Journal of Pharmaceutical Sciences xxx (2017) 1-10

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Drug Discovery—Development Interface

Evaluation of a Biologic Formulation Using Customized Design of Experiment and Novel Multidimensional Robustness Diagrams

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ARTICLE INFO

Article history:
Received 5 June 2017
Revised 14 October 2017
Accepted 17 October 2017

Chemical compounds with the PubChem CID:
L-Histidine (PubChem CID: 6274)
L-Histidine hydrochloride monohydrate (PubChem CID: 165377)
Sucrose (PubChem CID: 5988)
Polysorbate 80 (PubChem CID: 5281955)
Distilled Water (PubChem CID: 962)

Keywords:
protein formulation
multivariate analysis
biotechnology
stability
excipients
formulation
quality by design
protein excipient interactions
pharmaceutical sciences
biopharmaceuticals characterization

ABSTRACT

Formulation development includes selection of appropriate excipients to stabilize the active pharmaceutical ingredient throughout its recommended shelf life, against potential excursions in its life cycle and sometimes to aid in the delivery of therapeutics into the patient. Identity and quantity of every ingredient in a therapeutic formulation are critical to achieve their intended purpose. Deviations from a target composition can result in manufacturing, safety, and efficacy challenges. It is mandatory to establish robustness of a formulation for the expected changes in its composition arising from the qualified "process variability" of the impacting process steps during manufacture. The approach for carrying out a robustness study evolved through improved understanding of a therapeutic stability and exploration of new tools, including the quality by design elements strongly recommended by regulatory agencies. An approach is presented here to study formulation robustness in multidimensional space using a customized experimental design and novel multidimensional diagrams, which present a unique way of identifying robustness limits. The concept is universally applicable to any multivariate analysis and such diagrams would be useful to comprehend the outcome on all variables at a glance. Interpretation of these diagrams is discussed, some of which are applicable in general to any statistical design of experiment.

Introduction

Development of protein therapeutics is quite challenging due to complexity of their structure and several possible degradation pathways. Chemistry, manufacturing, and controls (CMC) development includes multiple functions, each having its own challenges that often require hand-in-hand cross-functional efforts to address. While expertise in each function may help in fixing a local issue, an unavoidable circumstance in one function may be addressed by planned strategies in other function(s). One such challenge is commonly observed with the development of the ultrafiltration/diafiltration (UFDF) step in the downstream processing of the purified protein, where deviations from the target values of the formulation ingredients are commonly observed due to Donnan's effect on the charged molecules.[1] The difference that can take place between the actual and the target levels is termed as "process variability," and it can be defined for each ingredient in the formulation. Great models and strategies are available to minimize this issue locally through proper development and optimization of the UFDF process step, which may require quite a lot of resources and time.[2-4] Despite these efforts, other factors such as accuracy in weighing of the excipients (including the instrumental variability) in preparation of the diafiltration buffer or the drug product manufacturing steps such as compounding, mixing, or filtration may still impact the excipient levels in the

Abbreviations used: ANOVA, analysis of variance; API, active pharmaceutical ingredient; CMC, chemistry, manufacturing and controls; CQA, critical quality attribute; HPLC, high performance liquid chromatography; ICH, International Council for Harmonization; cIEF, capillary isoelectric focusing; KDa, kilo daltons; MWCO, molecular weight cutoff; PS-80, polysorbate 80; QbD, quality by design; TFA, trifluoroacetic acid; UFDF, ultrafiltration/diafiltration.

This article contains supplementary material available from the authors by request or via the Internet at https://doi.org/10.1016/j.xphs.2017.10.024.

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https://doi.org/10.1016/j.xphs.2017.10.024
0022-3549/

final drug product. Appropriate control strategies may be built up by tightening the acceptable limits on weighing the excipients or the acceptance criteria in qualification of the impacting process step(s). Such strategies can only help reduce the level of variability but cannot absolutely eliminate it or help in maintaining consistent excipient levels through different lots of the drug substance and/or the drug product. As a result, there always exists some level of variability for each of the ingredients in the final formulation, including the active pharmaceutical ingredient (API). The ability of a formulation to remain unaffected for its intended purpose (stabilizing API throughout the shelf life and against pharmaceutically relevant stress conditions) due to anticipated changes in its composition is generally known as its "robustness." If the formulation can be demonstrated to be robust for the anticipated variability in composition, semioptimized process steps could be sufficient and a lot of time can be saved in the process development. If the formulation is not robust enough to such variabilities, it can lead to challenges on manufacturability, stability, safety, and efficacy.[5] Furthermore, poor robustness of a formulation could be one of the reasons for product recalls since the shelf life can potentially be overestimated based on the stability data of the drug products typically filled with the target formulation.

Therefore, it is mandatory to establish robustness of a formulation, more sensibly in the drug product configuration, against changes anticipated in the formulation through the manufacturing process. Regulatory requirements for demonstrating the formulation robustness may be contemplated from excerpts in the International Council for Harmonization (ICH) Q8 (R2) Pharmaceutical Development guidelines which state that "any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in the Pharmaceutical Development section of the application," and "critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product".[6] In addressing such requirements, the U.S. Food and Drug Administration encourages the use of innovative approaches such as the implementation of quality by design (QbD), which is a science- and risk-based approach for pharmaceutical development. For biopharmaceutical products, application of QbD concepts was accelerated by the pioneering work presented by Rathore and Winkle.[7,8] The applications of QbD in specific areas of development have been discussed in greater details by industry experts, including the formulation and manufacturing process of biologics.[9,10] The use of QbD elements specifically in biologics formulation development was well demonstrated with a case study on a lyophilized monoclonal antibody.[11] In addition to formulation development, demonstrating its robustness is a key area, where QbD approach is required to make more appropriate evaluation.[10] Although demonstrating formulation robustness is a requirement to be addressed in a marketing application, there are no straightforward guidelines on "how" to demonstrate. Robustness is one of the characteristics recommended in ICH Q2 (R1) guidelines for validation of the analytical methods.[12] An excellent source of guidelines to determine a method's robustness was published by Vander Heyden et al.[13] In drug product development aspect, robustness evaluation of a formulation seems to have commonly been less focused despite its necessity and significance. With development of understanding on the protein stability and availability of new tools, the approach to evaluate formulation robustness seems to have evolved from univariate to multivariate studies, initial time point evaluation to stability monitoring, and simple verification of predefined limits to their exploration. The current state of art on evaluating robustness of a biologic formulation in multidimensional space appears to have picked up pace after a publication, which described the use of statistical design of experiment in robustness evaluation with case studies.[14] A more recent publication described a QbD approach for evaluation of formulation robustness and it further complements with many insights to improve the evaluation.[15]

Design space is a major element of QbD, which has been improved with the use of statistical tools. Beginning with full-factorial designs for simple formulations, less cumbersome fractional factorial designs of varied resolutions have been implemented for complex formulations with some compromise on the information to obtain.[14] Poor resolution might necessitate follow-up experiments using augmented designs. Mixture designs have also been used in specific contexts.[16,17] More comprehensive response surface methodologies are commonly used with specific purpose to study possible nonlinear responses. One experimental design increasingly used for a similar purpose is the "definitive screening design," which can study quadratic effects efficiently in a minimal number of runs. Minimum run resolution designs are helpful to decrease the number of formulation runs by not studying the higher order interactions. However, all these designs cannot allow complete control over the type and level of information to obtain. Custom designs offer great flexibility to selectively choose the interactions or nonlinear responses to study and thus helps to achieve better control over the information to obtain or compromise. However, it does not seem to have been explored much.

While generation of abundant information from a multivariate study is merited, the same could be a challenge for presenting the generated information in a concise and easily understandable format. Many display formats have been developed to understand the final outcome of a series of experiments. For example, empirical phase diagrams were developed for a broad overview of the protein stability.[18,19] Radar charts were created to visualize the effects of formulation variables across a wide range of stress conditions and quality attributes.[20] A response surface output was built using an innovative stability parameter known as "robustness index score."[21] They were mainly intended to build robustness into the formulation, which is more useful early in development. No such efforts seem to have been made to demonstrate formulation robustness in late-stage development and robustness is often assessed based on a "virtual" design space perceived through several figures or data sets. A novel and effective approach to visualize the robustness from a palpable or an "actual" design space while considering all effects and interactions across multiple quality attributes is presented in this article. Basis for this approach is a rational and systematic overlaying of the contour plots generated with all possible 2-factor combinations of the variables. The final overlaid contour chart is termed as "robustness diagram" in the present context, which allows unique way of identifying robustness limits in a potentially more conservative manner.

Materials and Methods

Materials

A monoclonal antibody (mAb) from Teva Biologics was used for this study. All excipients were purchased from Avantor Performance Materials (Center Valley, PA), which were of multicompendial grade. Dialysis cassettes were purchased from Fisher Scientific (Durham, NC).

Methods

Custom Design of Experiment

A custom design in JMP version 11 SAS (Cary, NC) was used to make the study design and analyze the data. Formulation variables