Start

At-A-Glance

Browse by Day

Browse by Topics

Author Index

Keyword Index

Personal Scheduler

Annual Meeting Webpage

461268 Utilization of Quality By Design Principles to Define Formulation Best Practices for a Direct Compression Excipient

Friday, November 18, 2016: 10:20 AM
Continental 4 (Hilton San Francisco Union Square)

Kathryn Hewlett, True Rogers,, Karen Balwinski, Jaime Curtis-Fisk, Robert Schmitt and Shrikant Khot, Dow Pharma and Food Solutions, The Dow Chemical Co., Midland, MI

Utilization of Quality by Design Principles to Define Formulation Best Practices for a Direct Compression Excipient

Kathryn O. Hewlett (KOHewlett@Dow.com), True L. Rogers (TLRogers@Dow.com), Karen M. Balwinski (KMBalwinski@Dow.com), Jaime L. Curtis-Fisk (JLCurtisFisk@Dow.com), Robert L. Schmitt (SchmitRL@Dow.com), Shrikant N. Khot (SNKhot@Dow.com) ***Introduction:*** Quality by Design (QbD) initiatives enable pharmaceutical manufacturers to proactively design quality and performance into drug products, with the ultimate goal to maximize safety and efficacy for the patient. Hydrophilic matrix tablets represent one of the most prevalently utilized modified-release oral drug delivery systems, which are relatively straightforward to develop and cost-efficient to manufacture. Hydroxypropyl methylcellulose (HPMC) is a common rate-modifying polymer incorporated into hydrophilic matrices. The water-soluble HPMC particles are uniformly distributed throughout the matrix tablet. Upon contact with aqueous gastrointestinal media, the particles hydrate and swell. The particles coalesce to form a swollen polymer network layer. The release of active pharmaceutical ingredient (API) from the tablet is modulated by both diffusion through the swollen network and erosion of the outermost surface. Matrix tablet performance can be impacted by a number of variables, such as API physicochemical properties (solubility, crystalline morphology), physicochemical properties of the rate-modifying polymer (particle shape and size, viscosity grade), formulation composition (filler, glidant, lubricant selection) and manufacturing methodology (blending, direct compression vs. granulation, tableting conditions). The Dow Chemical Company has recently begun commercial-scale production of a new direct compression grade HPMC, METHOCEL™ DC2, to complement the finer particle size, but less flowable controlled release grade, METHOCEL™ CR. We used QbD principles to characterize properties and performance of matrix tablets containing METHOCEL™ DC2 in order to determine and balance optimal performance regimes for tablet physical properties and modified-release (MR). The results of these investigations will be presented along with formulation guidances and best practices. Particular emphasis will be placed on filler selection, HPMC molecular weight and morphology grade, and polymer concentrations utilized to ensure robust MR performance.

Methods: Gliclazide is a poorly soluble sulfonylurea used to treat non-insulin dependent *diabetes mellitus* and was used as model API. HPMC concentrations of 10, 20, 30, 40, and 50% (w/w) were investigated to cover the performance design space. The new K100LV, K4M, and K100M DC2 grades of HPMC were utilized as rate-modifying polymers, and the corresponding CR grades were used as comparative controls. Fillers investigated were Flow-Lac lactose (Meggle), Avicel PH102 microcrystalline cellulose (FMC), Starch 1500 pregelatinized starch (Colorcon), DiTab dicalcium phosphate (Rhodia), and Manogenn powdered mannitol (SPI Polyols). Tablets were produced via direct compression on a pilot-scale Manesty Beta Press at 50-rpm turret speed. Tablet physical properties, such as weight and tensile strength, were characterized using a Sotax HT 100 - 500NV instrument. Modified-release performance was characterized using the USP II paddle method in either a Varian VK 7010 dissolution system equipped with a Varian Cary 50 UV visible diode array spectrophotometer (Agilent Technologies, Santa Clara, CA USA) or a Distek 2100 single-bath dissolution system (North Brunswick, NJ USA) equipped with an Agilent 8453 diode array spectrophotometer (Agilent). Each tablet tested for MR performance was positioned in a hanging basket to minimize dissolution measurement error.

Results: Figure 1 shows the modified release performance of METHOCEL™ K100LV CR and DC2 as a function of time for formulations with differing HPMC content. Burst release occurred at low HPMC concentrations (10 and 20%) with both morphology grades. Increasing the level of HPMC in the formulation resulted in a shift into a robust MR performance regime. Above this robustness transition, modified release performance from both CR and DC2 matrix tablets was consistent.

Further increase of HPMC level minimally impacted API release rate once the robust regime was reached, so there is a diminishing impact with further increase in HPMC concentration once inside the robust regime.

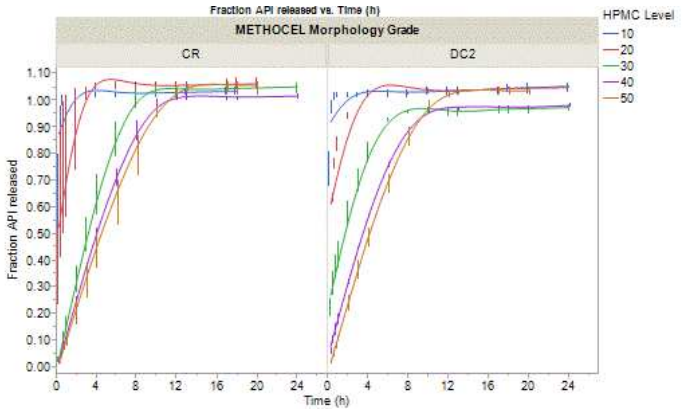

Figure 1. Release of gliclazide over time, as a function of METHOCEL grade and formulation level. Optical imaging reflected the trends observed from dissolution testing. Figure 2 shows images taken after 4 hours of swelling for tablets comprising 10% (a) and 40% (b) METHOCEL™ K100LV CR. At lower HPMC concentration, the polymer content was insufficient to achieve a continuous swollen network. As a result, the swollen network was unable to maintain structural integrity, causing burst API release as the tablet rapidly eroded. Higher HPMC concentration delivered a continuous swollen network. Dark regions in the figure represent water and areas devoid of swollen network, and the dry or partially hydrated matrix appears as grey or white. The white line in approximately the center of each image represents the location of the initial dry tablet surface. After 4 hours, the swollen network of the 10% HPMC formulation was noncontiguous (Fig. 2a). A large region near the top of the image was devoid of swollen network. The presence of voids in the swollen network is consistent with the observed burst release at lower HPMC concentrations. By contrast, the 40% formulation had a contiguous, swollen network layer surrounding the tablet and delivered robust MR performance (Fig. 2b).

(b)

(a)

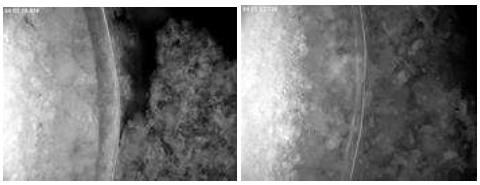

Figure 2. Optical images of (a) 10% and (b) 40% CR tablets after 4 hours of swelling. Tablet filler selection also impacts MR performance. Figure 3 shows MR profiles of the gliclazide formulation containing 30% METHOCEL™ K4M DC2 with a range of soluble and insoluble fillers. Depending upon filler solubility, the API release rate can be increased or decreased. Once inside the robust regime, filler solubility can be used to adjust MR performance to the desired target.

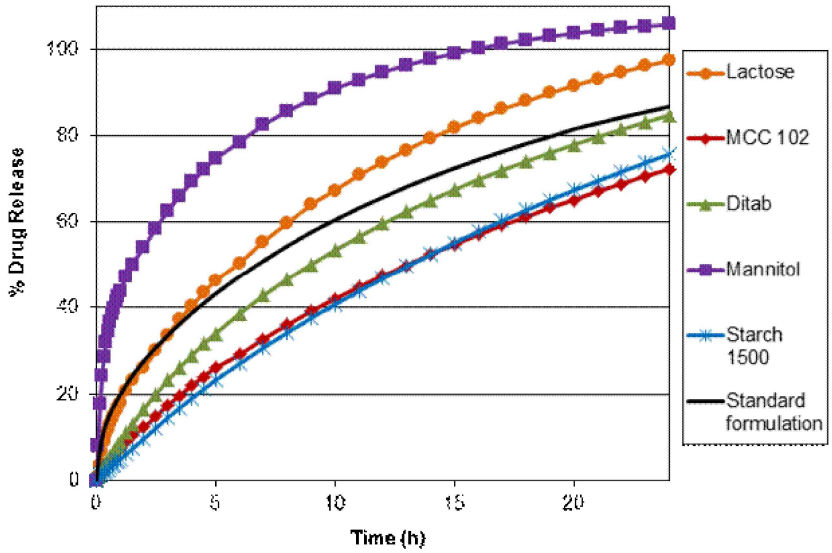

Figure 3.The effect of filler solubility on gliclazide release rate. Tablets were formulated with 30% METHOCEL DC2.

Conclusions: When working with matrix tablets, many factors must be considered to obtain robust MR performance. This work focused on examining the role of filler selection, the molecular weight and morphology grade of HPMC, and polymer concentration necessary to ensure robust MR performance. A new, direct-compression grade HPMC, METHOCEL™ DC2, was compared to METHOCEL™ CR, and both morphology grades enabled robust MR performance at comparable levels. As the HPMC concentration was increased, the formulation transitioned into a robust regime of consistent MR performance. Further increase in HPMC concentration had diminishing impact once inside the robust MR regime. Filler solubility also impacted MR performance and could be used to fine-tune the desired release rate. The systematic framework utilized while conducting this study enabled us to define formulation guidances and best practices for the new direct compression grade of HPMC. There is now a clear understanding of the influences of HPMC grade, polymer level, and filler selection on MR performance.

Extended Abstract: File Not Uploaded

See more of this Session: Quality By Design in Drug Product Formulation, Design, & Process Development II
See more of this Group/Topical: Pharmaceutical Discovery, Development and Manufacturing Forum