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Excipients Market Growing But Novel Technologies Needed

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Nigel Walker

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- That's Nice

Excipients, once considered as far less important than the active pharmaceutical ingredient (API) in formulated medicines, today are receiving significantly more attention from both manufacturers and regulators. Many excipient technologies are no longer considered as simply inactive ingredients. Their potential to increase efficacy through enhancement of solubility and bioavailability, enable specialized delivery performance (disintegration, controlled/sustained release, etc.) and provide technologies targeting pediatric and geriatric patient populations (taste masking, oral biologic drug delivery) is now recognized. Excipients are today, in fact, seen as crucial to product development and differentiation, particularly for patent extensions and competitive advantage in the generic/biosimilars space, and the possible key to the formulation of many exciting drug candidates that were rejected in the past due to their poor physicochemical and/ or pharmacokinetic properties. There is also greater awareness of the potential of excipients to significantly impact the safety of drug products. Both industry-wide groups and regulators have consequently taken steps to establish processes for ensuring the quality and safety of excipients across the entire excipient supply chain.

Healthy Growth

The global pharmaceutical excipients market is growing at a modest pace. Grandview Research estimates a 6 percent compound annual growth rate (CAGR), with the sector reaching a value in 2020 of $5.22 billion[1]. In addition to the general growth in demand for pharmaceutical products, there are numerous other factors contributing to this healthy rate of expansion. Significant numbers of branded small- and large-molecule drugs are losing patent protection, which is driving originator companies to seek excipient technologies that enable patent extensions and generic/biologic producers to explore excipients that provide differentiation and competitive advantage. On the development side, more than half of small-molecule drug candidates suffer from solubility/bioavailability issues that require the use of excipients designed to address this problem. New co-processing technologies are also affording excipient manufacturers the ability to develop more complex and multifunction products.

There are many types of excipients: lubricants, anti-adherents, fillers/diluents, binders, disintegrants, coating materials, solvents, flavorants and colorants, preservatives, surfactants, thickeners, buffers, emulsifiers, glidants, and more. Many of these materials are polymeric (45% of the global market in 2014), according to Grandview Research[1]. Demand for sugars/carbohydrates will grow the fastest (7.0% CAGR) due to growing demand for geriatric and pediatric formulations that require sweetening agents and disintegrants that are inexpensive yet stable, odorless, and provide longer disintegration times, according to the market research firm. On the other hand, consulting firm Kline & Company expects the overall market for excipients used in oral solid dosage forms (OSDFs) to expand at a rate of 7.4% annually through

2018, with excipients that influence the release profiles of these drugs to experience the greatest growth in demand[2].

Results of the first Nice Insight survey of users and manufacturers of pharmaceutical excipients, which was published in 2015, found similar trends[3]. The five most often-used excipients by drug formulators that responded to the survey (n=412) included coatings (60%), acids (57%), solvents (51%), binders (51%), and emulsifiers (49%). Coatings, binders, and emulsifiers are typically polymeric materials. The former two are used in solid (tablet/capsule) formulations, while the latter is used in liquid and topical formulations.

Interestingly, while most excipient buyer participants indicated that they expected to use each type of excipient at the same level in 2015 as compared to the previous year, there were several categories for which 10% or more of the respondents expected to see large growth in demand: surfactants (15%); solvents (14%); disintegrants, sorbents, lubricants, and flavors (12%); sweeteners and glidants (11%); and anti-adherents, colorants, solubilizers, and thickeners (10%). Notably, many of these excipients are used to enhance the solubility and bioavailability of small-molecule drugs, enable the formulation of biologic actives, which account for an increasing portion of both drugs under development and newly approved treatments, or allow for specialized delivery mechanisms.

The Biologics Challenge

Biopharmaceuticals have different requirements with respect to excipient performance than small-molecule drugs, in particular the need to prevent aggregation and degradation during manufacturing, distribution and storage, both of which can negatively impact immunogenicity and efficacy. Protein engineering can only lead to small gains in stability, and thus excipients are required to provide stabilization against changes in conditions (temperature, pH, ionic strength, shearing, shaking, protein concentration, purity, and pressure); due to the presence of metal ions additives, solvents; and as the result of surface adsorption or morphism. In addition, liquid formulations tend for be more unstable than dried formulations[4].

Excipients that minimize protein aggregation can do so by decreasing the stability of the denatured state or increasing the forces that stabilize the folded state. In some cases they bind directly to the protein. The types of excipients most commonly used in biopharmaceutical formulations include buffers, salts, amino acids, polyols/disaccharides/ polysaccharides, surfactants, and antioxidants, and generally a combination of some or all of these types of compounds are required. Choosing the most appropriate excipients is difficult because often these additives have both positive and negative impacts on the active drug. The challenge is to choose the right combination of excipients that provide the desired stabilization but do not undergo undesired interactions4. The potential physical and chemical interactions of each excipient with the protein and with one another must be considered. Because the structures of different proteins differ significantly, no one has yet developed a universal strategy for the selection of stabilizing excipients, and thus extensive screening is generally required to identify optimum solutions. Preformulation studies designed to identify degradation pathways and the use of design-of-experiment (DOE) approaches can facilitate the process.

Excipients For Extended-Release Parenteral Formulations

It has become common practice in recent years to extend patent protection of small-molecule drugs through the development of sustained-release versions of older drugs. This approach is also used by generic manufacturers as a product differentiation strategy. Not surprisingly, there is significant interest in applying this technology to parenteral formulations. Biodegradable polymers are allowing such longer-term delivery of injectable medicines[5]. Polyesters, and particularly poly(lactic-co-glycolic acid) (PLGA), are the most widely used polymers. Originally used as suture materials, they are well characterized, their degradation mechanism and final end products are well understood with an established safety profile, and their degradation kinetics are predictable. Importantly, their degradation rates can be adjusted by varying the composition of the monomers, the overall molecular weight of the polymers, and their end groups. When

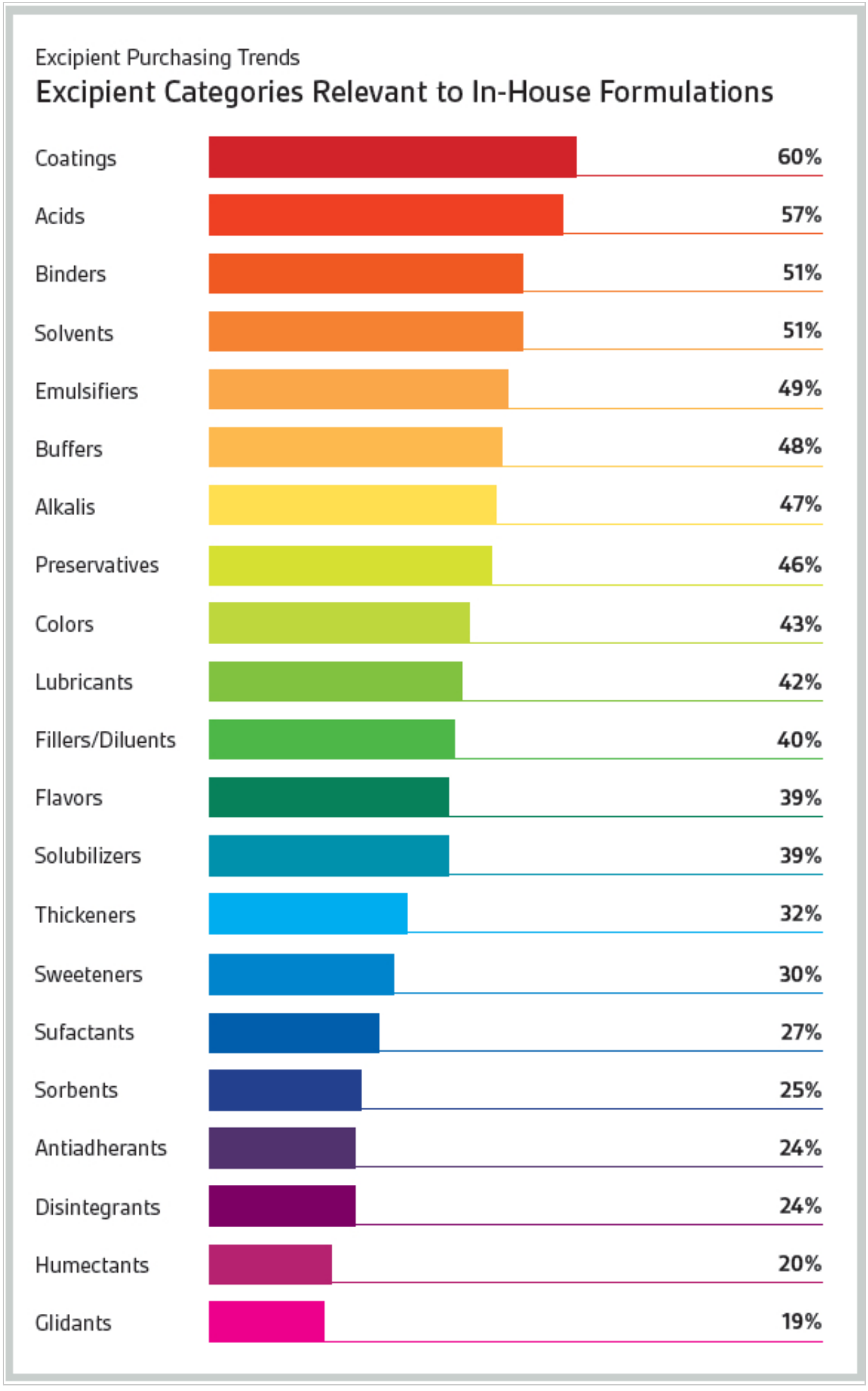
exposed to biological fluids, the polymers swell as water is adsorbed, and then the ester linkages are randomly hydrolyzed, resulting in degradation and release of the drug substance. The final breakdown products are glycolic acid and/or lactic acid, which are naturally occurring, endogenous compounds.

This technology is increasingly being combined with biodegradable medical devices to allow for the incorporation and sustained release of steroids, antibiotics, and/or anti-inflammatory agents around the implant to improve overall performance and reduce negative side effects[5]. There is also interest in combining sustained release technology with targeted drug delivery for long-term treatment with minimization of systemic toxicity.

Recently, Celanese developed foamed ethylene vinyl acetate (EVA) excipients for the controlled release of Class II and IV small-molecule APIs, biologics, growth factors, and stem cells[6]. Conventional EVA copolymers from Celanese have been used in a wide range of drug delivery applications. The foamed excipients have engineered, three-dimensional microcellular microstructures that can be seeded with therapeutic agents and implanted as delivery vehicles for the controlled release of APIs. Most interestingly, the technology may also be useful for the development of oral dosage controlled-release forms for biologic actives as an alternative to parenteral formulations that require injection.

Focus On Sustained/Controlled Release For Small-Molecule Drugs Too

Several new technologies related to the controlled release of smallmolecule drugs have been introduced in the last two years. Lubrizol LifeScience Polymers (LSP) introduced its Pathway pharmaceuticalgrade thermoplastic polyurethane (TPU) excipients for controlled release drug delivery systems and other applications[7]. Lubrizol has been offering medical-grade TPUs for many years, but now is producing the materials under GMP conditions, allowing their use as excipients.



Meanwhile, in 2013 the Dow-Colorcon Controlled Release Alliance (CR Alliance), developed METHOCEL DC2, a next-

generation polymeric hydroxypropyl methylcellulose (HPMC) excipient specifically designed to improve the flow properties of powder blends, facilitating roller compaction and direct compression of matrix tablets and allowing drug manufacturers to switch to these dry production techniques that involve fewer processing steps, reduced waste production and development times, and lower costs, according to the company[8]. In late October 2015, EMD Millipore introduced Parteck SRP 80, a new polyvinyl alcohol (PVA)-based functional excipient specifically designed for oral sustained-release formulations, particularly direct-compression processes[9]. Key advantages of the product, according to the company, are its reliable performance profile and ability to facilitate the development of robust and cost-efficient manufacturing processes.

Controlled release products were also developed in 2014. DuPont Nutrition & Health launched Alginate Pharma Grade, the first in a new series of alginate-based excipients developed to ensure that the APIs in tablet formulations are released only after being delivered to their biological targets[10]. MannKind Corporation also received approval from FDA in July 2014 for AFREZZA, a non-injectable (orally inhaled) mealtime insulin therapy for improving glycemic control in adult patients with diabetes mellitus. A novel excipient–fumaryl diketopiperazine (FDKP)–is the key to the effectiveness of the inhaled form of insulin[11]. The FDKP is inert and serves as a particle matrix (crystalline or amorphous), carrying the API and dissolving at the prevailing physiological pH in the lungs, where it is absorbed into the systemic circulation. MannKind is also exploring the potential application of this technology for the pulmonary delivery of other drug substances.

Finally, the company Disruptive Materials is commercializing a waterfree, disordered, amorphous magnesium carbonate first synthesized by researchers at Uppsala University[12]. The material, which they refer to as Upsalite, is extremely porous with a very high surface area and has been shown to enable the controlled release of APIs, including ibuprofen[13,14]. It is thought that trapping of the drug molecules in the narrow pores of the material prevents them from adopting a poorly soluble, crystalline form.

What It Means To Be A Novel Excipient

Despite the fact that novel excipients have the potential to improve patient compliance by enabling the development of more patientfriendly dosage forms, increase safety and efficacy, and enable the use of novel drug substances that cannot be appropriately formulated using existing excipient technologies, very few truly novel excipients have been developed in the last couple of decades.

As defined by the FDA, novel excipients include[15]:

- New co-processed excipients made from two or more previously approved excipients (typically manufactured using a physical process such as spray drying or melt extrusion);
- Existing excipients used at higher levels for previously approved routes of administration or for new routes of administration;
- New chemically modified grades of existing excipients (minor changes to existing excipients); and
- New chemical entity excipients (NCEs).

These novel excipients only get reviewed in the US if they are included in a new drug application (NDA) or new abbreviated drug application (ANDA), and that requires that a drug manufacturer be willing to accept the risks associated with a new excipient. The excipient is only approved if the drug is approved, and only for that level of use and route of administration. If the drug fails, even if the excipient was not at fault, the clinical trial data cannot be used. It takes years to develop and adequately characterize and test novel excipients, and then additional years for them to go through the drug development process, often leaving minimal time under patent protection. As a result, there is little

incentive for the development of novel excipients.

There are efforts underway to tackle this issue, however. At the July 15, 2015 FDA public meeting the reauthorization of the Prescription Drug User Fee Act (2002) (PDUFA), International Pharmaceutical Excipients Council (IPEC)-Americas representative David R. Schoneker, Director of Global Regulatory Affairs for Colorcon and IPEC-Americas Past Chairman and current Vice-Chair for User and Maker Relations, commented on the review and qualification of novel excipients. IPECAmericas followed up in August 2015 with submission to the FDA docket on PDUFA Re-authorization with detailed written comments that describe the need for an independent FDA safety review/ qualification process for novel excipients outside of the normal drug approval process[16].

The organization has proposed to FDA that it adopt a new regulatory review or qualification process for novel excipients that provides for stand-alone (independent) review and qualification of excipients by the agency. The intent would be for this new regulatory review or qualification to help mitigate the uncertainty associated with novel excipient use and involve preliminary safety and qualification assessments independent of the drug but based on safety data that exists to support the intended route(s) of administration and intended use level(s). IPEC-Americas has also offered to collaborate with FDA to define what the Agency would need to review in such a process and recognizes that a unique type of user fee system would also be needed to fund FDA's activities in this area. IPEC-Americas is also working with the IQ Consortium to explore the development of joint best practices for preclinical safety (testing and specification) requirements and the creation of a process for designing a well-defined, pre-clinical data package for novel excipients.

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If you want to learn more about Nice Insight, please contact Nigel Walker by sending an email to nigel@thatsnice.com

Survey Methodology: The Nice Insight Excipient is deployed to R&D and Formulation personnel and excipient buyers in the purchasing function. The 2015 report includes responses from 412 participants. The survey is comprised of 60+ questions and randomly presents ~25 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~45 excipient manufacturers and distributors serving the pharmaceutical industry. Five levels of awareness, from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six key influencers to purchase: Quality Assurance, Financial Stability, Regulatory Track Record, Affordability, Product Specifications and Reliability of Supply. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on supplier selection criteria and formulation requirements as they relate to excipients.

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