Land O'Lakes Pharmaceutical Analysis Conference
Posters 102-108 presented in 2017

102

Dissolution Method Development of a Delayed Release Product

Margaret Roeder, Zheng (Jen) Zhao, Sanjaykumar Patel, and Justin Pennington, Pharmaceutical Sciences and Clinical Supply, Merck Research Labs, Rahway, NJ

Dissolution testing measures the rate of drug substance release into solution, impacting the extent of drug absorption. Drug manufacturers and regulatory agencies use dissolution testing to identify drug products that do not meet the desired clinical performance. Formulation composition and manufacturing processes can impact the material attributes of a drug product, which directly affect the dissolution mechanism. The dissolution method must be robust and sensitive in order to accurately measure these attributes. The establishment of dissolution specifications involves the creation of a test method as well as acceptance criterion driven by regulatory and internal expectations. Here, we will present the dissolution method development of a solid dispersion comprised of API and polymer. The compound is a modified (delayed) release drug product, designed to resist drug release in the stomach using a pH sensitive polymer in the solid dispersion, creating an amorphous solid solution with the API. Since the compound is a delayed release drug product, dissolution testing should adhere to USP <711> Dissolution for Delayed-Release Dosage Forms, which utilizes 0.1N HCl (pH 1) as the first stage acid medium. Early dissolution method development utilized 0.01N HCl (pH 2) as the first stage acid medium based on consistent drug release obtained in buffer stage. Continued dissolution method development of this compound focusing on the impact of the concentration of the acid media, optimization of surfactant level, particle size, and discriminatory power of the method will be presented. This development work will provide justification for selecting the appropriate dissolution method for further analytical development and commercialization of this drug product.

103

Investigation and Mitigation of Discoloration in Pediatric Powder-for-Suspension Formulations

Nathan D. Contrella, Leah Xiong, Andreas M. Abend, Yongjun Li, Dina Zhang, Matthew Lamm, Majid Mahjour, David Harris, Merck & Co., Inc., Rahway, NJ

Oral suspension formulations are well-suited for pediatric patients that are too young or otherwise unable to swallow tablets or capsules and also benefit from flexible dosage amounts. Multi-dose suspension products typically contain a thickening agent to maintain API particles in suspension, a preservative to inhibit microbial growth, and a pH modifier to achieve an appropriate pH. Prototype powder-for-suspension formulations containing xanthan gum as thickener, potassium sorbate as preservative, and citric acid as acidulant, were found to exhibit discoloration during stability studies. **Objective:** Quantitate the discoloration of these formulations, understand the root cause and mitigate the discoloration risk. **Methods:** The underlying cause was explored by testing excipient compatibility and identifying a signature degradation product. Color assessment by reflectance spectrophotometry and UV-visible absorbance was applied to facilitate comparison of different formulations. **Results:** Excipient compatibility experiments identified discoloration in mixtures of xanthan gum and citric acid. Xanthan gum can be hydrolyzed into its constituent sugars, and these are known to further degrade into reactive compounds including 5-hydroxymethylfurfural, which was identified in discolored formulations. Reflectance colorimetry was found to be effective for measuring discoloration and was used to evaluate several possible alternatives to citric acid. **Implications:** Discoloration was attributed to xanthan gum hydrolysis with subsequent tautomerization and dehydration reactions, catalyzed by citric acid. The use of an alternative acidulant reduces but does not eliminate the discoloration, and refrigeration is ultimately a more effective mitigation strategy. These are important considerations for any formulation that contains xanthan gum and acidifier, irrespective of the API.

104

Cutting Edge Concepts in Pharmaceutical analysis: AQbD a way to achieve robust methods through its lifecycle

Lúcia Volta e Sousa[a,b], João Matos[a], Claudia Gama[a], António Ramos[a], Rui Loureiro[a], José C. Menezes[b]
[a]Hovione Farmaciência S.A., Process Chemistry Development, Sete Casas, 2674-506 Loures, Portugal;
Institute for Biotechnology and Biosciences, Instituto Superior Técnico, Lisbon, Portugal

Method robustness and reliability are the major concerns when developing methods in Pharmaceutical Analysis. In order to address these concerns, it is becoming a trend in the pharmaceutical industry the introduction of some new concepts during the analytical method development and its lifecycle [1]. Here we present how to combine these cutting edge concepts during analytical method development, as part of a workflow model for drug substance analysis by liquid chromatography. As an outcome, a structured and scientific based approach, known as Analytical QbD (**AQbD**), is obtained. This approach encompasses several steps, such as: setting pre-defined objectives or Analytical Target Profile (**ATP**); selection of an appropriate technology; prior-knowledge collection through a risk assessment process where potential sources of variability affecting method performance are identified, then method understanding is explored via design-of-experiments (DoEs) using factors from the risk assessment stage. This AQbD methodology ends up with ATP verification and a risk mitigation phase, where all sources of variability are reduced and controlled through a formal definition of a method control strategy over lifecycle, Analytical Control Strategy (**ACS**). The overall workflow **Lifecycle Management** contains as key enablers Risk Management (**RM**) and Knowledge Management (**KM**), that ensure a method is fit for its intended purpose over the entire lifecycle of the method.

[1] C. Burgess, P.D. Curry, J. Ermer, G.S. Gratzl, J.P. Hammond, J. Herrmann, et al., Stimuli article: Proposed New USP General Chapter : The Analytical Procedure Lifecycle 1220, Pharmacopeial Forum 43(1). (2017).

105

Integration of Fully Automated Dissolution in New Product Development of Solid Dosage Pharmaceutical Products

Jeffrey Magalski, Noah PreFontaine, Don Zeilenga, Consumer Health Care R&D, Perrigo Company, Allegan, MI

While pharmaceutical drug release can be measured *in-vivo* by testing for the active ingredient in blood plasma, this approach is significantly limited by obvious impracticalities. *In-vitro* drug dissolution is used as a practical and effective alternative. However, *in-vitro* drug dissolution can be a time and labor intensive process for pharmaceutical companies, often being a rate-limiting factor for development in analytical laboratories. A fully automated dissolution system was implemented and proven to significantly reduce analyst effort, improve efficiency, and accelerate productivity. Multiple dissolution parameters and candidate formulae can be screened rapidly to determine viability, thus improving development cycle time in the analytical laboratory.

106

Multivariate Quantification of API Release from Combination Tablets in the Presence of Matrix Effects Using Fiber Optic Dissolution

Joseph Medendorp, Taryn Ryan, Mahidhar Shapally and Ivelisse Colon, Vertex Pharmaceuticals, Boston, MA

The purpose of this research was to develop a fiber optic (FO) dissolution method for combination pharmaceutical tablets. FO dissolution allows direct API quantification in the vessel, obviating the need for error prone facets of standard dissolution methods. However, FO dissolution is potentially challenged by matrix effects: UV active excipients, API interactions with excipients and media, or undissolved components attenuating the UV signal. These obstacles might render FO dissolution method development more complex than LC-end dissolution. This presentation describes a case study with the added complexity of a combination product, where the two actives have similar release kinetics and UV spectra. Multiple methods were employed for the quantification of actives, including: single wavelength per active, a modified classical least squares (CLS) approach modeling matrix effects as a third component, and partial least squares for multivariate calibration and prediction using LC-end dissolution as reference data. Single wavelength quantification requires unique features for the actives of interest, which are not always readily available. The initial pass with the CLS approach requires that linear combinations of standards adequately describe the behavior of the actives in situ. And the multivariate approach requires manual reference data for calibration. Since a combination tablet typically demonstrates collinear API release, individual quantification is non-trivial. The advantages of each of these methods of quantification will be discussed in the context of the test systems under investigation. Additionally, some guidelines will be suggested for the development of FO methods for other test systems.

107

Lifecycle of Analytical Methods: Development of Equivalent Dissolution Methods for Immediate-release Oral Dosage Forms Post-approval

Ivelisse Colón, Taryn Ryan and Joseph Medendorp, Vertex Pharmaceuticals, Boston, MA

Monitoring the performance and capability of quality control methods is a key component of the analytical methods lifecycle in the pharmaceutical industry. It is an integral part of the Analytical Quality by Design (AQbD) paradigm and promotes continuous improvement of analytical methods. However, the evaluation and implementation of newer technology can be challenging during the commercial phases of the product lifecycle due to regulatory & GMP requirements, laboratory capabilities and the demonstration of equivalency. Appropriate demonstration of equivalency is not only important from a regulatory standpoint, but also prevents false trends, false product failures and increases the confidence in the analytical capability of the method and its degree of variability. This study presents different statistical approaches for demonstration of equivalency between reference and test profiles across instruments and dissolution methods. These principles were applied to a case study for the development of alternate dissolution methods for an immediate release tablet in order to decrease analytical variability (e.g. use of fiber-optic UV analysis and automatic sampling stations). Using known variability from actual tablet dissolution profiles, theoretical reference and test batches were simulated and evaluated for similarity. Global and local similarity rejection rates will be presented for the tests of interest in the context of regulatory relevance for dissolution testing cases referenced in the SUPAC-IR FDA Guidance for Industry. While focused primarily on similarity between dissolution methods, lifecycle management of analytical methods suggests the need for principles such as these to apply equally to the evaluation of tablets manufactured at different sites, tablets with minor differences in formulation or manufacturing processes, and as a gauge of analytical variability across labs.

108

Confronting Contamination: Analytical Case Studies

Rachel A. Rensing and Albert C. Lee, EAG Laboratories, Maryland Heights, MO

Contaminant identification is of great concern to the pharmaceutical and medical device industry. Therefore, it is critical to understand and find a potential contaminant's origin quickly. Two contaminant identification case studies will be presented. The use of multiple analytical techniques is paramount to determining a contaminant's identity. These case studies include analytical techniques such as Fourier Transform Infrared Spectroscopy (FT-IR), Scanning Electron Microscopy Energy Dispersive X Ray Spectroscopy (SEM/EDS), and Gas Chromatography Mass Spectrometry (GC/MS). The first case study is a contaminant identification of a brown material present on a pharmaceutical tablet. This brown material was the source of a potential field recall of an entire lot of a drug product. After isolation and rush analysis, the contaminant was identified, it clearly came from an external source at the consumer end and a field recall was unnecessary for the product. The second case study presented is material isolated during the cleaning validation of medical grade tubing. The yellow material observed was analyzed by FTIR and SEM/EDS in order to determine the bulk chemical identification. The material was determined to be consistent with polymeric material of the bulk tubing material that was causing issues to downstream processes. After identification, the material was quantified using Gel Permeation Chromatography (GPC). This allows the client to be able to monitor the cleaning procedure.