J Pharm Innov (2013) 8:187–194
DOI 10.1007/s12247-013-9158-x

RESEARCH ARTICLE

A Small-Scale, Material-Saving Approach to Rank-Order Lyophilized Formulations Based on Reconstitution Time

Sachin Chandran · Vishal Nashine · Mary Morcos · Atul Saluja

Published online: 25 June 2013

Abstract
Purpose The goal of this manuscript is to describe a system amenable to automation that could estimate reconstitution times, and thus rank-order lyophilized systems using a small-scale, miniaturized, plate-based approach.
Methods Multiple formulations of proprietary BMS protein molecules were lyophilized in 96-well plates with individual formulations assigned to each well. The lyophilized cakes were reconstituted using Water for Injection (WFI), and the 96-well plates were read using a UV–Vis plate reader. The corresponding reconstitution was monitored by observing the decreasing absorbance, or the increased transmittance within the wells over time. A minute amount of *n*-octanol was used to suppress foam that would otherwise interfere with the UV–Vis readings. Reconstitution times of the same formulations following lyophilization in a conventional vial system were also measured via visual inspection, for sake of comparison.
Results There was linear correlation between data obtained from the miniaturized 96-well approach and that from the conventional manual reconstitution experiments. Qualitatively, the rank-ordering between the different formulations allowed rapid identification of best formulation compositions to facilitate reconstitution of the lyophilized cake.
Conclusion This miniaturized high-throughput approach allows rapid screening and rank-ordering of different lyophilized formulations for optimal reconstitution time. The information obtained is invaluable in early development of parenteral products when material is scarce and data has to be gathered quickly. The novel approach presented here can be easily incorporated into larger automation workflows that have the potential to improve overall efficiency of the development process.

S. Chandran (✉) · V. Nashine · M. Morcos · A. Saluja
Bristol-Myers Squibb Company, 1 Squibb Drive,
New Brunswick, NJ 08903, USA
e-mail: sachin_chandran@yahoo.com

Keywords Lyophilization · High-throughput · Small-scale · Automation · Reconstitution

Introduction

Recent advances in recombinant DNA technology have given rise to the discovery of numerous protein and peptide drugs. The most common route for administration of this class of drugs is via intravenous (IV) or subcutaneous [1] injection. In order to enable administration, proteins and peptides are typically formulated as ready-to-use solution systems or lyophilized cakes which must then be reconstituted prior to administration. Lyophilization, or freeze-drying, offers the advantage of stabilization by storing the product in solid state. Since protein-based therapeutics often undergo physical and chemical degradation when stored as solutions, development of lyophilized formulations is undertaken to mitigate some of these potential liabilities. However, a lyophilized formulation requires the right combination of excipients in order to maintain, maximize and improve stability, biological activity, and safety of a product. A well-developed lyophilized formulation will have a few desirable characteristics, viz. long-term physical and chemical stability, acceptable reconstitution time, isotonicity, preservation of the original dosage characteristics upon reconstitution and good cake appearance [2]. Current literature addresses the issues regarding stability, isotonicity, and cake appearance [3, 4]. In addition, there is also a significant amount of literature surrounding scale-up of the lyophilization process, application of process analytical techniques during the lyophilization runs, and the integration of lyophilization with the fill-finish process [1–8].

The majority of formulation development efforts are typically focused on optimization of late-stage products. Consequently, one area that is relatively poorly addressed in literature is the optimization of lyophilization formulations