Effect of manufacturing process and container closure configurations on critical quality attributes of generic parenteral drug product: A case study of pH

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Purpose/Introduction: Product development of generic parenteral products involves extensive studies to optimize formulation process and manufacturing conditions such that the developed product is like Reference Listed Drug (RLD) in terms of all Critical Quality Attributes (CQA) over stability. CQA's are properties of drug product which have significant effect on product quality. Typical CQA's for a drug product include pH of the formulation, assay of the chemical of interest, impurities, visual appearance, particulate matter, color and clarity of the solution. In this present work, we present two case studies of generic parenteral product development to optimize pH of the drug products under study.

Methods: pH of a formulation is a critical quality attribute as it significantly affects solubility and stability of the drug product. In addition, pH of a parenteral drug product has significant clinical effects such as electrolyte imbalances. In first case study, we evaluated effect of container closure configurations on pH of the drug product. We formulated the drug product and filled it in various treated and non-treated glass vials, stoppered, sealed and placed on stability as per International Conference on Harmonization (ICH) guidelines. In the second case study, we evaluated effect of nitrogen sparging during compounding on pH of the drug product. We prepared three batches of drug product. First batch was prepared under ambient atmospheric conditions without nitrogen sparging, another by sparging the water for 30 minutes before addition of Active Pharmaceutical Ingredient (API) and blanketing the formulation with nitrogen for rest of compounding process; and third batch with continuous nitrogen sparging throughout compounding. pH of all the three batches are monitored at pre-determined time intervals throughout the manufacturing process.

Results: Stability data of the drug product in case study 1 monitored over 6 months at 25C/65% RH and 40C/75% RH suggest that the formulation in untreated vials showed drastic change in pH, with the data at 3M and 6M even failing to meet pH specifications for the finished product. However, formulation filled in treated vials has well controlled pH and within specifications at all conditions up to 6M on stability. Data analysis of various batches from case study 2 suggests better control of pH in the second batch with sparging the water for 30 minutes before addition of nitrogen and blanketing throughout the compounding process.

Conclusion: Both the case studies suggest that appropriate container closures and optimal manufacturing process have significant effect on pH of parenteral drug products and should be closely evaluated during product development.

Speaker Biography

Lakshmi Prasanna Kolluru is currently working as Sr. Formulation Scientist at Medefil, Inc, a generic pharmaceutical company. She is responsible for leading product development project teams all the way from kick-off to product approval. Prior to joining Medefil, she has served in formulation, analytical and clinical development groups across brand pharma, generic pharma and contract research organizations. She has graduated with a PhD in Pharmaceutical Sciences from Mercer University, Atlanta, GA. Her thesis research focusing on development of novel targeted drug delivery system for tumor theragnosis has been recognized internationally by American Association of Pharmaceutical Scientists (AAPS) for excellence in graduate research. In addition to her active research, she serves as Editorial Board Member and Peer-Reviewer for several international journals.

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