2016 AIChE® Annual Meeting
November 13 – 18, 2016 • San Francisco, CA
www.aiche.org/annual
16AIChE Annual Meeting, San Francisco, CA

Start

At-A-Glance

Browse by Day

Browse by Topics

Author Index

Keyword Index

Personal Scheduler

Annual Meeting Webpage

466851 Prediction of Tablet Dissolution from API and Excipient Polymer Properties

Friday, November 18, 2016: 3:35 PM
Continental 5 (Hilton San Francisco Union Square)

Jaime Curtis-Fisk[1], True Rogers,[1], Karen Balwinski[1], Kathryn Hewlett[1], Robert Schmitt[2] and Shrikant Khot[1], (1)Dow Pharma and Food Solutions, The Dow Chemical Co., Midland, MI, (2)Dow Pharma and Food Soluitons, The Dow Chemical Company, Midland, MI

Prediction of Tablet Dissolution from API and Excipient Polymer Properties

Jaime L. Curtis-Fisk[1] (JLCurtisfisk@dow.com), True L. Rogers[1] (TLRogers@Dow.com), Karen M. Balwinski[1] (KMBalwinski@Dow.com), Kathryn O. Hewlett[1] (KOHewlett@Dow.com), Robert L. Schmitt[2] (SchmitRL@Dow.com), Shrikant N. Khot[1] (SNKhot@Dow.com)

[1] The Dow Chemical Company, Midland, MI USA

[2] The Dow Chemical Company, Collegeville, PA USA

Purpose: Modified-release (MR) matrix tablets are typically produced using hydroxypropyl methylcellulose (HPMC) as rate-modifying polymer. HPMC effectively sustains release of a broad range of active pharmaceutical ingredients (APIs), but specific dissolution behavior varies depending on the API properties, excipient properties, and formulation. Recently, a new line of HPMC, METHOCEL™ DC2 grades, have been introduced to facilitate direct compression formulations given its enhanced flowability. The ability to predict performance based on properties of components could streamline formulation development and provide a more direct route to troubleshooting challenging APIs. Combined such a capability with a direct compression manufacturing technique would mean faster and less expensive development and manufacturing. The intent of this study was to identify the API and polymer properties that most directly impacted dissolution performance, connect the observed performance to fundamental API and polymer chemistry, and develop predictability that connects this fundamental understanding to efficient formulation design.

Methods: The impact of API and polymer properties on dissolution was investigated by evaluating dissolution performance of APIs covering a broad range of solubility, shown in Figure 1. Tablets contained a standard formulation of 50% API, 30% METHOCEL DC2 HPMC, 19% impalpable lactose, and 1% magnesium stearate. A standard formulation was utilized for all APIs to make a direct comparison of the structure/activity relationship between API properties and dissolution performance. Tablets were prepared by hand-feeding powder formulations into the tablet press to remove variability in die fill due to powder flow differences between API formulation blends.

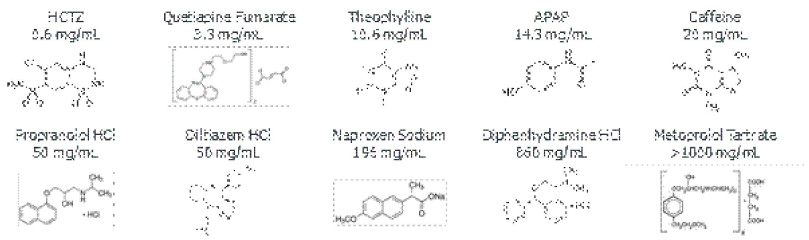

Figure 1. APIs with a broad range of solubility were evaluated in order to connect drug properties to dissolution performance.

Results: API dissolution performance was evaluated for three viscosity grades of METHOCEL DC2 (K100LV, K4M, K100M). Figure 2 displays the results of tablet formulations containing METHOCEL K4M DC2; percent API release at 2, 4 and 12 hours is plotted as a function of API solubility. The amount of API released at a given time point is greater as API solubility increases. The sensitivity to API solubility is most dramatic for intermediate solubility, with very low or high solubility API reaching a plateau where small changes in solubility to do not significantly impact release.

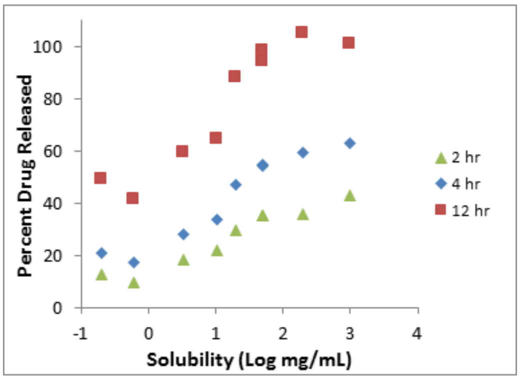

Figure 2. Percent API release as a function of API solubility, demonstrating a similar correlation at 2, 4, and 12 h dissolution time points.

The correlation of API solubility with drug release rate was also evaluated using t_{50} as a measure of release rate. This different perspective on the same datasets provides new insight into dissolution mechanisms of the tablet and the implications to formulation optimization. Figure 3 displays t_{50} values as a function of API solubility for three viscosity grades of METHOCEL DC2. All three viscosity grades demonstrate similar behavior; at low solubility there is a strong correlation between solubility and t_{50}, but at higher solubility the observed t_{50} value is constant. This behavior can be explained considering the competing mechanisms that occur during tablet dissolution. For poorly soluble APIs, the rate limiting step is API exposure to the greater sink of dissolution media as the outermost layer of swollen matrix erodes, followed by API dissolution into the media. When API solubility is greater, the limiting factor becomes diffusion of dissolved API through the swollen polymer layer and subsequent release into the greater sink of dissolution media. While K100M results in greater t_{50} values for all APIs evaluated, followed by K4M and lastly K100LV, the differentiation between grades was greatest for poorly soluble APIs. The difference in performance indicates that for low solubility APIs, polymer viscosity is a critical variable in formulation design.

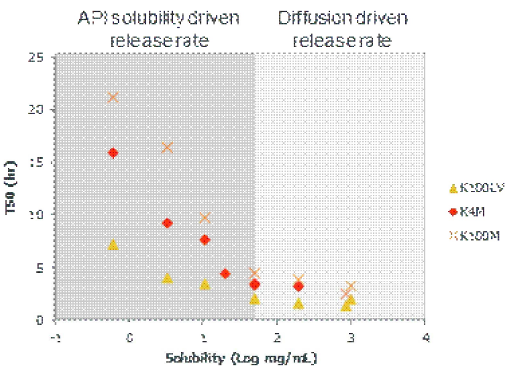

Figure 3. Dissolution rate described by t_{50} ***as a function of API solubility for three viscosity grades of METHOCEL DC2, demonstrating the correlation to API solubility.***

Conclusions: A key learning from this study is that API release from matrix tablets prepared with the METHOCEL DC2 product line is strongly impacted by API solubility and polymer viscosity. APIs of low solubility are released through a dissolution mechanism limited by API solubility and erosion of the outermost surface of the swollen polymer layer, but at higher solubility the release is driven by diffusion of dissolved API through the swollen polymer network. While higher viscosity polymers demonstrated greater extended release, the impact of this effect is more pronounced for lower solubility APIs and became negligible for higher solubility APIs. These relationships provide formulation guidance on selecting the appropriate viscosity grade of METHOCEL DC2 based upon API solubility.

Extended Abstract: File Not Uploaded

See more of this Session: Materials Science in Pharmaceutical Process Development II
See more of this Group/Topical: Pharmaceutical Discovery, Development and Manufacturing Forum