

Nanocapsules for controlled drug delivery

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Researchers in Germany have developed a novel microencapsulation technology that could have wide-ranging applications in drug delivery, from drug targeting to controlled release. The group, at the Max-Planck Institute of Colloids and Interfaces (Potsdam, Germany), believe it is more versatile than previous technologies because it separates the mechanism of storage from that of release control. It is being commercialized by Capsulation NanoScience AG, a start-up company based in Golm, Germany.

Encapsulation is an attractive delivery option for a variety of drugs. For example, it can reduce systemic toxicity, protect vulnerable molecules from degradation in the digestive tract, provide controlled-release properties or mask an unpleasant taste. Encasing drug particles in solid shells is a recognized method of improving their pharmacokinetic or toxicity profiles, but problems with dispersity, uneven shell coverage and core solidification are common. Liposomes have been used but their applications are limited by their instability and poor permeability to polar molecules¹. Other approaches include microemulsions, microgels, polymer micelles, microspheres and colloid dispersions, but each technique has to be developed individually for every class of compound, which is costly and time-consuming.

Manipulating capsule properties

The Max-Planck group's capsules are made from polyelectrolyte multilayers (PEM) and produced using a patented process called layer-by-layer deposition¹. The building blocks are naturally occurring charged polymers, such as pectins,

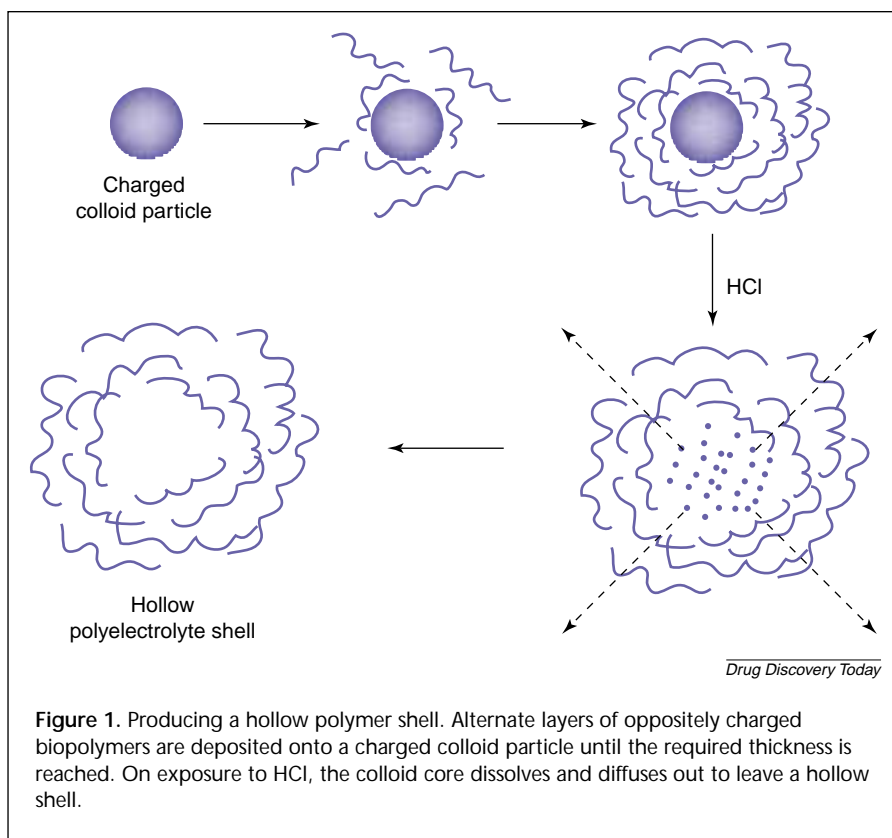


Figure 1. Producing a hollow polymer shell. Alternate layers of oppositely charged biopolymers are deposited onto a charged colloid particle until the required thickness is reached. On exposure to HCl, the colloid core dissolves and diffuses out to leave a hollow shell.

gelatins, polyglutamic acid, chitosan and hyaluronic acid. These are adsorbed around the drug particle in alternating layers of oppositely charged material. The supramolecular structure is held together electrostatically through the formation of complexes between the polycations and polyanions. The resulting capsules have a wall thickness of 10–40 nm and range from ~20 nm to 20 mm in diameter, with the exact size controlled via the production process. Their physical, chemical and pharmacokinetic properties can be manipulated as required by varying the polymers used and incorporating other materials into the layer structure, including lipids,

nanoparticles and biological molecules, such as ligands or receptors. Drug particles can be either carried in the lumen of the capsule or incorporated into the wall layers.

'We have fabricated capsules which include magnetic, photochemical, fluorescent dye, enzymatic and ligand properties in one structure,' says Capsulation NanoScience's Andreas Voigt. 'They can be as complex as we want in the radial direction. Antibodies, peptides, oligonucleotides, enzymes, PEGs and others can be used as ligands, and functional groups like amino or hydroxyl groups permit established surface chemical modifications.' Their fate in the body can

also be controlled. 'We have observed that the destruction of biocompatible capsules by enzymes can be varied from nearly indestructible to rapidly destroyed,' Voigt continues. 'It depends on the components used and the medium conditions, like pH, salt, temperature and light.'

If the properties of the drug make it impossible to encapsulate directly, colloidal particles or even cells can be used as templates² (Fig. 1). Once the polyelectrolyte shell has been constructed, the core template is dissolved away to leave a hollow structure. This can be reversibly opened, for example, by a change in pH, enabling even large drug molecules to enter. Alternatively, the drug can be precipitated in by generating nucleation centres in the capsule lumen.

Controlled release

Controlled-release delivery is likely to be an important application. The PEM capsules are semi-permeable and the wide range of possible encapsulation materials gives plentiful scope for adjusting permeability properties. Researchers at the Max-Planck Institute created simple ibuprofen PEM microcapsules using polysaccharide layers as the coating³. Ibuprofen has low solubility in water. Drug release was studied *in vitro* in simulated gastric (pH 1.4) and intestinal

(pH 7.4) fluids. The ibuprofen crystals dissolved and the drug diffused out of the intact capsule. The rate of release was found to depend on the size of the crystal, the thickness of the capsule wall and the solubility of the drug in the given medium. There was no rapid initial burst of drug release or incomplete release of the drug dose from the carrier, both of which are problems that are usually associated with the use of micro-carriers.

Future prospects

Voigt is optimistic about the versatility of PEM capsules. 'We have found that all the limitations we thought would exist have vanished after a few months' work,' he says. 'I don't see any limitation to the type of molecules we can encapsulate.' However, the technology has not yet been tested *in vivo*. Capsulation NanoScience hopes to start animal studies with an encapsulated drug in early 2002. Toxicity is not expected to be a problem because all the polymers used will be taken from the generally recognized as safe (GRAS) list.

'I am confident that we will begin to see several applications of the layer-by-layer coating technology over the next five years, including drug delivery,' says John Lally, Head of Polymers and Interfaces at Ciba Vision Corporation

(Duluth, GA, USA). 'Its main advantage is the ease of fabrication and the ability to incorporate a wide range of entities. However, more work is needed in defining the toxicity profile of the nanocapsules, especially to determine their fate and distribution in the body through animal studies. In addition, some model drugs may need to be studied to demonstrate a tangible benefit for drug delivery applications. Depending on the route of administration, the stability of the nanocapsule wall could become an issue'.

The direction of future work will depend on client requirements: Capsulation NanoScience hopes to attract interest from companies wishing to formulate a range of new and existing drugs. The technology is also being developed for use in diagnostics, cosmetics and plant protection products.

References

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Budding new HIV therapies?

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The first insights into the molecular mechanism underlying the process of viral budding in HIV-infected cells are suggesting a whole new range of drug targets that could prove useful in the suppression of AIDS in HIV-positive patients. Wesley Sundquist's group at the

University of Utah School of Medicine (Salt Lake City, UT, USA), working in conjunction with collaborators at Myriad Genetics (Salt Lake City, UT, USA), have recently revealed that HIV-1 uses cellular machinery to bud from infected cells and the protein Tsg101 is an essential

requirement of this process. Blocking Tsg101 could, therefore, prevent HIV-1 budding.

The life cycle of HIV-1

The life cycle of HIV infection is known to consist of six major events: attachment