Development of a Targeted Polymorph Screening Approach for a Complex Polymorphic and Highly Solvating API

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ABSTRACT: Elucidation of the most stable form of an active pharmaceutical ingredient (API) is a critical step in the development process. Polymorph screening for an API with a complex polymorphic profile can present a significant challenge. The presented case illustrates an extensively polymorphic compound with an additional propensity for forming stable solvates. In all, 5 anhydrous forms and 66 solvated forms have been discovered. After early polymorph screening using common techniques yielded mostly solvates and failed to uncover several key anhydrous forms, it became necessary to devise new approaches based on an advanced understanding of crystal structure and conformational relationships between forms. With the aid of this analysis, two screening approaches were devised which targeted high-temperature desolvation as a means to increase conformational populations and enhance overall probability of anhydrous form production. Application of these targeted approaches, comprising over 100 experiments, produced only the known anhydrous forms, without appearance of any new forms. The development of these screens was a critical and alternative approach to circumvent solvation issues associated with more conventional screening methods. The results provided confidence that the current development form was the most stable polymorph, with a low likelihood for the existence of a more-stable anhydrous form. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3874–3886, 2010

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INTRODUCTION

Polymorphism can be thought of as the state in which a solid chemical compound exists in more than one crystalline form[1] with only one polymorph being the thermodynamically most stable form at a specific temperature and pressure. This phenomenon is very common to most pharmaceutical APIs. It is well known that polymorphs of the same substance can have dramatic differences in pertinent pharmaceutical properties, such as solubility and stability that can often have a significant impact on bioavailability and overall drug product performance. A number of excellent texts on polymorphism and their influence on pharmaceutical development are available.[2] Thus, identifying the most appropriate solid form, typically the thermodynamically stable form, is a key element in the early developmental process for a new drug candidate. In regard to polymorph screening approaches, there are many common techniques employed that are designed to typically uncover all metastable and low-energy polymorphic forms. These include, for example, crystallizations through solvent evaporations, antisolvent crystallizations, slow and fast cooling of saturated API solutions to induce precipitation, and slurrying of solid API for extended periods of time.[3] A significant number of solvents and cosolvents of varying polarity and chemical composition are usually employed, while variable temperatures are also incorporated in the design to assess enantiotropic behavior. These approaches have been incorporated into our practices for polymorph screening and are typical throughout the pharmaceutical industry.

In most cases, a thoroughly designed API form screen employing the approaches previously discussed should typically identify the thermodynamically stable polymorph. However, there are numerous

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exceptions in the literature[4,5] that describe the appearance of a lower energy form at late stages in development. In these cases, common polymorph screening approaches were clearly unsuccessful, as unique physical and structural properties of the molecule hindered the anticipated cascade to the most stable form based on Ostwald's rule.[6] In this article, we describe another such example.

Axitinib (Fig. 1) is an oncology candidate under development at Pfizer. This API targets the vascular endothelial growth factor (VEGF) to prevent the growth and proliferation of cancer cells via interruption of tumor angiogenesis (formation of vascular supply tissue).[7] This compound has shown considerable promise in the treatment of carcinomas in a number of target tissues and organs and is currently in late stage clinical development.[8]

Understanding the polymorphism of axitinib has been a subject of considerable focus and effort, which we have initially reported.[9] In this work, polymorph investigations using the traditional approaches previously mentioned, which incorporated well over 300 experiments, identified a surprisingly high total of 23 unique solid forms. Distinction of these forms was assigned on the basis of powder X-ray diffraction (PXRD) patterns and thermal characteristics such as melting onset, melting enthalpy, and desolvation temperatures. This group of solid forms included three anhydrous forms with the remainder solvates (refer to Tab. 1). The anhydrous form IV was characterized as a robust developmental form with acceptable solid-state properties and was advanced for early clinical studies.

It was apparent that axitinib had a high tendency to form solvates. There was some question whether certain polymorph screening approaches may be challenged by this phenomenon, and the risk of not observing critical anhydrous forms (of which three had been already discovered) could exist. In particular, axitinib had a propensity to form relatively stable solvated structures, as a majority of these solvates were characterized as possessing relatively high temperatures of desolvation (desolvation temperatures significantly higher than the normal

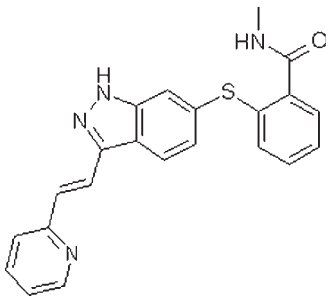

Figure 1. Structure of axitinib.

Table 1. Summary of Axitinib Solid Forms

Name	Form	Solvent
Form I (1)	Anhydrate	—
Form II (2)	Hydrate	Water
Form III (3)	Solvate	Ethyl acetate (EtOAc)
Form IV (4)	Anhydrate	—
Form V (5)	No solid form designation	
Form VI (6)	Anhydrate	—
Form VII (7)	Solvate	Isopropyl alcohol (IPA), IPA/water
Form VIII (8)	Solvate	Dioxane, tetrahydrofuran (THF)
Form IX (9)	Hydrate	Water
Form X (10)	Solvate	Dimethylformamide (DMF), DMF/water
Form XI (11)	Solvate	THF/water, THF
Form XII (12)	Solvate	Dichloromethane (DCM), ethanol (EtOH)
Form XIII (13)	Solvate	Acetonitrile (ACN)
Form XIV (14)	Solvate	Acetic acid
Form XV (15)	Solvate	EtOH
Form XVI (16)	Solvate	IPA
Form XVII (17)	Solvate	Acetone
Form XVIII (18)	Solvate	Methylisobutyl ketone (MIBK)
Form XIX (19)	Solvate	Methylethyl ketone (MEK)
Form XX (20)	Solvate	Methyl benzoate
Form XXI (21)	Solvate	2,2,2-CF_3CH_2OH/ether/hexane
Form XXII (22)	Solvate	1-Pentanol
Form XXIII (23)	Solvate	Pyridine
Form XXIV (24)	Solvate	Chloroform
Form XXV (25)	Anhydrate	—
Form XXVI (26)	Solvate	THF/water, THF
Form XXVII (27)	Solvate	Dimethylsulfoxide (DMSO)
Form XXVIII (28)	Solvate	Benzyl alcohol
Form XXIX (29)	Solvate	Trichloroethylene
Form XXX (30)	Solvate	Dimethylformamide (DMF)/octanol (1:1)
Form XXXI (31)	Solvate	Octanol
Form XXXII (32)	Solvate	Methanol
Form XXXIII (33)	Solvate	1-Butanol
Form XXXIV (34)	Solvate	3-Methyl-1-butanol
Form XXXV (35)	Solvate	MEK
Form XXXVI (36)	Solvate	Pyrrole/1-pentanol pyrrole/*p*-cymene
Form XXXVII (37)	Solvate	Allyl alcohol
Form XXXVIII (38)	Solvate	Pyrrole allyl alcohol
Form XXXIX (39)	Solvate	Acetic acid
Form XL (40)	Solvate	EtOH
Form XLI (41)	Anhydrate	—
Form XLII (42)	Solvate	2-Butanol
Form XLIII (43)	Solvate	2-Methyl THF
Form XLIV (44)	Solvate	2-Methyl THF
Form XLV (45)	Solvate	Toluene
Form XLVI (46)	Solvate	*N*-Methylpyrrolidone
Form XLVII (47)	Solvate	Isoamyl acetate
Form XLVIII (48)	Solvate	Methylcyclohexane
Form XLIX (49)	Solvate	Cyclohexanone
Form L (50)	Solvate	Cyclohexanone
Form LI (51)	Solvate	1,2-Dichloroethane
Form LII (52)	Solvate	Propionic acid
Form LIII (53)	Solvate	*Tert*-butanol
Form LIV (54)	Solvate	Dimethoxymethane
Form LV (55)	Solvate	2-Pentanone
Form LVI (56)	Solvate	Dimethyl acetate (DMA)
Form LVII (57)	Solvate	Nitromethane
Form LVIII (58)	Solvate	1,2,3,4-tetrahydronaphthalene
Form LIX (59)	Solvate	Tetramethylene sulfone
Form LX (60)	Solvate	Methyl acetate
Form LXI (61)	Solvate	*p*-Xylene
Form LXII (62)	Solvate	Trichloroethylene
Form LXIII (63)	Solvate	*n*-Butyl acetate
Form LXIV (64)	Solvate	Isobutyl alcohol
Form LXV (65)	Solvate	Cyclohexanol
Form LXVI (66)	Solvate	Isopropyl acetate
Form LXVIII (67)	Solvate	*p*-Cymene/pyrrole (1:1)
Form LXIX (68)	Solvate	*t*-Amyl alcohol
Form LXX (69)	Solvate	4-Methyl-2-pentanone
Form LXXI (70)	Solvate	Cyclohexane
Form LXXII (71)	Solvate	1,2-Dichlorobenzene
Form LXXIII (72)	Solvate	*p*-Cymene/acetone (1:1)