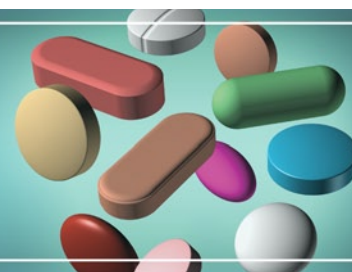


The Solid Dose

February 2010

Colorcon® News



IN THIS ISSUE:

- Low Dose, High Risk in Direct Compression Applications
- Conversation with Dr. Ali Rajabi-Siahboomi
- Drug Release Modulation from Inert Matrices with Surelease®, Aqueous Ethylcellulose Dispersion
- Formulation Robustness Study in Hydrophilic Extended Release Matrix Tablets
- An Inside View of the AAPS Focus Groups
- Product Spotlight
- Colorcon Events
 - Generic Pharmaceutical Association's (GPhA) Technical Advisory Committee
 - Colorcon Seminar
 - Q2 Conferences/Trade Shows
 - Educational Events

Low Dose, High Risk in Direct Compression Applications

*Author: Ngoc Do, PhD
Sr. Manager – Product Development*

As API candidate screening becomes more refined and potent, low dose concentrations are often micronized to improve content uniformity, as well as increase dissolution rate. But, low dose medicines may still be a challenge to formulate in tablet or capsule dosage forms due to content uniformity. Traditionally, these drugs have been manufactured through wet granulation to assure that each tablet contains an accurate and reliable dose. This process can, however, be costly and time-consuming because of the many steps involved. Direct compression is a preferred manufacturing tablet method to deliver any drug, and more specifically, low dose actives to reduce time and cost, and avoid any stability concerns. In selecting direct compression, one must optimize the process and find the suitable excipient to 'carry' the API, resist segregation and ensure content uniformity.

The successful use of Starch 1500®, partially pregelatinized maize starch, in low dose drug products prepared by direct compression has been previously documented by Colorcon. Most significantly, it was determined that Starch

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Conversation with...

Dr. Ali Rajabi-Siahboomi



Having held various academic positions for seven years prior to joining Colorcon, Dr. Ali is not only a leader in the industry, but a committed teacher at heart. In 2009, he was elevated to Senior Director of Technical Affairs, responsible for product & applications development and technical service for Colorcon. With over 150 published articles, book chapters, abstracts and patents, he continues his career focus in the field of pharmaceutical technology; from film coating to general principles of design, formulations, manufacturing and biopharmaceutical consideration of oral drug delivery systems.

Recently, Dr. Ali has been elected to lead the Controlled Release Society's (CRS) Oral Drug Delivery (ODD) Focus Group. We asked, "What will be your main focus for this forum – and why?" He responded, "Oral drug delivery remains the most preferred route for administering drugs to patients. Although it is the most commonly used route of drug delivery, with a long, rich history and science, there are still many unknown and complex aspects that require focus and investigation. The main objective of the CRS-ODD focus group is to facilitate interactions among like-

continued on next page ►

► Low Dose, High Risk in Direct Compression Applications

1500 provided content uniformity in a directly-compressed tablet formulation with an API concentration of only 0.07%. On a production scale of 4 million tablets, the average API assay was 99% of the label claim with a variation of only 2% relative standard deviation (RSD)¹. These results were confirmed on a smaller scale with two different drugs, chlorpheniramine maleate² and indomethacin³. One study attributed the fact that Starch 1500 produces homogeneous mixtures to its superior adhesive characteristics, which result from its partially pregelatinized nature and inherent moisture content of ~10%. Indomethacin studies further suggested that the physical features of Starch 1500, namely micro-crevices in the surface, may further promote association and subsequent hydrogen bonding, in part via tightly bound moisture.

These results have been further corroborated by Colorcon scientists, who have investigated eight additional low dose APIs (most of which had been micronized) formulated and manufactured by direct compression using Starch 1500. The water solubility characteristics of the model drugs varied from practically insoluble to freely soluble. The dose range was between 2mg-10mg, and the drug load from 2.5%-10% of the tablet weight. In all cases, the average drug content of the experimental formulas met label claim requirements with RSD values in the range of 0.4%-3.9%. The USP drug content uniformity acceptance values (AV) of the eight formulas were within the range of 1.0 - 9.8, which all met the USP requirement for content uniformity with an AV value of <15. In addition, the release profiles of all tablet formulations were determined to be stable through six months storage at 40°C/75% relative humidity. This data will be published in subsequent Colorcon papers.

[1 - Study Link \(PDF 234.61 KB\) >>](#)

[2 - Study Link \(PDF 114.63 KB\) >>](#)

[3 - Study Link \(PDF 684.63 KB\) >>](#)

Drug Release Modulation from Inert Matrices with Surelease[®], Aqueous Ethylcellulose Dispersion



Formulators today are looking to utilize inert matrices as an extended release (ER) drug delivery technology and recognize the need for a flexible technology - one that is able to provide a range of drug release profiles to meet the needs of their API, disease state and patient population.

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► Conversation with... Dr. Ali Rajabi-Siahboomi

mindful scientists around the globe and across different disciplines. For example, we had an excellent satellite meeting in Vienna last year focusing on multiparticulate drug delivery systems. This year we have planned a roundtable session at the annual meeting of CRS in Portland. The title of the session is: 'Can one size oral dosage form fit different patient populations?' This session will focus on variation in age, gender and ethnicity that may lead to alternation in drug dosing, metabolism, and efficacy. These variations yield important implications for the drug development process. It is intended to encourage a roundtable discussion among presenters and audience to debate and exchange views and perspectives."

Once again, taking the role of leader and teacher, this past November, Dr. Ali was the main presenter for a Colorcon hosted webinar titled, POLYOX[™] – New Applications in ER Matrices. When asked, "Why was POLYOX selected as the topic for the webinar?" He explained, "POLYOX is an interesting polymer and may provide options to be considered in response to the elevated health and safety standards, new challenges and trends seen in the pharmaceutical industry. It's a hydrophilic polymer, widely used in osmotic pump technology, and is now being considered for increased use in hydrophilic matrix applications."

"Scientists are looking for new polymeric materials to meet

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► Drug Release Modulation from Inert Matrices with Surelease®, Aqueous Ethylcellulose Dispersion

Surelease®, a fully formulated aqueous ethylcellulose dispersion, has previously been studied as a wet granulating agent and release retardant binder in inert matrix applications. The potential for drug release modulation from Surelease based inert matrices, using simple monolithic tablets or as compression coated dosage forms, has also been investigated using theophylline as a model drug. The influence of filler type (soluble vs. insoluble), filler content and dosage form type on drug release profiles was studied.

Theophylline granules were prepared by top spray fluid bed granulation using Surelease as a binder. These granules were used in the preparation of simple monolithic tablets and compression coated formulations, using additional soluble or insoluble fillers and neat API as extra-granular components. These modifications demonstrated the modulation flexibility of this approach.

Monolithic tablets formulated using granulated theophylline showed ER properties; however, only 80% of the release was observed at the end of 24 hours. The addition of extra-granular theophylline and fillers resulted in an ER profile and complete drug release in 12-14 hours. In the compression coated formulations, the nature and amount of filler in either the immediate release (IR) core or outer ER coating layer had a significant effect on the drug release rate. For example, the use of insoluble filler at high concentrations in the inner IR core or ER coating resulted in pulsatile release.

Results of this study indicated that drug release from Surelease based inert matrices can be modulated by using simple monolithic tablets or by designing compression coated formulations. The type of fillers and where the fillers were added in compression coated formulations influenced the drug release rate from matrices.

[Study Link \(PDF 220.71 KB\) >>](#)

Formulation Robustness Study in Hydrophilic Extended Release Matrix Tablets

*Author: Marina Levina, PhD
Sr. Manager – Product Development*

Robustness of pharmaceutical oral solid dosage forms can be defined as consistent product performance from batch to batch. To ensure this, formulators set limits for key variables that most influence product quality. These critical quality attributes include specifications for active pharmaceutical ingredients, manufacturing process(es) and may require a tightening of specifications for the pharmaceutical excipient(s) used in the formulation. Ideally, scientists would work with raw material batches at specification

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► Conversation with... Dr. Ali Rajabi-Siahboomi

the challenges of formulations encountered by new active pharmaceutical ingredients (APIs) and elevated safety and functional performance requirements. With rapid hydration, unique swelling capability and ease of use, POLYOX has attracted a great deal of interest amongst formulators for various applications, inclusive of hydrophilic matrices. Even though the polymer has been manufactured by the Dow Chemical Company and available for pharmaceutical use for over 25 years, only in recent years have scientists begun to study and use POLYOX as an alternative polymer to hypromellose (METHOCEL™, premium cellulose ethers) for matrices. As part of the Controlled Release Alliance between Colorcon and Dow, we have collectively invested a significant amount of resources to better understand this unique polymer and explore its applications in hydrophilic matrix formulations and their manufacture," said Dr. Ali.

Impressed by the response to the webinar, Dr. Ali indicated that the number of people from around the globe who attended is a good testimony to the level of interest on this topic. He said, "The session turned out well. It was very interactive with relevant questions. To my good fortune, we had two experts; Dr. Robert Schmitt from Dow Chemical Company and Dr. Hiep Huatan of H2 Pharma, both with many years of experience in handling and using

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► Formulation Robustness Study in Hydrophilic Extended Release Matrix Tablets

extremes during development to assess the impact of excipient variability on formulation robustness. However, realistically, the ability of a supplier to produce materials at extremes of specification is challenging given that manufacturing processes are designed to produce an excipient well within specifications.

One way of assessing the impact of specification extremes on a formulation is to engineer the excipient to those extremes. As an example, samples of polyethylene oxide (POLYOX™ 1105, MW of 900,000) were selected. The extremes of their viscosity specifications were prepared by blending POLYOX grades with lower (POLYOX 205, MW of 600,000) and higher (POLYOX N-12K, MW of 1,000,000) nominal viscosities to approximate samples of POLYOX 1105 at the low and high limits of its viscosity specification. Molecular weight and polydispersity for the POLYOX blends were consistent with those of POLYOX 1105, which all showed typical unimodal distributions. Model formulations comprising theophylline and the POLYOX blends representing the viscosity specification extremes for POLYOX 1105 gave dissolution profiles that were statistically similar. These results suggested that a formulation of hydrophilic matrix with POLYOX 1105 was robust with consistent drug release. The study demonstrated a reasonable approach to assess the impact of potential excipient variability in formulation development by blending standard excipient products, and has practical implications in the design of robust, extended release, POLYOX based matrix formulations.

[Study Link \(PDF 235.32 KB\) >>](#)

POLYOX™ is a trademark of The Dow Chemical Company.

An Inside View of the AAPS Focus Groups



As we shared with you last April, Dr. Tom Farrell, Colorcon - Director of Product Development, was elected to be the 2010 Chair of the Excipients

Focus Group of AAPS for a one-year term. Now that Farrell has been in his role for a few months, we have an insider's view of the AAPS Focus Groups and how they work.

Focus Groups were established within AAPS to align members and establish programming for members with a common interest in a particular discipline. There are currently 40 Focus Groups. The Excipients Focus Group is one of the largest with 1,000 members.

The top three objectives of the Excipients Focus Group in 2010 are:

1) solicit, review and archive articles for an excipient theme issue in the AAPS PharmSciTech online journal; 2) conduct a webinar series on 'hot' topics; and

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► Conversation with... Dr. Ali Rajabi-Siahboomi

POLYOX, to respond in the live Q&A session."

Dr. Ali shared two questions asked at the webinar. First, "Are there any recent matrix applications for POLYOX that you have developed?" He replied, "Yes, working together, Colorcon and Dow have invested in POLYOX to bring our customers real case studies, where POLYOX has been used with various filler-excipients and different APIs. As a result of these case studies, we have built a high level of know-how and capability in applications of this polymer in extended release technologies."

The second question posed, "What does the future look like for this polymer?" Dr. Ali explained, "The potential applications with added benefits of using POLYOX are great. The industry's cautious approach to new materials and concepts means more questions and debates to follow. But, since the polymer has a long safety record and there are R&D centers that have developed excellent expertise and know-how on applications, we foresee a rapid growth in utilization of POLYOX as a complement to hypromellose in the marketplace. Its ease of manufacturing, flexibility for use with different drug release profiles and possible superior in vivo performance is expected to gain tremendous momentum within the next couple of years."

When asked if he was surprised by some of the questions, Dr. Ali stated that, "It is normal in the pharmaceutical

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► An Inside View of the AAPS Focus Groups

3) shape programming in accord with membership interests for the AAPS annual meetings.

The specific theme of the AAPS PharmSciTech issue is “Advances in Pharmaceutical Excipient Research and Use: Novel Materials, Functionalities and Testing.” The Focus Group expects to receive a few submissions for the theme issue this spring, but will be soliciting additional contributions through 2010.

The first webinar is entitled, “Excipient Variability and the Effect on Drug Product Quality” and is expected to be offered early in 2010.

Farrell said, “I find it rewarding to bring the ideas of the Focus Group from over the last two years to fruition. I’ll be working with the Steering Committee and membership at large to identify additional ‘hot’ topics that we can try to include in future programming or other developmental/educational activities.”

Some additional hot topics include: QbD and drug-excipient compatibility. Farrell and Colorcon have done a significant amount of work on the latter topic, including a poster published at AAPS -Determination of Trace Formic Acid and Formaldehyde in Film Coatings Comprising Polyvinyl Alcohol (PVA) - link below. Farrell’s work in this area of drug-excipient compatibility has led to an invitation to speak at next year’s round table at AAPS.

“As 2010 Chair of this Focus Group, it’s great to work with colleagues from a range of industrial and academic organizations. To work with people who have a common interest provides an opportunity to go beyond the customer-supplier relationship, said Farrell.”

Any reader with proposals for the AAPS PharmSciTech issue, the Webinar series or annual meeting programming should feel free to [contact Dr. Tom Farrell](#).

[Study Link \(PDF 50.7KB\) >>](#)

Colorcon Events

Generic Pharmaceutical Association's (GPhA) Technical Advisory Committee

On Wednesday, January 20, 2010, Colorcon gave a presentation, via teleconference, on inactive ingredients and ANDA filing issues. Speakers from Colorcon included David Schoneker - Director of Global Regulatory Affairs, Alexa Smith - Global Regulatory Services Manager and Chris DeMerlis - Manager, Regulatory Affairs.

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► Conversation with... Dr. Ali Rajabi-Siahboomi

industry to be ‘cautious but curious’ and the response to this webinar and the questions were no exception. Attendees were keen to understand the chemical and physical properties of POLYOX and their influence on manufacturability, its stability as a polymer and in-tablet, process applications and key functional parameters for its use in matrix systems.”

To provide further information on POLYOX, included below are links to a list of questions and answers from the webinar and a poster presented at AAPS 2009. Dr. Ali’s confidence about this polymer is a testament to his belief in the work being done as part of the Controlled Release Alliance.

[Study Link \(PDF 207.38 KB\) >>](#)

Click [here](#) to watch the recorded version of the Colorcon POLYOX Webinar, including the Q&A session.

Click [here](#) for Webinar Q&A.

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► Colorcon Events

Inactive ingredients are frequent reasons for the Office of Generic Drugs (OGD) to refuse an ANDA authorization. In particular, proprietary inactive ingredients can be especially challenging in regard to identification and quantification of the individual components. Nevertheless, this information is often essential for OGD to make a filing decision.

During the presentation, Colorcon described the type of information necessary to support the use of proposed inactive ingredients from an FDA perspective. The discussion also reviewed best practices for manufacturers when seeking supportive information from excipient vendors, the time needed by vendors to provide supportive information on excipients, the need and timing for confidentiality agreements from an excipient vendor perspective, the availability of tox data from vendors, and other issues.

Gordon Johnston, GPhA - Vice President of Regulatory Sciences provided this feedback on the event. "The teleconference with Colorcon and the FDA attracted more than one hundred participants from GPhA member firms. The comprehensive presentation by Colorcon Global Regulatory Affairs staff, along with the introduction and regulatory overview of inactive ingredient issues by the FDA, resulted in one of the most successful "virtual" training programs to date. Following the program, a number of GPhA members noted that the presentation provided invaluable insight and recommendations on how to improve communications with vendors when seeking information on inactive ingredients to support filing of an ANDA."

To request more information please [Contact Us](#) and select Regulatory.

Colorcon Seminar

Solid Oral Dosage Product Development

April 6, 2010

Museum of Science

Boston, MA

This seminar will include informative presentations and technical updates given by both Colorcon and special guest experts from Micron Technologies, Long Island University, Pharmatek, Pfizer, Novartis and The Dow Chemical Company.

For the agenda and more information click [here](#).

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Product Spotlight ...



As a part of the Controlled Release Alliance with The Dow Chemical Company, POLYOX™, water soluble resin, is a polymer that offers tremendous value to the pharmaceutical formulator.

POLYOX are nonionic poly (ethylene oxide), hydrophilic polymers available in a wide range of molecular weights and are supplied as white, free flowing powders. POLYOX has an established history of successful use in extended release (ER) applications of osmotic pump technologies, hydrophilic matrices, hot-melt extruded products, gastro-retentive dosage forms and other drug delivery systems.

An ideal choice for use in ER systems, POLYOX offers;

- rapid and reproducible hydration and swelling for use in osmotic pump and matrix technologies
- wide range of molecular weights from 100,000 to 7,000,000 - for formulation flexibility
- excellent flow, compressibility and lubricity for direct compression ER applications
- thermoplastic, highly crystalline with low melting temperature for hot melt extrusion and melt granulation

Globally compliant, POLYOX has excellent safety records of use

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► Colorcon Events

Q2 Conferences/Trade Shows

Come visit us at these events:

Show	Date	Location
Supply Side East	April 26-28	Secaucus, NJ
Excipient North	April 29	Montreal, Canada
CPhI Japan	April 21-23	Tokyo, Japan
ExcipientFest Americas	May 5-6	San Juan, PR
Vitafoods	May 18-20	Geneva, Switzerland
FCE	May 25-27	Sao Paulo, Brazil
CPhI China	June 2-4	Shanghai, China
Excipient North	June 24	Toronto, Canada

Educational Events

For a complete list of all Colorcon Educational Programs, please use the links provided below:

[Modified Release Forums](#)

[Colorcon Formulation School®](#)

[Colorcon Coating School®](#)

Product Spotlight ...

in pharmaceutical products and meets the requirements of the US Pharmacopeia (USP) or National Formulary (NF) specifications. Additionally, POLYOX is approved for use in Japan and Europe, and meets the requirements of Food Chemicals Codex, the International Codex Alimentarius.

Colorcon's dedicated team of technical specialists provides design expertise to meet unique applications. Local technical support from Colorcon is available for applications advice, trials, scale up and troubleshooting.

For more information on POLYOX click [here](#).

POLYOX™ is a trademark of The Dow Chemical Company.

For more information on any products or services mentioned in this newsletter, please [Contact Us!](#)

To access previous versions of The Solid Dose, please click [here](#).

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