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POLYOX™ ... A Unique Polymer Option

Author: Pankaj Rege
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POLYOX™, water soluble resin, has been widely used in the formulation of osmotic drug delivery, and more recently in gastro-retentive delivery systems. However, its application in matrices remains relatively unexplored. Hypromellose (METHOCEL™, premium cellulose ethers) typically is the polymer of choice as the rate-controlling carrier.

While the polymer properties of POLYOX (polyethylene oxide), nonionic nature, and pH independence are similar to METHOCEL, it has unique properties such as fast onset of hydration, high swelling capacity, and excellent compressibility and flow. These properties allow for its utilization with METHOCEL in a complementary manner to produce matrices using both direct compression and wet granulation techniques. Due to its rapid hydration, POLYOX can reduce initial drug release (burst effect) and whether utilized in a matrix application alone, or with METHOCEL, allows for faster erosion in the terminal phases of drug release.

These phenomena contribute to release profile modulation, which may approximate to zero order, thereby affording flexibility to the formulator when developing a matrix formulation. In addition, the excellent flow properties of POLYOX give direct compression potential to blends incorporating the polymer. Self-lubricity and plastic deformation under low compression loads further facilitate direct compression tableting operations.

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Partnership - A Formulation for Success?

Colorcon understands the changing needs of the pharmaceutical formulator and how critical it is in today's environment to get your product to market faster. That is why we focus not only on providing solutions, but options and flexibility within those solutions. To grow our formulation partnership, we are eager to share our application and product knowledge to help you achieve your ultimate goals.

The Solid Dose newsletter illustrates our outreach, providing development studies and other timely information that we hope brings value to you and your work. In this special edition, we bring you information on matrices including: the performance of METHOCEL™, applications of Surelease®, and the continued exploration of POLYOX™ as a matrix polymer option. To start off this edition, we'd like to highlight Colorcon's partnership with Dow Wolff Cellulosics (DWC). Our Controlled Release Alliance provides the foundation for bringing value to the formulation community in matrix, osmotic and multiparticulate dosage forms.

As part of this alliance, DWC provides three of the most trusted polymers used in oral controlled-release applications: METHOCEL™ premium cellulose ethers, ETHOCEL™ premium ethylcellulose polymers and POLYOX™

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► POLYOX... A Unique Polymer Option

POLYOX is commercially available in a wide range of molecular weights, offering formulation flexibility for usage with low to high solubility actives. Its FDA acceptance, unique properties, and scope for intellectual property retention, make POLYOX an attractive option to formulate your extended release product.

Click [here](#) for more information on the formulation of POLYOX ER matrices for a highly soluble active.

Click [here](#) for more information on the physico-mechanical characterization of POLYOX for tablet manufacture.

The Affect of Alcoholic Beverages on Extended Release Matrices

*Author: Marina Levina
Sr. Product Development Manager*

In response to the recent Food and Drug Administration alert to healthcare professionals regarding the potential negative influence that alcoholic beverages may have on oral extended release systems, scientists at Colorcon investigated the performance of METHOCEL™ premium cellulose ether matrices in ethanol water solutions.

Since the integrity and performance of an HPMC matrix formulation depends on rapid hydration and gel formation upon ingestion, it is important to determine what affect alcohol has on this mechanism. The hydration, gel formation and drug release from three matrix formulations containing drugs of various solubility: felodipine, gliclazide and metformin hydrochloride, were tested in media with 0%, 5% and 40% v/v of ethanol. None of the three matrix formulations resulted in dose-dumping when exposed to 5% or 40% v/v ethanol solutions for up to 12 hours. However, in the case of metformin hydrochloride, drug release was slower, which was related to the relatively lower solubility of this active pharmaceutical ingredient in the hydro-alcoholic media at the same ethanol volume ratios.

[Study Link \(PDF 118.34 KB\) >>](#)

An additional study showed all formulations had consistent hydration, swelling and gel formation when exposed to hydro-alcoholic media. Further studies indicated that hydro-alcoholic solutions had little effect on the textural and mechanical properties of hydrated compacts, while the rheological behavior of HPMC showed dependency on the ethanol content of the media.

[Study Link \(PDF 118.25 KB\) >>](#)

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► Partnership - A Formulation for Success?

water soluble resins. Colorcon adds its formulation and application expertise, tailored formulation and systems, and its unmatched global technical service and distribution network.

Since the launch of the Alliance in July 2007, Colorcon has developed further application data to assist the formulator in developing hydrophilic and inert matrices, best practice guidelines for barrier membrane coating, and osmotic applications. Much of this information is featured in today's and previous newsletter editions. Going forward, product, application and service additions are planned for 2010 to extend the utility of the alliance.

"Through Colorcon's network of technical experts and understanding of customer needs, this Alliance provides an opportunity for us to focus on developing new and improved technologies to enhance performance during pharmaceutical manufacturing, distribution and use," said Hirotosugu Furukawa, Global Strategic Marketing Manager, Dow Wolff Cellulosics.

Colorcon's General Manager of Formulation Technologies, David Bain, agreed with Mr. Furukawa. "Our goal is to provide products and services to help our customers modulate drug release from tablet, multiparticulate and osmotic platforms. The Alliance has significantly extended our scope to develop options for our customers

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► The Affect of Alcoholic Beverages on Extended Release Matrices

A full text article on the attached poster topic was published online at AAPS PharmSciTech – January 16, 2009.

Overall, these studies indicate that METHOCEL provides a solid platform to develop hydrophilic matrix systems, which resist the deleterious dose dumping effects of alcohol consumption.

Matrix Tablet Design: The Affect of Shape and Color

Tablet geometry, in combination with colored film coatings, is often used to differentiate a product in the market, or to re-brand a line extension for life cycle management.

In the case of an extended release matrix tablet, formulators are reluctant to modify the shape of the tablet, or to add a film coating once the release profile has been established, for fear of changing the profile. This is especially true in drugs where the release is controlled by erosion or diffusion.

In a recent study, our tablet design and formulation technology experts evaluated the effect of geometry on two extended release model drugs at the extreme range of dose and solubility. Various tablet shapes were evaluated to determine if the hypothesis that surface area-to-volume ratio is the key parameter in controlling drug release, and moreover, if by maintaining a constant surface area-to-volume ratio, constant drug release could be maintained from significantly different tablet designs. The study also looked at the effect of a pigmented immediate release coating on the drug release profile. The results indicate that shape and color can be used as design options without changing the targeted release profile.

[Study link \(PDF 221.53 KB\) >>](#)

Surelease® - Wet Granulation Binder for Inert Matrices

*Author: Hua Deng
Manager - Product Development*

Our focus on matrix applications led to investigating the use of Surelease®, aqueous ethylcellulose dispersions, as an inert matrix former. Two model drug candidates: theophylline, a sparingly soluble drug and metformin HCl, a freely soluble drug, were used for the study. Results showed that Surelease was successfully used to granulate both.

Extended drug release was achieved for both theophylline and metformin HCl formulations, and rate of drug release decreased with increasing Surelease

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► Partnership - A Formulation for Success?

and deliver solutions through a global and consistent technical service and supply chain.” David added, “The Alliance capabilities were put to the test during recent supply shortages of HPMC. By working closely with our customers and implementing our strategic Business Continuity Plan, the Alliance was able to employ our unequaled production and distribution network to minimize the impact on our customers.”

It’s clear that both Colorcon and DWC are working diligently to ensure that this partnership brings great value to their customer – the pharmaceutical formulator. With this Alliance, you can rely on Colorcon for worldwide application development, local technical support and global supply chain support. DWC can be relied on for an unparalleled manufacturing capability of the Alliance products. Not to mention, the development of new and improved excipient technologies, based on polymer science and manufacturing expertise. The Controlled Release Alliance is one example of how a partnership, when aligned for the benefit of the customer, can prove to be a great formulation for success.

► Surelease® - Wet Granulation Binder for Inert Matrices

concentration. Granulated formulations exhibited good powder flow and narrow particle size distribution. The compressed tablets exhibited good mechanical strength and low friability at relatively low compression force.

It should be noted that choice of filler may significantly impact the tablet physical properties and drug release performance. For example, tablets containing microcrystalline cellulose (MCC) laminated during dissolution testing to expose more surface, and hence, accelerate drug release two fold after the initial stages, whereas other fillers maintained the integrity of the tablet and resulting drug release. The use of different fillers, with soluble, insoluble and swellable properties, may be utilized to modulate drug release and improve manufacturing operations.

The low dose, smaller size metformin inert matrix tablets showed faster drug release than the high-dose, larger theophylline tablets. This could be attributed to the larger surface area-to-volume ratio and shorter diffusional path length for the smaller tablets, which further facilitated release of the more water soluble drug.

Figure 1: Effect of fillers on theophylline release from Surelease inert matrices.

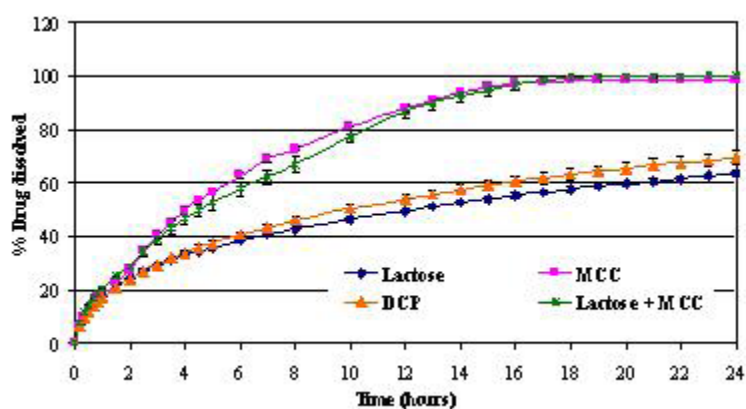
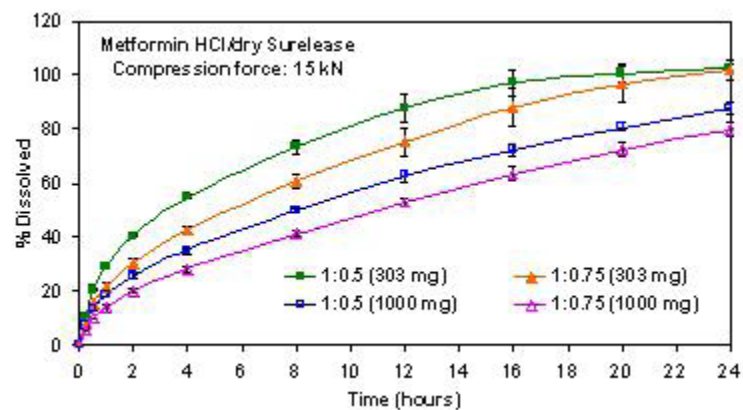


Figure 2: Effect of Surelease content and dose level on metformin release from Surelease-based inert matrices.



[Study Link \(PDF 244.61 KB\) >>](#)

[Study Link \(PDF 724.47 KB\) >>](#)

Colorcon Associate Wins Award



Colorcon is proud to recognize Chris DeMerlis for being selected as this year's co-recipient of the

IPEC Foundation's Marshall Steinberg Award for his contributions in the area of Excipient Safety and Toxicology.

Chris will be receiving this award along with Dr. Jay Goldring (Wyeth) for their work in developing the IPEC New Excipient Evaluation Procedure. The Procedure can be used by world class toxicologists to assess the safety of new excipients for their intended uses and provide an expert report. This report can be used in submissions of NDAs and ANDAs to help minimize regulatory risk when using new excipients. Colorcon has already utilized this process for evaluation of various Surelease® aqueous ethylcellulose dispersion products.

Chris expressed his sentiments, "After five years on this project it feels good to be recognized by peers and IPEC - a worldwide trade association. We put a great deal of work into it, so it's very satisfying."

The Award will be formally presented to Chris and Jay at the Award Luncheon of the Annual Meeting of the American College of Toxicologists (ACT) on November 2nd in Palm Springs, California. Chris will be coordinating a technical session on November 3rd concerning Excipient Innovation and Safety Assessment, which will be followed by an Award Winner's Recognition Dinner.

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Achieving Complex Release Profiles with METHOCEL™ Matrices

Author: Viena D. Dias
Manager – Product Development



Hypromellose (METHOCEL™, premium cellulose ethers) matrices offer advantages of simplicity and ease of manufacture. Such systems, however, can be used to obtain both simple and complex release profiles either alone or in combination with other extended release (ER) technologies. Two case scenarios were investigated:

1. Certain therapies are most effective when the overall dose of the API is formulated to be released in two stages (biphasic release profile). Therefore, the dose fraction released in the first phase alleviates the disease symptoms, while the second slow release phase provides the dose fraction required to maintain an effective drug plasma concentration until the next dose. In our investigation, a biphasic release profile was obtained by coating hypromellose matrices with a drug layer as proof of concept. Drug embedded in the coating provided the first phase of drug release, while the second phase of release was controlled by the hypromellose core. The core formulation was designed using a start formulation from Colorcon's HyperStart® service. The percent drug released at each phase could be modulated by fine-tuning the dose fractions within the matrix and the coating. Solubilizers or other excipients may be added to the drug layering solution/dispersion to further modulate the release. An Opadry® complete film coating system was applied to the dosage form and showed no impact on the biphasic release profile.

2. When highly soluble APIs are formulated with hypromellose matrices, they may show a burst of drug release due to the time required for formation of an efficient gel layer. Top coating such matrices with the insoluble, yet permeable Surelease®, aqueous ethylcellulose dispersion, provided a zero order extended release profile for a highly soluble API without the initial burst effect. Surelease prevented rapid drug dissolution and release from the surface of the matrix, thus retarding drug release at the initial stages of dissolution.

Click [here](#) to read the complete article published in Pharmaceutical Technology Europe – September 2008.

► Colorcon Associate Wins Award

Please join us in congratulating Chris on a great accomplishment as a result of his efforts. This work will help Colorcon develop new products and provide the appropriate level of regulatory support to our customers as they begin to utilize these new materials in drug applications.

Opadry: No Effect on Drug Release from Hypromellose Matrices

Author: *Ali Rajabi-Siahboomi*
Senior Director, Scientific Affairs

The overall benefits of aqueous film coatings have been well documented and these coatings are extensively used on immediate release tablets. The benefits include:

- Increased mechanical strength
- Masking unpleasant tastes and odors
- Improving the ease of esophageal transit
- Shielding the core against light, moisture or oxygen permeation
- Product branding and identification
- Authentication and anticounterfeiting protection

Formulation scientists may, however, hesitate to use aqueous coatings on hydrophilic matrices for extended release tablets. This hesitation may be due to concerns over immature polymer hydration in the core and consequential effect on drug release.

Colorcon scientists investigated this concern using several Opadry® II, complete film coating systems, on two model drug extended release matrix formulations (chlorpheniramine maleate and theophylline) and have shown no effect on performance of the matrices.

METHOCEL™, premium cellulose ethers, K4M Premium was used as the rate controlling polymer for the formulations and showed excellent reproducibility and stability of the release profile.

The Opadry II immediate release film coating system was shown to enhance the mechanical strength of the matrix tablets without affecting the drug release characteristics of the core, even under elevated storage conditions.

[Study Link \(PDF 69.36 KB\) >>](#)

For more information...

To learn more about matrices, please click [here](#).

Upcoming Colorcon Webinar:
POLYOX™ - New Applications in Extended Release Matrices -
Click [here](#) to register!

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