Using green chemistry to deliver cutting-edge drugs

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Green chemistry is being employed to develop revolutionary drug delivery methods that are more effective and less toxic — and could benefit millions of patients.

Chemists at The University of Nottingham are developing new methods for coating drugs in plastics, using methods that do not damage the latest generation of delicate 'biopharmaceutical' drugs which are at the cutting edge of modern medical treatment.

Conventional methods of coating drugs can use high temperatures and harsh solvents — damaging the active components of biopharmaceuticals before they have even reached the patient. But using green chemistry techniques pioneered at Nottingham, the bioactive elements of the drug remain completely effective, so the patient receives the maximum benefit of the therapy. The plastic is designed to release the drug over a controlled period of time; minimising the number of injections a patient will need, and maximising the effect of the drug.

The principles of green chemistry herald a radical new approach that is 'benign by design' — both in terms of the process itself, its impact on patients and on the environment. Green chemistry promises to make the chemical industry cleaner and safer, while producing better, purer products in the process.

In a presentation at the British Association for the Advancement of Science Conference in York on September 12, Professor Steve Howdle

outlined the green chemistry processes being pioneered at The University of Nottingham, particularly the use of supercritical fluids to replace conventional solvents such as benzene and chloroform.

Professor Howdle's research focuses on exploiting the unique properties of supercritical carbon dioxide (CO2). A supercritical fluid is a solvent, with physical properties between those of a gas and a liquid. At near-room temperature and under modest pressure, supercritical carbon dioxide blurs the boundaries between liquid and gaseous states.

The process can be used to make polymer drug coatings, using biodegradable plastics, just like those used in dissolvable surgical stitches. The polymer is used to encapsulate the drug before it is injected into the body.

Conventional chemical processes often use high temperatures or volatile, and potentially toxic, solvents such as chloroform, benzene, and other volatile organic compounds (VOCs). Solvent residues may remain in the product after manufacture and these can be toxic to the patient and to the environment — requiring special handling and recycling measures to prevent them from escaping into the atmosphere.

They can also cause degradation of the drug. Many bioactive drug compounds are adversely affected by high temperatures and conventional solvents, which can destroy up to 50 per cent of the drug molecules intended to help the patient.

But the clean green chemistry techniques being developed at Nottingham aim to remove these conventional solvents from the process altogether. Because supercritical fluids can be used to support solvent-free chemical processes, creating new techniques that would be difficult or impossible to achieve in normal solvents or by conventional processing.

Professor Howdle's research has demonstrated that biodegradable polymers can be plasticised at near room temperatures using supercritical CO2.

The low temperature means delicate bioactive components, such as growth factors or proteins, can be mixed into the plasticised polymer without any loss of activity.

The process overcomes a major obstacle to the development of new drug delivery devices because it means that patients will be able to receive biopharmaceuticals which do not survive conventional chemical processing because they are either solvent or sensitive to heat.

Professor Howdle said: "Many very potent new drugs based on proteins are being discovered all the time. But a major problem the pharmaceutical industry faces is that they have to be wrapped up in plastic to be delivered to the patient, so that there is controlled release of the drug over time.

"Many of these new proteins are fragile and are damaged by high temperatures and harsh solvents used in conventional processes. Our process works in CO2 at close to room temperatures so the molecule is not damaged by the mixing process, and we don't use normal solvents we don't have toxic residues left behind in the product and potentially ending up in the patient.

"The plastics are solids but when they are put under high pressure from CO2, they turn into liquids — they melt, and under these conditions, the bioactive drugs can be mixed in. So we take particles of the drug and wrap every single one up in biodegradable polymer, for injection under the skin."

Once injected, the polymer begins to degrade and the drug starts to be

released and is picked up by the bloodstream — but this is a gradual process, occurring over the course of several days or a week. This provides a controlled release of the drug prolonging the length of time over which active therapeutic is released at the delivery site.

The polymer used is a biodegradable plastic based on lactic acid, which is a natural compound produced in the body that the body is able to get rid of in the usual way. It is used in dissolvable stitches and has been used in the pharmaceutical industry in various guises for 30 years.

Compared to conventional methods for giving drugs to patients, controlled drug delivery via injection has many advantages including reduced dosing frequency and toxicity, improved efficiency and convenience and therefore increased patient compliance.

Professor Howdle added: “Biodegradable polymers are particularly attractive for use in drug delivery, as once introduced into the body they require no retrieval or further manipulation and are degraded into soluble, non-toxic by-products. Different polymers degrade at different rates within the body and therefore polymer selection can be tailored to achieve desired release rates.

“Thus the process allows for gradual, controlled release of a drug, reducing side effects and improving quality of life. For the patient, it could mean the end of twice-daily injections — in favour of an injection once a week.”

Drug encapsulation techniques using green chemistry techniques are currently in advanced tests at spin-out company Critical Pharmaceuticals Ltd. — set up in 2002 by Prof Howdle and colleagues — and expected to proceed to clinical trials soon. Since the drugs and polymers being used have already been approved separately, the process is likely to be available for patients sooner than might otherwise be expected with an

entirely untested process.

As well as new methods of drug delivery, the use of supercritical fluids offers cleaner, residue-free processes that can be harnessed to produce other new polymer materials ranging from enhanced bullet proof plastics through to detergents and coatings and even porous scaffolds for tissue engineering.

Source: University of Nottingham