International Journal of Pharmaceutics 469 (2014) 111–120

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Quality by design development of brivanib alaninate tablets: Degradant and moisture control strategy

Sherif I.F. Badawy *, Judy Lin, Madhushree Gokhale, Sachin Desai [1], Vishwas V. Nesarikar, Keirnan R. LaMarche, Ganeshkumar A. Subramanian, Ajit S. Narang

Drug product Science and Technology, Bristol-Myers Squibb Research and Development, New Brunswick, NJ, USA

ARTICLE INFO

Article history:
Received 17 November 2013
Received in revised form 3 April 2014
Accepted 23 April 2014
Available online 26 April 2014

Keywords:
Quality by design
Control strategy
Stability
Hydrolysis
Sorption–desorption moisture transfer
Brivanib alaninate
BMS-540215

ABSTRACT

A quality by design approach was applied to the development of brivanib alaninate tablets. Brivanib alaninate, an ester pro-drug, undergoes hydrolysis to its parent compound, BMS-540215. The shelf-life of the tablets is determined by the rate of the hydrolysis reaction. Hydrolysis kinetics in the tablets was studied to understand its dependence on temperature and humidity. The BMS-540215 amount versus time profile was simulated using a kinetic model for the formation of BMS-540215 as function of relative humidity in the environment and a sorption–desorptiom moisture transfer model for the relative humidity inside the package. The combined model was used to study the effect of initial tablet water content on the rate of degradation and to identify a limit for initial tablet water content that results in acceptable level of the degradant at the end of shelf-life. A strategy was established for the moisture and degradant control in the tablet based on the understanding of its stability behavior and mathematical models. The control strategy includes a specification limit on the tablet water content and manufacturing process controls that achieve this limit at the time of tablet release testing.

1. Introduction

Brivanib alaninate (BMS-582664) is a potent, orally active inhibitor of vascular endothelial growth factor (VEGF) receptors (Huynh et al., 2008). Brivanib alaninate is an ester prodrug containing L-alanine pro-moiety. Conversion to the parent molecule (BMS-540215) occurs rapidly in vivo through hydrolysis by esterases. The prodrug was selected for development to enhance the aqueous solubility and oral bioavailability of the parent molecule. Chemical structures of brivanib alaninate (BMS-582664) and BMS-540215 have been previously reported (Zhao et al., 2012). Brivanib alaninate is weakly basic with pK_a of 6.9 and intrinsic solubility of <10 μg/mL. Brivanib alaninate API is a neat crystalline free form with melting point of 143 °C (Badawy et al., 2012).

The principles of quality by design (QbD) were applied during the formulation development of brivanib alaninate film-coated tablets. Using a risk-based approach, the development strategy was established which comprises: (1) identifying the desired product attributes, (2) identifying risks in development, (3) performing experiments to understand how risk factors impact product attributes, and (4) identifying and adopting the appropriate strategy to mitigate or reduce risks (Yu, 2008). Quality risk assessments and development studies were performed to understand the quality of the input raw materials required for a robust formulation and the impact of manufacturing process parameters on the critical quality attributes (CQAs) of the drug product. The data obtained from development studies were used to define the control strategy for the manufacture of brivanib alaninate film-coated tablets which includes controls on process parameters, input material, and in-process material attributes.

Hydrolysis of brivanib alaninate to BMS-540215 (Zhao et al., 2012) is the only degradation pathway identified in the tablet dosage form. BMS-540215 is the only degradant observed in the drug product in accelerated and long-term stability studies, and hence, rate of the hydrolysis reaction in the tablet is directly linked to shelf-life. As hydrolysis of brivanib alaninate involves water as a reactant, it is expected that water (moisture) content has a direct impact on the rate of BMS-540215 formation, and hence, tablet shelf-life. Understanding the effect of water content on the kinetics of brivanib alaninate hydrolysis in tablets is, therefore, essential to predict product shelf-life. On the other hand, tablet water content during product storage is dependent on the relative humidity inside the package which is expected to be a function of package characteristics and tablet initial water content. If this is the case, then tablet initial

* Corresponding author at: Bristol-Myers Squibb Company, One Squibb Dr, New Brunswick, NJ 08903, USA. Tel.: +1 732 227 6451; fax: +1 732 227 3990.
E-mail address: sherif.badawy@bms.com (S.I.F. Badawy).
[1] Current address: MCPHS University, Boston, MA, USA.

http://dx.doi.org/10.1016/j.ijpharm.2014.04.059
0378-5173/

water content at the time of drug product release should be considered a CQA and needs to be controlled. Development studies should, therefore, aim to identify a tablet water content limit, and manufacturing process that can achieve it, which together with appropriate package design produce relative humidity profile that results in acceptable shelf-life.

In this manuscript, model-based approach was used to study the hydrolysis of brivanib alaninate and the impact of relative humidity on the formation of BMS-540215 in tablets. A kinetic model was developed to link relative humidity to the rate of hydrolysis in tablets. In addition, a sorption–desorption moisture transfer (SDMT) model (Badawy et al., 2001) was developed to predict the humidity profile in the package during shelf-life and to study the effect of tablet initial water content on the humidity profile. Knowledge generated from the models was used to design the product and the manufacturing process to ensure acceptable product shelf-life according to the QbD development paradigm.

2. Experimental

2.1. Tablet manufacturing process

2.1.1. Wet granulation and fluid bed drying

Brivanib alaninate tablets are manufactured by a wet granulation process. Composition and details regarding the wet granulation unit operation were previously reported (Badawy et al., 2012). Briefly, intragranular components (brivanib alaninate, microcrystalline cellulose, hydroxypropyl cellulose, and croscarmellose sodium) were blended in a high shear mixer (Fielder PMA-300, GEA Pharma Systems, Columbia, MD), and then water was added to granulate the blend. The wet mass was mixed for 30 s after water addition is complete. The wet mass was wet milled (U20 Comil, Quadro, Waterloo, ON) and then Fluid bed dried (Niro-Aeromatic MP-4, GEA Pharma Systems, Columbia, MD) until a predetermined granulation loss on drying (LOD) is achieved. The dried granulation was then milled (U10 Comil, Quadro, Waterloo, ON). The milled granulation was blended with extragranular components and lubricated with magnesium stearate in a bin blender. The blend was compressed into tablets of 800 mg tablet weight (400 mg strength)

2.1.2. Tablet film coating

Core tablets were preheated in a pan coater (30 inch pan, O'Hara Technologies, Richmond Hill, ON or 48 inch Accela Coata, Thomas Engineering, Hoffman Estates, IL) until a specified tablet LOD limit is reached. The tablets were then coated by applying a suspension (15% w/w of solids) of a hydroxypropyl methylcellulose based formulation (Opadry, Colorcon, West Point, PA). Coating suspension was applied until a 4% w/w weight gain (3.5–4.5%) is achieved. After application of coating suspension is completed, the tablets were dried until LOD lower than a specified limit is reached.

2.2. Tablet moisture uptake

Tablet moisture uptake isotherm was determined at 25 °C and 40 °C using the Dynamic Vapor Sorption system (DVS-2, Surface Measurement Systems Ltd., Alperton, UK). Sample was dried at 0% RH until a constant weight is obtained. Subsequently, moisture uptake by the sample was determined as the relative humidity was increased in increments of 10%. Equilibrium moisture uptake was determined by measuring weight gain at each relative humidity.

2.3. Stability studies

2.3.1. Open dish studies

A stability study was conducted by placing the tablets in an open dish in humidity chambers set to specified temperature and humidity conditions. Seven different combinations of temperature and humidity conditions were selected to provide a temperature range of 25–60 °C and humidity range from 30% to 75% RH. Tablets were pulled at different time intervals and analyzed for impurities by a validated HPLC method. Amount of BMS-540215 in the tablet was determined from its peak area in the chromatogram and reported as a percent relative to the total area of brivanib alaninate and related substances.

2.3.2. Packaged tablet studies

Sixty film coated tablets (400 mg strength) with tablet water content of 1.7% w/w by LOD were packaged in induction sealed high density polyethylene (HDPE) bottles with 3 g silica gel desiccant canister. Tablets were also packaged in cold form aluminum blisters. Both bottles and blisters were placed in stability chambers at 40 °C/75% RH (accelerated ICH condition). Bottles were also placed in the ICH Zone I/II long term stability chambers at 25 °C/60% RH while blisters were placed in the ICH Zone IV long term stability chambers at 30 °C/75% RH. Bottles and blisters were pulled at different time intervals, and tablets were analyzed for BMS-540215 content by a validated HPLC method as described above.

2.4. Mathematical modeling

2.4.1. Chemical kinetics modeling

A modified Arrhenius approach was used to model the formation of BMD-540215 in the tablets. A model was developed which assumes reaction to take place in a non-crystalline reactive phase in the tablet. This is consistent with the literature which suggests that majority of hydrolysis reactions in predominantly crystalline materials occur in amorphous regions or crystal defects (Waterman et al., 2002). Brivanib alaninate concentration is assumed to be constant in the non-crystalline phase as the extent of brivanib alaninate degradation in the reported studies is sufficiently low. A pseudo-zero order reaction model is, hence, assumed as follows:

$$\frac{dX}{dt} = kC_sV_t \quad (1)$$

where V_t is the volume of the non-crystalline phase where reaction takes place. In order to account of the falling reaction rate with time observed during the course of the stability study, V_t is assumed to decrease with time in a first order manner from an initial value of V_0 with a rate constant k_2 as follows:

$$V_t = V_0 e^{-k_2 t} \quad (2)$$

The rate of BMS-540215 formation can, therefore, be expressed as:

$$\frac{dX}{dt} = kC_sV_0 e^{-k_2 t} \quad (3)$$

k is assumed to follow modified Arrhenius dependence on temperature and humidity (Waterman et al., 2007), so Eq. (3) can be written as follows:

$$\frac{dX}{dt} = Ae^{-E_a/RT} e^{B_1 RH} C_sV_0 e^{-k_2 t} \quad (4)$$

where A is the frequency factor, E_a is the activation energy, R is the gas constant, B_1 is the moisture sensitivity parameter, and RH is the relative humidity.

Substituting A_1 for the constants AC_sV_0 and C_1 for $-E_a/R$ yields:

$$\frac{dX}{dt} = A_1 e^{C_1/T} e^{B_1 RH} e^{-k_2 t} \quad (5)$$