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SPECIAL FEATURE - Wanted: New Excipients to Meet the Demands of a Challenging Industry

Current trends in the pharma market, such as the discovery of increasingly lipophilic APIs, macromolecules, and biological actives have created a need for a more in-depth understanding of existing excipients, as well as the creation of new excipients, says Karen A. Coppens, Global Marketing Manager for Dow. “For example, there are few excipients that are designed for processes such as hot melt extrusion or spray drying to enable solubility enhancement of highly lipophilic insoluble APIs,” she says. As such, a number of new products have been introduced that are modifications of existing monographed excipients.

In addition, continuous manufacturing has put increased demand on the performance of existing excipients, says True L. Rogers, RPh, PhD, Technologies Leader at Dow. Similarly, for the delivery of biosimilars, there are few approved excipients that can be successfully utilized.

“Overall there is a strong trend that suggests the current monographed ingredients will not continue to be sufficient to support the newly discovered actives in the near future and new excipients will be required,” says William Porter III, PhD, Dow Associate Research Scientist.

Thus, the rising demand for functional excipients. While the pharmaceutical excipients market will be worth $8.1 billion by 2021,[1] much of that growth will be driven by functional excipients. The extensive use of advanced drug delivery is a key factor promoting the growth of functional excipients. Yet, few companies, with the help of latest technologies, are focusing on innovations in these excipient categories.[2]

Drug Development & Delivery magazine recently spoke with some of the leading excipient innovators to find out what types of excipients they are developing, the advantages they offer to formulations, and where they see the industry focusing over the next few years.

BASF Corp.: High-Purity Poloxamer Designed for Biologics Manufacturing

Cell cultures used in biologics manufacturing have stringent requirements that must be met to ensure high cell viability and consistent biologic drug yields. For protection from shear stress, BASF’s Kolliphor® poloxamer 188 has a long publication history, as well as documented use in the manufacturing of approved biologics.

Resource Directory

Company Profiles

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- Ajinomoto Althea, Inc.
- Alcami
- AmerisourceBergen
- Ascendia Pharmaceuticals
- Avista Pharma Solutions
- Avomeen Analytical Services

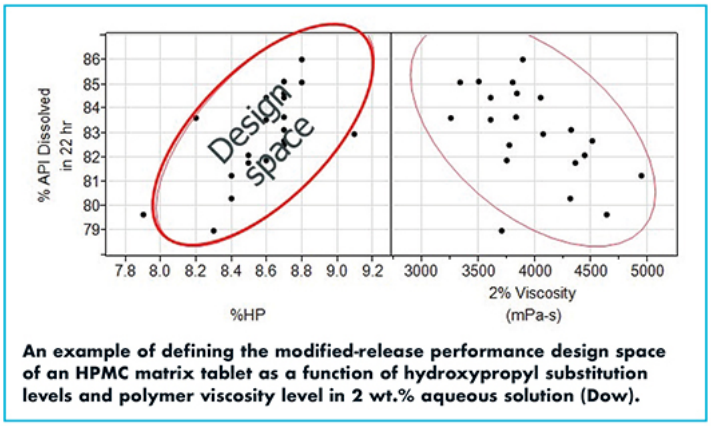
"Excipients that can mitigate biological production risks and improve process yield are in high demand," says Chattopadhyay, PhD, Business Director Pharma Solutions, BASF Corporation.

In cooperation with certain users in the biotech industry and with more than 50 years of experience in ethylene oxide/propylene oxide chemistry, BASF has committed to providing Kolliphor P 188 Bio, which is designed to meet needs in quality, consistency, and performance in cell culture systems.

In addition to biologic applications, BASF helps pharmaceutical companies solve unmet formulation needs and offers intelligent solutions in the areas of instant and modified release, solubilization, skin delivery, and softgels, explains Dr. Chattopadhyay.

Dow: Multi-Functional Excipients Improve Formulation & Delivery Flexibility

"Today, less than 10 drugs represent more than 50% of biologic drug sales, and we can foresee good growth opportunities for biosimilars in the coming years," says Christophe Massip, Global Marketing Director, Dow. Biosimilars tend to use similar excipients as the innovator drugs. The emergence of biosimilars increases the need for larger scale manufacturing capabilities for excipient suppliers as they tend to drive growth due to an expanded patient base.



An example of defining the modified-release performance design space of an HPMC matrix tablet as a function of hydroxypropyl substitution levels and polymer viscosity level in 2 wt.% aqueous solution (Dow).

Biobetters, on the other hand, and new biologic molecules such as mAbs, recombinant proteins, peptides, and vaccines, are sometimes developed using novel excipients. For instance, Dow has development activities with key customers to design new stabilizers that improve drug potency and shelf life, and can overcome some of the issues seen with polysorbates.

"We are also working with our customers' manufacturing, process, and quality teams to provide best-in-class silicon tubing and connectors," says Mr. Massip. "Those are made of USP Class VI-compliant Silastic® biomedical grade elastomers in our dedicated FDA and ISO-registered production facility in Michigan. We provide extensive extractables, physical properties, and engineering data, and support our customers with validation, qualification, and regulatory support services."

In addition to an increased interest in biobetters, Dow customers are actively looking for multi-functional excipients that improve the manufacturing process while

- BASF Corporation
- BioScreen Testing Services
- Capsugel
- Captisol, a Ligand Company
- Catalent Pharma Solutions
- CordenPharma International
- Credence MedSystems, Inc.
- Croda Health Care
- EG-GILERO
- Enable Injections, Inc.
- Frontage
- Gateway Analytical LLC
- Gattefosse Corporation
- Impact Analytical
- Insulet
- Latitude Pharmaceuticals, Inc.
- Lyophilization Technology, Inc.
- Metrics Contract Services
- Minnesota Rubber & Plastics
- Multisorb Technologies
- Nemera
- Noble
- Patheon
- Pfanstiehl, Inc.
- Pfizer CentreOne
- PharmaCircle
- Pion, Inc.
- Polymer Conversions, Inc.
- PYRAMID Laboratories
- REVOX Sterilization Solutions
- SGW Pharma Marketing
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- UPM Pharmaceuticals, Inc.
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London, United Kingdom

BIO 2017
June 19 - 22
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Controlled Release Society Meeting
July 16-19 Boston, MA

CPhI Worldwide
October 24-26
Frankfurt, Germany

Universe of Prefilled Syringes & Injection Devices Europe
November 7-8
Vienna, Austria

AAPS
November 12-17
San Diego, CA

imparting functionality during drug delivery. For example, in the case of controlled-release matrices, there is a need to improve flow properties while maintaining a robust release profile and adequate tablet properties, explains True L. Rogers, RPh, PhD, Technologies Leader, Dow.

“We also see that pharma companies prefer to work with compendial excipients with a long and proven history in the market,” adds Kevin P. O’Donnell, PhD, Associate Research Scientist, Dow. “To the extent possible, we modify our existing grades within the approved limits thanks to our unique understanding of the product’s physical and chemical properties.”

As an example, Dr. Rogers points to METHOCEL™ DC2 where Dow has been able to achieve step-change improvement in flow without co-processing or blending with other excipients. Further examples for solubility enhancement include the development of AFFINISOL™ HPMCAS High Productivity to increase the solids loading in the spray drying process while providing solubility enhancement, and the development of AFFINISOL™ HPMC HME to provide extrudability to HPMC while enabling both controlled and immediate-release formulations.

“We have demonstrated that HPMCAS formulations are highly sensitive to the acetate and succinate substitution levels and can provide customers with sample sets that will define their specification in the formulation,” says William Porter III, PhD, Associate Research Scientist, Dow. “Similarly, we have a library of METHOCEL CR HPMC materials that can be used by the formulator to proactively determine how sensitive an API formulation is to variations in HPMC attributes such as particle size, hydroxypropyl substitution, and polymer solution viscosity.”

While excipients are known to improve formulations, there are several ways that excipients can lower the cost of the production of medicines, says Dago Caceres, Global Marketing Leader, Dow. “For example, Dow’s METHOCEL DC2 can streamline the production process of modified-release formulations by allowing direct compression and tableting without the cost of wet granulation and drying steps. In addition, it has been demonstrated that METHOCEL DC2 makes the formulation robust not only to performance attributes but also with regards to in-process changes that occur within continuous manufacturing lines.”[3]

Evonik Health Care: Functional Excipients Enhance Formulation Possibilities

In oral drug delivery, there is increasing interest in excipients and new formulation techniques to enhance drug solubility and bioavailability. The industry is adopting more innovative formulation technologies, which appropriately target the improvement of the transcellular and paracellular uptake of both small molecules and biologics. This often requires the use of new types of excipients like permeation enhancers, enzyme inhibitors, and polymers with advanced functionalities, explains Dr. Thomas Riermeier, Vice President, Pharma Polymers & Services, Evonik Health Care.

In parenteral drug delivery, there is a great focus on developing more advanced complex formulations such as liposomes and polymer-based microparticles, allowing for specific drug targeting or extended release.

Established functional excipients like EUDRAGIT® and RESOMER® polymers, for example, used in conventional formulations, have become more prevalent for controlling drug release in advanced formulations.

“EUDRAGIT polymers have pioneered the concept of excipient use for modified drug delivery in the pharmaceutical industry,” says Dr. Riermeier. “They allow for simple solutions to the successful development of products with improved bioavailability and high patient compliance.”

The use of functional excipients that improve drug bioavailability can result in the reduction of the API dose while maintaining efficacy, reducing potentially undesired side effects and possibly dosing frequency, he says. Thus, the proper selection of excipients could improve safety profiles of medicines, decrease API demands, and reduce overall treatment costs.

“Excipients are usually not the primary cost driver for drug products, however, they can play a vital role with respect to the overall therapeutic costs,” says Dr. Riermeier. “A versatile excipient combined with an experienced drug formulator can significantly reduce the development costs of new drug products.”

Versatile excipients can represent significantly lower development costs and regulatory hurdles than the creation of completely new excipients. “These excipients can accelerate or even enable the development of new drug products that otherwise would not be possible,” he says.

For example, Evonik’s newly launched EUDRAGIT FS 100 is a solid version of the existing EUDRAGIT FS 30 D product. This new form allows pharmaceutical companies to use this polymer in new applications like in hot melt extrusion, solvent spray drying, and solvent coatings. “This was impossible to achieve previously when only the aqueous dispersion supply form was available,” he says. “This kind of versatility in an approved excipient allows for new development possibilities with pharmaceutical formulations.”

Pfanstiehl: Quantitative Analysis Ensures a Robust Bioprocess

Excipients are being evaluated not only for their ability to add value in the finished dosage form, but also well upstream to increase yields, prevent aggregation, and ensure consistent product quality. These additional applications require a thorough understanding of the impact that those components can have in those–often not fully optimized or controlled–environments. The result is greater demand for innovative, fit-for-purpose excipients, says Christopher Wilcox, PhD, Vice President, Business Development, Pfanstiehl, Inc.

“End users and biopharma organizations seek out platform-compatible materials that can be utilized upstream, downstream, and in the finished dosage form,” he says. “High-purity carbohydrates, such as Trehalose, are now being employed in this manner, due to their ability to enhance yield, improve protein product quality, prevent aggregation, stabilize a variety of biologics, and increase the overall robustness of the entire bioprocess.”

Quantitative analysis and reporting of key quality attributes, such as reducing sugars, elemental impurities, and endotoxin are crucial for scientists to know to get the most out of Design of Experiments (DoE) and develop robust formulations, he says. “Most end users now demand components that are very low in elemental impurities, endotoxin, and overall impurities, while engaging directly with manufacturers to ensure that the appropriate supply chain transparency and raw material control strategies are well documented.”

One of Pfanstiehl’s clients experienced a sudden shift in product quality of a recently approved biologic (mAb). No immediate root cause could be identified, which prompted the initiation of a detailed investigation of more than 60 components utilized in the bioprocess. “Upon engaging Pfanstiehl, the client was provided with a quantitative characterization assessment of one of the critical raw materials used, including elemental impurities well below what is required by ICH Q3D,” says Dr. Wilcox. “Up to that point, no product quality correlation had been made with

elemental impurities at the very low level identified. The matter was quickly resolved and control strategies implemented to prevent any recurrence. An investigation that may have taken months, was literally resolved in a few days, all because we had generated the quantitative data, had it available to share immediately upon request, and could quickly adapt our control strategies to the client's new found requirement."

Siegfried: Using Excipients to Improve Drug Properties

Siegfried develops drug products (solid/liquid) and uses excipients to improve certain properties of the drug products, such as solubility, bioavailability, and and stability of the API. For example, in liquid drug product formulations, APIs are often poorly soluble in water. Alcohols are common excipients to solubilize the API, as are vegetable oils to dissolve the API or to form emulsions. "With our knowledge, we are able to select the required quality grade of these excipients and we are able to maintain the quality during the manufacturing process to provide a stable drug product," explains Olaf Wegener, Head of Development at Siegfried.

There are a few issues that Dr. Till Röhrich, Head Development Drug Product, Siegfried, says are worth considering with regard to excipients. One is the use for direct compression in solid oral dosage drug products. He says direct compression is a much-appreciated process for manufacturing of solid dosage forms. Additionally, is the effectiveness of excipients to either increase the solubility for low-soluble drugs or to improve their stability (examples are antioxidants and moisture capture excipients).

With regard to liquid drug product specifically, Mr. Wegener says the route of administration, such as intravenous or ophthalmic delivery, as well as the type of formulation (e.g. emulsions or API in buffer solutions), are separate from material consistency and functionality of the excipient. "Keeping this in mind, a key factor to consider for a new development is the source of the excipient, and as well the regulatory acceptance in terms of toxicology," he says.

Excipients derived from natural animal sources tend to raise regulatory safety concerns due to transmissible infectious organisms. "Thus, both the quality and compliance of excipients has become increasingly important to both the choice and manufacturer of the excipient," he explains.

New excipients have unique characteristics, such as improved flow or compressability, but manufacturers should question the price versus the benefit. "Pharmaceutical manufacturers have to consider where possible to save in production to mitigate costs," says Dr. Röhrich. "If this is feasible, then a higher price or use of new excipient may be attractive. Because the costs for new development, process revalidation stability testing, and dossier filing are quite high, the desire for use of new excipients has to be considered/start in early development."

Cost is also an issue to consider regarding co-processed and multi-functional excipients. Dr. Röhrich says these excipients are of interest when there is demonstrated savings in either the handling process or when the process demonstrates significant advantages over a single excipient. "In general, the price of these materials is much greater than the individual components; thus, the benefit must be evaluated for each individual product. Only in a few cases are new excipients better (e.g. process ability, stability) than single excipients."

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