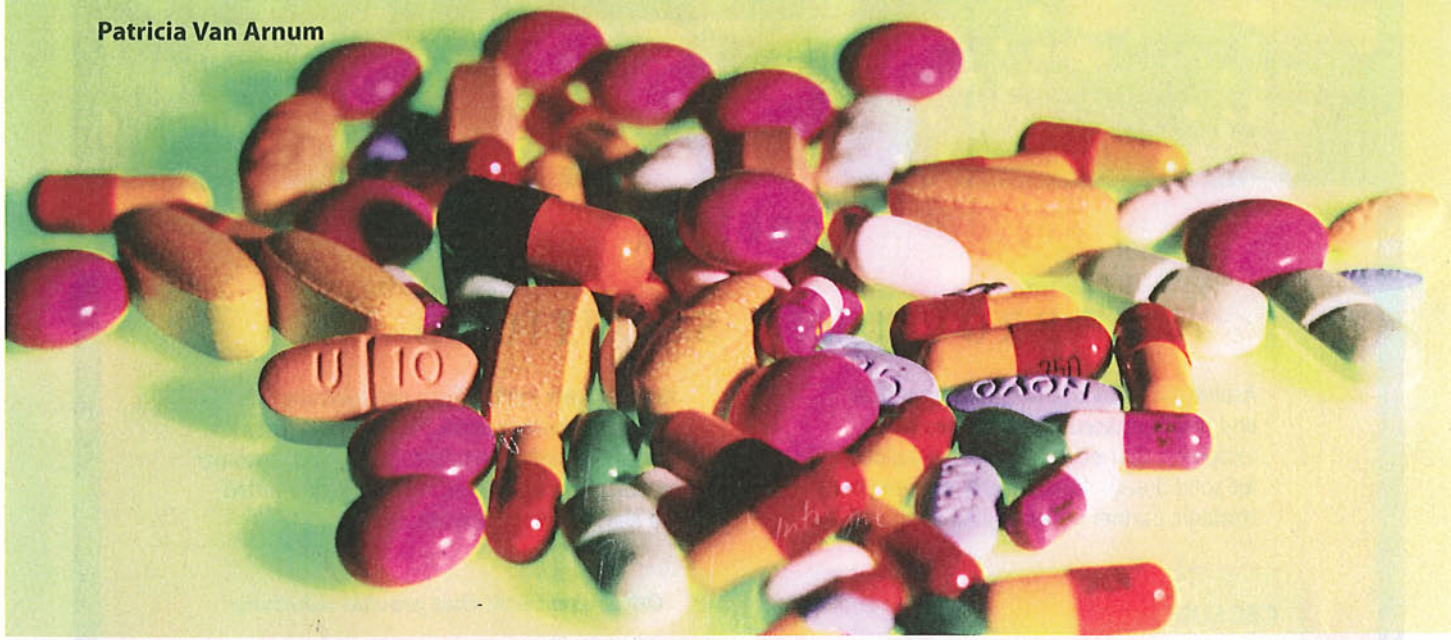
Tracking Excipients

Patricia Van Arnum



A review of recent product innovations, policy developments, and growth prospects in the excipients market.

Although constituting a relatively small value of the cost of manufacturing a drug, excipients play a vital role in the formulation of pharmaceutical products. Recent product innovations include applications in orally disintegrating tablets and controlled-release formulations. Broader issues affecting the excipient market include supply-chain integrity, quality by design (QbD), and longer term, the application of nanotechnology in formulations. As these issues unfold, moderate growth is expected for the global excipients market.

Patricia Van Arnum
is a senior editor at *Pharmaceutical Technology*, 485 Route One South, Bldg F, First Floor, Iselin, NJ 08830 tel. 732.346.3072, pvanarnum@advanstar.com.

Innovation in excipients

Although introducing new excipients may be a slow and costly process, the excipient market is not without innovation. Excipient makers use a strategy of developing excipient blends to achieve multifunctionality and introduce new grades of existing excipients to enhance performance for specified applications. Excipients for orally disintegrating tablets, controlled-release formulations, immediate-release applications, and topical formulations are recent examples.

Mallinckrodt Baker (Phillipsburg, NJ), a business unit of Covidien (St. Louis, MO) launched PanExcea MC200 for oral disintegrating tablet applications in November 2008. The excipient combines two ingredients that interact at a subparticle level to facilitate rapid disintegration and dispersion of a tablet in the oral cavity, increase active pharmaceutical ingredient (API) loading capacity, and enhance taste-masking. The excipient may be used with standard manufacturing and packaging equipment, which the company says can potentially eliminate licensing orally disintegrating technology and new equipment investment. Mallinckrodt also launched a performance excipient for immediate release-applications in 2008. It is based on microcrystalline cellulose, hydroxypropyl methylcellulose, and crospovidone, according to the release and company information.

In 2008, Mallinckrodt Baker teamed with the contract research organization Rubicon Research (Mumbai) in a licensing and commercialization agreement to expand its performance excipient platform. The two companies plan to develop and launch additional products under Mallinckrodt Baker's PanExcea line of performance excipients through 2009, according to an August 2008 joint press release. Under the agreement, Rubicon is providing technology development and formulation expertise.

Eastman Chemical (Kingsport, TN) added CA-3203 to its line of cellulose ester excipients in 2008. The

IMAGE: EMANUELE TARONI/GETTY IMAGES

product can be used in controlled-release applications involving membrane release or matrix release.

International Specialty Products (Wayne, NJ) expanded its Advantia line of coating systems with the addition of Advantia Preferred HS coatings in 2008. The new coatings are based on combinations of polymers and plasticizers for immediate-release film coating of oral solid dosage forms for pharmaceutical products and dietary supplements. The coating can be applied in up to 25% high-solid suspension, according to the company.

The product improves film adhesion and achieves good film strength and flexibility. The issue of film adhesion arises in tablet cores with ingredients that may make tablet surfaces either more hydrophobic or less porous, which in turn can comprise film adhesion. The company says that recent studies show that products do not slow tablet disintegration and dissolution, which are critical properties for film coatings applied to immediate-release dosage forms.

NuSil Technology (Carpinteria, CA) launched a new water-resistant dimethicone pharmaceutical excipient, MED-323, a trimethyl end-blocked polydimethylsiloxane, for pharmaceuticals and cosmetics in May 2008. The product offers water repellency and may be used as an excipient in topical pharmaceutical applications.

NuSil Technology also launched a line of silicone materials and services for drug delivery and combination medical device products in January 2009. The company provides silicone fluids, elastomers, and gels for drug delivery and medical devices, including matrix and reservoir-type delivery devices for transdermal, transmucousal, and long- and short-term implanted medical devices.

Excipients play an important role in orally disintegrating tablets.

Analytical tools to support formulation development are also an important part of innovation. In March 2009, Paraytec (York, England) introduced ActiPix Dissolution Imager, a quantitative ultraviolet (UV) area imaging system to provide real-time imaging of pharmaceutical tablet dissolution. The company says that the product offers an alternative to using terahertz spectroscopic imaging and magnetic resonance imaging to secure data needed to evaluate drug-release processes. The instrument consists of a specially designed tablet holder that is placed inside the UV imaging system to enable

Excipients need to be considered in quality by design.

real-time recording and review of data. When liquid flows over the surface of the formulation, the release of the active ingredient can be quantitatively monitored directly at the tablet surface. Paraytec is a scientific-instrument company that was formed as a spinout from the chemistry department at the University of York.

Shaping the excipient landscape

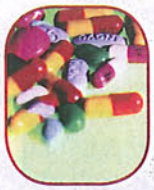
Increased globalization and strategies for securing the supply chain are important issues for excipient producers. The International Pharmaceutical Excipients Council (IPEC) expanded into China in July 2008 with the formation of IPEC–China. IPEC–China consists of manufacturers, distributors, and users of excipients. IPEC–China expects to work with China's State Food and Drug Administration in establishing standards for excipients, according to an IPEC–China 2008 press release.

IPEC is also considering a proposal to create a multiregional body, the IPEC Federation, which will provide advocacy and promote quality in excipients globally, according to recent information from IPEC Europe. The vision of the IPEC Federation would be to promote quality, safety, and functionality of excipients and to ensure that new excipients introduced into the market meet global standards. The federation would also seek to harmonize drug approval, technical, and pharmacopoeial standards and ensure that safe and effective dosage forms are circulated in the global supply chain. To meet these goals, the proposed federation would develop, implement, and promote voluntary, harmonized guidance and other programs for the pharmaceutical industry to ensure that excipients used in finished drug products meet appropriate standards for quality, safety, and functionality throughout the manufacturing and distribution process. The federation would collaborate with regulatory authorities in adopting scientifically suitable, risk-based, and global regulatory and compendial standards for excipients (1).

QbD will continue to play an important role in excipient usage. The goal of QbD is to improve process understanding, which includes the functional effects that excipients have on the drug-manufacturing process as well as understanding the process variability that may arise with an excipient in a formulation (2). As part of its ongoing Excipient Technical Applications Initiative, IPEC–Americas formed a working committee, the Quality by Design Product Development Committee, to consider issues relating to excipients in QbD. Some issues relating to excipients and QbD include the following:

- The proper selection and use of excipient performance tests
- The role of pharmacopeial monographs in meeting changing requirements
- Developing robust formulations according to QbD and process analytical technology
- Reducing barriers to excipient user–supplier collaboration to build on the shared knowledge base.

Nanotechnology is also an emerging issue in formulation development. In March 2009, the US Food and Drug Administration launched an initiative with the Alliance for NanoHealth (ANH). ANH and FDA cosponsored a scientific workshop, the FDA-ANH Nanotechnology Initiative Scientific Workshop, to obtain feedback from stakeholders in industry, the federal government, and academia to identify key scientific and translational challenges in nanoengineered medical product development. A goal of the workshop was to develop and publish a short list of existing translational gaps and the key elements needed to bridge these gaps, according to ANH. Member institutions of ANH include the Baylor College of Medicine, the University of Texas M.D. Anderson Cancer Center, Rice University, the University of Houston, the University of Texas Health Science Center at Houston, Texas A&M Health Science Center, University of Texas Medical Branch, and the Methodist Hospital Research Institute.



Annual growth for the global excipients market is nearly 4%.

Market growth and segments

As these issues evolve, moderate growth is projected for the global excipient market, which was valued at $3.5 billion in 2006, according to BCC Research (3, 4). The market is expected to increase at a compound annual growth rate (CAGR) of 3.8% through 2011, when it will reach $4.3 billion. The global excipients market is broken down into three major segments: organic chemicals, inorganic chemicals, and *United States Pharmacopeia* (*USP*) water.

Carbohydrates represent the largest share of global organic excipients on a value basis, followed by petrochemicals, oleochemicals, and proteins. Carbohydrates account for 39%, or $1.2 billion, of the global organic excipient market, based on 2006 data. Petrochemicals account for 30.3%, or $941 million, and oleochemicals 28.3%, or $880 million. Proteins represent a small percentage, only 2.2%, or $68 million, according to BCC Research (3, 4). Carbohydrates are the leading organic excipients because of their filling and taste-masking properties, according to BCC. Cellulosics hold the top spot in the carbohydrates segment on

ExcipientFest Americas

ExcipientFest Americas, which will be held April 22–23 in San Juan, Puerto Rico, will examine technical considerations in excipient selection and formulation development as well as sourcing and supply-chain issues for excipients (see www.excipientfest.com for further details). The Drug, Chemical, and Associated Technologies Association (DCAT) is the operator of ExcipientFest Americas.

Among the scheduled speakers are Janeen Skutnik, chair of the International Pharmaceutical Excipients Council (IPEC) of the Americas and director of quality and regulatory policy and global regulatory CMC at Pfizer. She will discuss the present and future activities of IPEC, including IPEC's guidance for excipient qualification and quality guidance, the role of IPEC–China, developments in Brazil, and the role of excipients in quality-by-design (QbD) initiatives.

Technical workshops will address strategies for improving the solubility of poorly soluble drugs, enhancing understanding of drug-excipient interactions, film coatings, and the role and functionality of coprocessed excipients.

Educational sessions will also address supply-chain and regulatory considerations for excipients. Topics include an update and review of the US Food and Drug Administration's guidelines for scale-up and postapproval change (SUPAC) and the role of QbD in SUPAC, supplier relationship management, strategies for business and operational excellence in materials supply, and how to navigate customs and import challenges.

a value basis. Sugars comprise the bulk of the market volume for carbohydrates. Micronized cellulose phthalate and hydroxypropyl cellulose compositions that have been converted to gels for transmucosal delivery systems are driving growth for cellulosics. BCC projects increased demand for compendial sugars for biopharmaceuticals and growth for artificial sweeteners, particularly in thin-film strips (3, 4).

Glycols and povidones are the leading petrochemical-based excipients. In glycols, the trend is toward more refined grades that can increase the stability of APIs. For povidones, an important trend is their use in very small tablets with rapid bioavailability, according to BCC (3, 4).

Inorganic chemicals used as pharmaceutical excipients include calcium salts, halites, metal oxides, and silicates. Calcium salts hold 73.2%, or $266 million, of the global inorganic excipients market, according to BCC.

Halites and metal oxides each comprise 8.5%, or $31 million, of the global market for inorganic excipients. Demand for sodium chloride as an osmotic agent in injections and sustained-release tablets provides halites at a CAGR greater than that of other inorganic excipients, according to BCC. The established use of titanium dioxide as a colorant is driving sales growth of metal oxides (3, 4).

Silicates account for 4.8%, or $17 million, of the global market for inorganic excipients. Small loading levels and the maturity of the glidant segment keep the market value for silicates low. Other inorganic excipients account for 5%, or $18 million, according to BCC (3, 4).

BCC Research classifies *USP* water as a general chemical in its analysis of the global excipient market. *USP* water includes water for injection (WFI) and purified water. Water must comply with *USP* standards for chemical purity and microbial content (i.e., < 0.25 ppm of endotoxins). WFI accounts for 76.5% of the *USP* water market, or $52 million, and purified water 23.5%, or $16 million. Pharmaceutical grades of water used in drug-process applications (i.e., enema and medical-irrigating fluids) and other than those used to formulate excipients are excluded from the analysis. Also excluded is water used in the following applications: a pharmaceutical manufacturing process aid (i.e., wet granulation); a solvent for aqueous-based, film-coating materials; a cleaning and rinsing material for containers and closures; a fermentation or cell-culture media ingredient; an extraction and purification solvent; a chemical-reaction solvent; or any other purpose except in a formulated drug-dosage form (3, 4).

References

1 IPEC–Europe, "Excipient Insights," Mar. 2009, www.ipec-europe.org, accessed Mar. 16, 2009.
2. IPEC–Americas, "IPEC Americas News," Dec. 2008, www.ipec-americas.org, accessed Mar. 16, 2009.
3. P. Van Arnum, "Measuring Excipient-Market Growth," *Pharm. Technol.* **32** (4), 56–62.
4. "Excipients in Pharmaceuticals," Report No. PHM010E, BCC Research (Norwalk, CT, 2006). **PT**