezolid polymorphs are different from those reported in literature [15-24].

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