

Size Matters: Great Things Come in Tiny Packages

By: Dan Stendahl

Dan Stendahl reviews the development of microencapsulation as a drug delivery solution

INTRODUCTION

If less truly is more, then Mies van der Rohe and Barry Green would both be proud. Mies van der Rohe is widely credited for coining the phrase he exemplified in his architecture, while Barry Green first discovered microencapsulation when working for the National Cash Register Company. Microencapsulation technology is widely gaining acceptance in agrochemicals, consumer care items, textiles, and adhesives and has been used in copy paper and elsewhere for decades. The act of encapsulating tiny active particles, generally from 1 to 1000 microns in diameter, from ambient conditions serves to protect them until such time when their active properties are needed. It economizes pesticide use, extends the effectiveness of deodorant, makes clothing more resistant to bacteria, and enables multiple copies without carbon paper.

Like other drug delivery mechanisms, microencapsulation also serves to improve dosage efficacy while minimizing potential side effects. The encapsulation of active pharmaceutical ingredients (APIs) enables drug delivery and pharmaceutical companies to engineer release profiles most appropriate for a given therapeutic. Examples include fast-dissolve formulas, extended release, targeted release, and delayed release. Microencapsulation technologies also enable taste-masking for bitter compounds in chewable tablets as well as oral administration without water. It has been estimated that some 65% of pharmaceutical products with a form of extended release use microencapsulation to achieve the desired effect.

Microencapsulation can be achieved through a number of processes, but generally traps an API within a reservoir or matrix. The most common techniques include spray drying, Wurster fluid-bed coating, pan coating, coacervation, liposomes, emulsion evaporation, and spinning disk. The process is carried out by a variety of drug delivery companies, contract research organizations, and large pharmaceutical companies on behalf of themselves or external clientele. Some of the larger microencapsulation specialists for drug delivery in the United States include A.P. Pharma, Cardinal Health's IPC division, Cima Labs, The Coating Place, Inc., Eurand, KV Pharmaceutical's Particle Dynamics division, Particle and Coatings Technologies, Inc., and Southern Research Institute.

While microencapsulation is already a widely accepted method of drug delivery, the aforementioned and other companies must continue to innovate in order to accommodate more sophisticated molecules. As biological assays are further refined and physiological responses are better understood, new chemical entities (NCEs) are becoming increasingly potent. Many of the new pharmaceutical compounds are extremely insoluble, requiring solubilization technologies to enhance bioavailability.

Particle size is also a deciding factor when selecting the appropriate microencapsulation technology for a given delivery route. For example, most injectable particles are ideally 20 to 80 microns in diameter. Smaller particle sizes increase the surface area-to-volume ratio, making them more readily soluble when encapsulated in smaller particle sizes, and thus more easily assimilated by the human body.

Frost & Sullivan has identified 37 microencapsulated prescription drugs marketed in the United States, of which over half are delivered orally. Injectable therapeutics account for more than one-third of the total, with the remaining balance distributed among dermal and ocular applications.

ORAL DELIVERY IS TRIED & TRUE

Microencapsulated APIs in tablets often achieve the desired release profile in combination with a solid matrix or enteric coating that slows the exposure of API to the digestive tract. Tableting technologies are proven, generally stable, and inexpensive for manufacturers.

Tableting technologies are proven, generally stable, and inexpensive for manufacturers, as well as compact, portable, and easy to self-administer for consumers. Furthermore, the intestinal epithelium has a total surface area of approximately 200 sq meters, giving the API ample surface area through which to diffuse. Orally dosed microencapsulation is becoming more commoditized than injectable technologies, and as such can usually be produced in batches of greater volume, but commands a lower price. Still, the convenience of tablets and patient aversion to injection and other invasive procedures usually make oral delivery the delivery method of choice when possible.

A fine example of an orally administered microencapsulated drug is Cipro XR. Bayer submitted a New Drug Application (NDA) in October 2002 to market Cipro XR (extended release) as a once-daily tablet to treat urinary tract infections (UTIs). The new 24-hour formulation uses a bi-layer matrix of active ingredients. In addition, Bayer jointly developed a once-daily form of Cipro-OD with Ranbaxy Laboratories of India. Because the drug was scheduled to lose patent protection in December 2003, Cipro XR's upgraded performance not only extends the product life, but also provides Bayer with additional exclusivity for the same molecule.

EMERGENCE OF BIOLOGICS PRESENTS ADDITIONAL OPPORTUNITIES FOR INJECTABLES

Advances in injectable drug delivery have made for smarter molecules that can stay in the bloodstream longer with fewer side effects. Microencapsulation allows for less-frequent injections, longer-lasting half-lives of drugs, more sophisticated site targeting, and reduced toxicity.

The harsh conditions in the stomach denature most peptides and proteins, rendering some conventional oral delivery routes useless for biologics. Consequently, they must be injected, and in order to achieve reasonable patient compliance, they require some sort of depot or extended release, which can already be done with existing polymeric encapsulation techniques.

Lupron Depot was the third depot approved to use the polylactide (PLA) polymer for extended-release action in 1989, and the first to be marketed in the US. Lupron Depot is approved for 1-, 3-, and 4-month dosages. Southern Research Institute was the first to develop the technology for drug delivery after working with the polymer for resorbable sutures for American Cyanamid. Lupron Depot is used to treat prostate cancer, endometriosis, and precocious puberty. The added convenience of the 4-month dosage enables TAP Pharmaceuticals to charge an additional \$100 premium over what four single-month dosages would cost.

DERMAL & OTHER ROUTES REMAIN IN THE MORE DISTANT FUTURE

Dwarfed by oral and injection delivery routes, nearly all dermal, ophthalmic, and inhalation therapeutics with microencapsulation technologies remain in clinical trials. Skin thickness and blood flow in the skin do vary with age, sex, and other characteristics. Yet for dermal applications, the skin is usually a difficult barrier for pharmaceutical molecules to penetrate, particularly those with high molecular weights. Even among those drugs in small enough particles to pass through the skin, permeation rates pose another potential obstacle to microencapsulated transdermal drug delivery. Another general detraction from dermal and ocular application is the potential for rashes or other unsightly physical responses to treatment.

A number of companies are involved in pulmonary drug delivery, particularly for inhalable insulin. The concept of sustained release in the lungs is particularly tricky due to challenges associated with cilia and particle residence time considerations when excipients are chronically deposited in the lungs over extended periods. Furthermore, microencapsulation is not always required for particle atomization.

Ortho Neutrogena's Retin-A Micro, which is prescribed to treat severe acne, is an example of a microencapsulated dermal drug. Retin-A Micro uses the Microsponge technology developed by A.P. Pharma to help extend the release profile of tretinoin and reduce irritation to the skin.

OVERCOMING PHYSIOLOGICAL BARRIERS ERECTS COMPETITIVE ONES

Beyond improved performance, microencapsulation offers strategic advantages in the delivery of therapeutic molecules. Performance advantages for an NCE may lead to the displacement of less-sophisticated incumbents in the market. For existing APIs, re-engineering with microencapsulation can generate new proprietary variations of a drug creating a platform for another NDA, and additional patent protection with which to fend off generic competition. Conversely, microencapsulation can provide a cost-effective method of value addition and product differentiation in commoditized generic markets in which compounds are no longer protected by patent.

These advantages on both sides of patent expiration are leading both large pharmaceutical companies and smaller generic competitors to pay more attention to microencapsulation, particularly with the number of blockbusters scheduled to lose patent protection over the course of the decade. While microencapsulation is not the only drug delivery solution, it has to be among the first technologies considered by companies in search of the next little thing.

These topics and other leading developments relating to the microencapsulation of drugs are described in the report: *Developments in Pharmaceutical Microencapsulation in the United States*, published by Frost & Sullivan. Please visit www.frost.com for more information.

BIOGRAPHY

Mr. Dan Stendahl is the Senior Industry Analyst, Chemical & Materials for Frost & Sullivan. Since joining Frost & Sullivan in 2000, Mr. Stendahl has researched a variety of Chemical industries in North and Latin America, as well as Energy and Environmental Equipment markets. He has played a significant role in consulting work for these industries throughout the Americas, specifically in the Chemicals arena. Mr. Stendahl has been quoted in *Coatings World*, the *Toronto Star*, *Inpra*, *Platts*, and a variety of industry portals for his knowledge of chemical markets.