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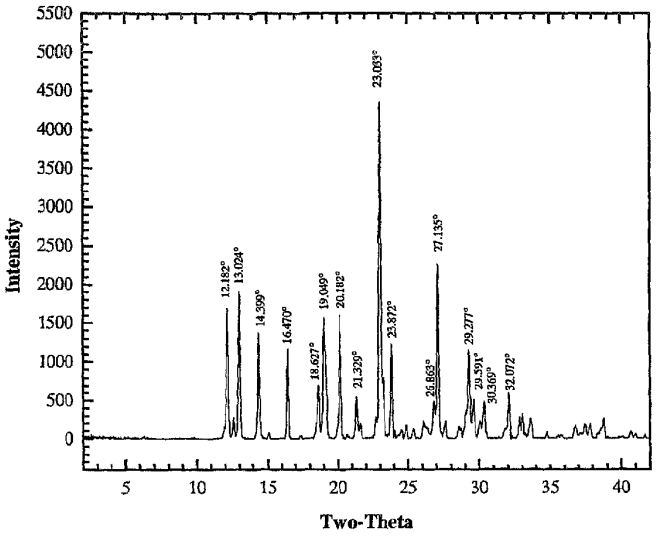
[Continued on next page]

(54) Title: FORMS OF 5-AZACYTIDINE

Figure 1. X-ray Powder Diffraction Pattern of Azacitidine, Form I, Labeled with the more Prominent 2θ Angles (Cu Kα Radiation)



(57) Abstract: The invention provides novel polymorphic and pseudopolymorphic crystalline forms of 5-azacytidine, along with methods for preparing said forms, wherein 5-azacythidine is represented by the formula (I). The invention also includes pharmaceutical compositions comprising said forms.

WO 2004/082619 A2

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FORMS OF 5-AZACYTIDINE

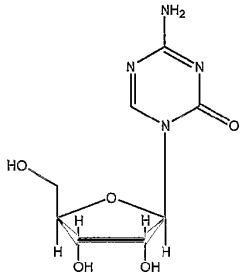
FIELD OF THE INVENTION

The invention relates to the isolation of crystalline polymorphic and pseudopolymorphic forms of 5-azacytidine (also known as azacitidine and 4-amino-1-β-D-ribofuranosyl-S-triazin-2(1*H*)-one). 5-azacytidine may be used in the treatment of disease, including the treatment of myelodysplastic syndromes (MDS).

BACKGROUND OF THE INVENTION

Polymorphs exist as two or more crystalline phases that have different arrangements and/or different conformations of the molecule in a crystal lattice. When a solvent molecule(s) is contained within the crystal lattice the resulting crystal is called a pseudopolymorph, or solvate. If the solvent molecule(s) within the crystal structure is a water molecule, then the pseudopolymorph/solvate is called a hydrate. The polymorphic and pseudopolymorphic solids display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial and mechanical properties (See H. Brittain, Polymorphism in Pharmaceutical Solids, Marcel Dekker, New York, NY, 1999, pp. 1-2). Polymorphic and pseudopolymorphic forms of the drug substance (also known as the "active pharmaceutical ingredient" (API)), as administered by itself or formulated as a drug product (also known as the final or finished dosage form, or as the pharmaceutical composition) are well known and may affect, for example, the solubility, stability, flowability, fractability, and compressibility of drug substances and the safety and efficacy of drug products, (see, *e.g.*, Knapman, K Modern Drug Discoveries, March 2000: 53).

5-azacytidine (also known as azacitidine and 4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one; Nation Service Center designation NSC-102816; CAS Registry Number 320-67-2) has undergone NCI-sponsored clinical trials for the treatment of myelodysplastic syndromes (MDS). *See* Kornblith *et al.*, J. Clin. Oncol. 20(10): 2441-2452 (2002) and Silverman *et al.*, J. Clin. Oncol. 20(10): 2429-2440 (2002). 5-azacytidine may be defined as having a formula of $C_8H_{12}N_4O_5$, a molecular weight of 244.20 and a structure of:



The polymorphic form of 5-azacytidine drug substance and drug product has never been characterized. It is an object of the present invention to characterize the polymorphic forms of 5-azacytidine.

SUMMARY OF THE INVENTION

It has been unexpectedly found that 5-azacytidine exists in at least eight different polymorphic and pseudopolymorphic crystalline forms (Forms I-VIII), in addition to an amorphous form. Form I is a polymorph found in prior art retained samples of 5-azacytidine drug substance. Form II is a polymorph found in some prior art retained samples of the 5-azacytidine drug substance; in those samples, Form II is always found in mixed phase with Form I. Form III is a hydrate, and is formed when prior art retained and current samples of the drug product are reconstituted with water to form a "slurry" prior to administration to the patient. Form VI is found in prior art retained samples of the 5-azacytidine drug product, either substantially free of other polymorphs, or in mixed phase with Form I.

The invention provides novel crystalline forms referred to as Form IV, Form V, Form VII and Form VIII. Forms I-VIII each have characteristic X-ray power diffraction (XRPD) patterns and are easily distinguished from one another using XRPD.

Also included in the present invention are methods for robustly and reproducibly synthesizing 5-azacytidine drug substance substantially as Form IV, Form V, or Form VIII. Also provided are methods for robustly and reproducibly synthesizing a Form I/VII mixed phase. The invention also provides pharmaceutical compositions comprising the various forms of 5-azacytidine together with one or more pharmaceutically acceptable excipients, diluents, or carriers.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 presents the X-Ray Powder Diffraction (XRPD) pattern of 5-azacytidine, Form I, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 2 presents the XRPD pattern of 5-azacytidine, mixed phase Form I and Form II, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 3 presents the XRPD pattern of 5-azacytidine, Form III, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 4 presents the XRPD pattern of 5-azacytidine, Form IV, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 5 presents the XRPD pattern of 5-azacytidine, Form V, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 6 presents the XRPD pattern of 5-azacytidine, Form VI, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 7 presents the XRPD pattern of 5-azacytidine, mixed phase Form I and Form VII, labeled with the most prominent 2θ angles (Cu Kα radiation).

Figure 8 presents the XRPD pattern of 5-azacytidine, Form VIII, labeled with the most prominent 2θ angles (Cu Kα radiation).

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