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Integrated Application of Quality-by-Design Principles to Drug Product Development: A Case Study of Brivanib Alaninate Film–Coated Tablets

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ABSTRACT

Modern drug product development is expected to follow quality-by-design (QbD) paradigm. At the same time, although there are several issue-specific examples in the literature that demonstrate the application of QbD principles, a holistic demonstration of the application of QbD principles to drug product development and control strategy, is lacking. This article provides an integrated case study on the systematic application of QbD to product development and demonstrates the implementation of QbD concepts in the different aspects of product and process design for brivanib alaninate film–coated tablets. Using a risk-based approach, the strategy for development entailed identification of product critical quality attributes (CQAs), assessment of risks to the CQAs, and performing experiments to understand and mitigate identified risks. Quality risk assessments and design of experiments were performed to understand the quality of the input raw materials required for a robust formulation and the impact of manufacturing process parameters on CQAs. In addition to the material property and process parameter controls, the proposed control strategy includes use of process analytical technology and conventional analytical tests to control in-process material attributes and ensure quality of the final product.

Introduction

The principles of Quality by Design (QbD) emphasize the need for understanding sources of variability in the manufacturing process and how it links to product quality as prerequisite for robustness. Risk-based approach is used to define the goals of QbD development and to design appropriate development studies to achieve these goals. Product quality attributes based on patient needs and clinical relevance are identified, and the risks to these attributes due to input material variability and manufacturing process parameters are assessed. The output of QbD development takes the form of a process and product quality control strategy which ensures that the final product consistently meets pre-established acceptance criteria for the critical quality attributes (CQAs).[1,2] Although QbD principles were introduced more than a decade ago by the ICH guidelines, there are hardly any published examples demonstrating how these principles are reduced to practice in the commercial development of a drug product as well as transfer and implementation of control strategy in a manufacturing plant. Although there are some published reports invoking QbD principles in the study of a specific issue,[3-11] none of them provide a wide view of the application of QbD to a comprehensive development program.

Brivanib alaninate (BMS-582664) is a potent, orally active inhibitor of vascular endothelial growth factor receptors.[12] A film-coated tablet formulation for brivanib alaninate has been developed using a wet granulation manufacturing process. The principles of QbD were applied during formulation and process development of brivanib alaninate film–coated tablets. Using a risk-based approach, the strategy for the formulation design and

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understanding was developed by (1) identifying desired product attributes, (2) identifying quality risks to the attributes during development, and (3) adopting the appropriate strategy and performing experiments to mitigate or reduce risks. Quality risk assessments and statistically designed experiments 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 CQAs of the drug product. The data obtained were used to establish acceptable material attribute and process ranges and to define the control strategy for the commercial manufacture of brivanib alaninate film–coated tablets. The proposed commercial manufacturing process uses process analytical technology and conventional analytical tests to control the in-process material attributes. The product quality is controlled and assured through a holistic approach of input material, in-process attribute, and parametric controls combined with appropriate finished product tests. The purpose of this article is to provide an integrated case study on the systematic application of QbD to product development and to demonstrate the implementation of QbD concepts in the different aspects of product and process design. The work presented demonstrates how QbD concepts, such as product robustness and scale-independent design space, were reduced to practice in the development of brivanib alaninate tablets.

Methods

Formulation Selection

Formulation and process screening studies were conducted to select a prototype formulation and manufacturing process for brivanib alaninate tablets. Key formulation selection studies focused on the selection of tablet disintegrant in which performance of both croscarmellose sodium (CCS) and crospovidone (CPVP) was evaluated. Formulation selection batches were manufactured at 600 g batch size by a wet granulation process in a 4-L high-shear Diosna granulator (Diosna Dierks & Söhne GmbH, Osnabrück, Germany). All batches were granulated using 45%-50% w/w water, relative to total batch size, at impeller speed of 5.2 m/s. Wet granulation was screened through 8 mesh screen, and granules were subsequently dried in a Glatt GPCG-1 fluid-bed dryer (Glatt Air Techniques, Ramsey, NJ) until the loss on drying (LOD) was $\leq$2% w/w. Dried granulations were milled using a conical mill (Comil 197S, Quadro, Waterloo, Ontario, Canada) and then blended with the extragranular excipients in a bin blender. The final blend was compressed into 400 mg of strength tablets (800 mg tablet weight) on a 6 station Korsch PH 100 tablet press (Korsch AG, Berlin, Germany) using embossed tooling. Batches were characterized using methods described below.

Formulation Optimization

After the prototype formulation was identified, a formulation design of experiment (DoE) study was conducted to assess formulation ruggedness and optimize composition with respect to the binder (hydroxypropyl cellulose [HPC]), disintegrant (intra- and extragranular), and lubricant (magnesium stearate). A split-plot full-factorial experimental design was used to complete the DoE. The design entails the manufacture of a larger scale granulation batch and splitting the batch into 2 parts to study the 2 levels of magnesium stearate, instead of manufacturing separate batches for each combination. This design reduces the number of granulation batches that need to be manufactured by half, while still providing sufficient information to understand the main effects and interactions of the various excipients. Experimental design batches are shown in Table 1.

Table 1
Experimental Design for the Formulation Optimization Study

Batch Number	Croscarmellose Sodium (%)	Hydroxypropyl Cellulose (%)	Crospovidone (%)	Magnesium Stearate (%)
1	3.0	3.0	3.0	1.0
2	3.0	3.0	3.0	0.5
3	4.5	1.5	1.5	1.5
4	4.5	1.5	1.5	0.5
5	1.5	1.5	4.5	1.5
6	1.5	1.5	4.5	0.5
7	4.5	4.5	4.5	1.5
8	4.5	4.5	4.5	0.5
9	4.5	1.5	4.5	1.5
10	4.5	1.5	4.5	0.5
11	1.5	4.5	1.5	1.5
12	1.5	4.5	1.5	0.5
13	1.5	4.5	4.5	1.5
14	1.5	4.5	4.5	0.5
15	4.5	4.5	1.5	1.5
16	4.5	4.5	1.5	0.5
17	3.0	3.0	3.0	1.0
18	3.0	3.0	3.0	1.0
19	1.5	1.5	1.5	1.5
20	1.5	1.5	1.5	0.5

DoE batches were manufactured in a Fuji high shear granulator with a 25-L bowl at 5 kg total batch size. The impeller speed was maintained at 240 rpm (equivalent tip speed of 4.8 m/s), chopper run at low speed (1000 rpm). A peristaltic pump was used to add water at a rate of 100 g/min/kg over a period of 4 min and 30 s. The wet massing time was kept constant at 15 s for all batches while maintaining same impeller and chopper speeds. The wet granulation was passed through a conical mill (Comil 197S) with 0.125-inch (3.2 mm) round opening screen at impeller speed of ~1350 rpm. The granulation was then dried using the GPCG-1 fluid-bed dryer at 70°C to a moisture content of $\leq$1.50%. The dried granulation was milled using a conical mill (Comil 197S) with 0.045-inch (1.1 mm) screen opening at impeller speed of ~1350 rpm. The milled granulation was split into 2 equal sublots and then placed in a bin blender (8.3 L) and mixed with the extragranular excipients and appropriate amount of magnesium stearate per the experimental design. The final blend was compressed into 400 mg strength tablets (800 mg tablet weight) on the 6 station Korsch PH 100 tablet press using embossed tooling. Batches were characterized using methods described below. Statistical analysis of response data was performed by regression analysis in SAS JMP (SAS Institute Inc., Cary, NC).

QbD Methodology

After formulation composition was established, studies were conducted to evaluate effect of material attributes and process parameters on product attributes of the selected formulation. CQAs for brivanib alaninate tablets were identified as tablet potency, dosage uniformity, impurities, dissolution rate, and appearance. Appearance was considered a CQA as it is perceived to affect patient compliance and hence outcome of therapy.

Subsequent to the identification of the CQAs, failure mode effect analysis was conducted to identify material attributes and process parameters to be studied for their impact on CQAs. Although all material attributes and process parameters that can potentially affect CQAs were considered as part of the risk analysis, only a subset of these attributes and parameters were selected for development studies as warranted by the risk analysis. Studies were conducted to generate knowledge regarding the effect of the selected input material attributes and process parameters on CQAs and identify critical material attributes (CMAs) and critical process