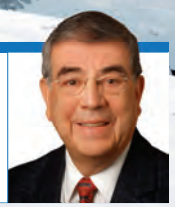
Ready for take-off

Controlled-release drugs have been around for some time and have many benefits, particularly for patients with chronic or autoimmune diseases, but ongoing research has revealed that this market's potential is only now about to take off, as **Patrick P DeLuca** and **Heidi M Mansour** of the University of Kentucky College of Pharmacy explain to Nic Paton.

It's not hard to see the benefits that can come from the controlled-release (or sustained-release) injectable delivery of drugs. Unlike the single hit that a patient might get from simply taking a drug orally or through a conventional injection, controlled-release delivery offers reduced dosing frequency, better therapeutic control, fewer side effects and, consequently, a better acceptance of the dosage form by the patient.

Although advances in polymer material science, particle engineering design, manufacturing and nanotechnology have all contributed to the introduction of more sustained-release products on the market, with a large amount of cutting-edge

Dr Patrick P DeLuca
Dr Patrick P DeLuca is emeritus professor and Sullivan Medallist at the University of Kentucky College of Pharmacy and former president of the American Association of Pharmaceutical Scientists.



Dr Heidi M Mansour
Dr Heidi M Mansour is assistant professor of pharmaceutics and pharmaceutical technology at the University of Kentucky College of Pharmacy. She also holds an appointment at the UK Center of Membrane Sciences.

R&D work ongoing, the concept of controlled-release has been around for years, says Patrick P DeLuca, emeritus professor at the University of Kentucky College of Pharmacy, Kentucky, US.

"Sustained-release has been around for a long time so it is not new," he says. "It developed first within the oral form with the aim of prolonging the levels of certain drugs that were rapidly absorbed into the blood and therefore got eliminated quickly; for example, prolonging the residency or transit within the gastro-intestinal tract."

Drugs cannot be prolonged in the gastro-intestinal tract for long periods, which means that by using oral forms of sustained-release, the patient may need to take the drug once or twice a day. This depends on the clearance of the drug from the bloodstream, which can take from 30 minutes to three to four hours; however, with controlled-release injectables, it is much easier to target the delivery of the drug within the body and, crucially, how long it stays in the patient's system.

"You can actually have a depot site where you can localise the drug in the tissue, either intramuscular or subcutaneous," explains DeLuca. "But the main advantage is that it can then be prolonged for a much longer time, perhaps three or four months."

Chronic situation

Such novel methods of delivery can be particularly helpful when it comes to treating a range of chronic or autoimmune diseases such as multiple sclerosis or arthritis, according to Dr Heidi M Mansour, assistant professor of pharmaceutics and pharmaceutical technology at the University of the Kentucky College of Pharmacy.

> "Respiratory and pulmonary conditions such as asthma or COPD could benefit significantly from sustained-release inhalation aerosols directly to the lung."

"There are products for osteoporosis and prostate cancer that are hormone-based and ideally need to be sustained-release, but for which you do not want people having to inject themselves every day, week or month," she says.

"Similarly, with mental disease such as schizophrenia there are issues with the patient remembering when they need to take their medication, so this sort of advance can really help with compliance and disease management, as well as help with maintaining costs."

Long-acting polymers

The development of advanced drugs using long-acting biodegradable polymers, especially peptide and protein-based drugs, has contributed immensely to this trend, points out Mansour. The past few years have seen a number of controlled-release products containing polypeptide drugs and protein drugs, or ones that retain their therapeutic activity over pharmaceutical timescales following encapsulation in biodegradable materials, enter the market.

"Sustained-release is often used with polymer-based drugs, with a lot of polypeptide biological drugs starting to come through, although it very much depends on the polymer and the chemical structure," she explains. "In the initial design development stage, which polymer to use can be an issue. The encapsulation of the drug can be another challenge, as can scaling up to manufacture.

"Most of the time the process will be tweaked so that the drug inside the polymer stays that way throughout the development process, or it is a question of trying another polymer or increasing the amount of the drug."

DeLuca expects to see new polymeric systems enter the market, ones that can help achieve a steady state of blood levels over an extended period of time. Other types include pen-based polymer devices for administering insulin and other biological drugs.

"It is about making the treatment more advantageous by having it in controlled-release form," says DeLuca. "There are some conditions that are difficult to treat unless they are in controlled-release form, so that is where a lot of the research is currently focused. What is certain is that we will in time come up with a lot of systems that can be applied to a wide range of drug classes."

Potential advances

Mansour predicts that there will be an increase in the number of sustained-release injectable products being approved for human use, particularly in the sphere of protein and peptide-based drugs, and especially those used by the elderly population where there tends to be more frequency of chronic disease, as well as in areas such as cancer, autoimmune diseases and schizophrenia.

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Table 1: Examples of US FDA-approved long-acting formulations on the market.*

Drug	Brand name	Dosage (mg/ml)	Form	Administration	Dosing frequency	Theraputic area	Company
Fluoxetine hydrochloride	Prozac	90	Capsule	Oral	Once a week	Major depressive disorder	Eli Lilly
Alendronate sodium	Fosamax	70	Tablet/ solution	Oral	Once a week	Osteoporosis	Merck & Co
Risedronate sodium	Actonel	150	Tablet	Oral	Once a month	Osteoporosis	P&G
Ibandronate sodium	Boniva	150	Tablet	Oral	Once a month	Osteoporosis	Roche
Ibandronate sodium	Boniva	3/3	Injection	IV bolus	Every 3 months	Osteoporosis	Roche
Zoledronic acid	Reclast	5/100	Injection	IV infusion	Once a year	Osteoporosis	Novartis
Goserelin acetate	Zoladex	3.6, 10.8	Implant	SC	Every 1–3 months	Advanced prostate cancer	AstraZeneca
Buserelin acetate	Suprefact depot	9.9	Implant	SC	Every 3 months	Advanced prostate cancer	sanofi-aventis
Leuprolide acetate	Viadur	72	Implant	SC	Once a year	Advanced prostate cancer	ALZA
Etonogestrel	Implanon	68	Implant	Subdermal	Every 3 years	Hormone therapy	Merck & Co
Dexamethasone	Ozurdex	0.7	Implant	Intravitreal	Every 2–3 months	Macular edema	Allergan
Ganciclovir	Vlitrasert	4.5	Implant	Intravitreal	Every 5–8 months	Cytomegalovirus retinitis	Bausch & Lomb
Fluocinolone acetonide	Retisert	0.59	Implant	Intravitreal	Every 30 months	Uveitis	Bausch & Lomb

*** Does not include injectable sustained-release drug-delivery systems. IV: intravenous SC: subcutaneous**
Credit: Rhee YS, Park CW, DeLuca PP and Mansour HM. 'Sustained-Release Injectable Drug Delivery Systems. An Invited Paper'. *Pharmaceutical Technology: Special Issue Supplement-Drug Delivery.* (2010) November: 6-13.

"These advances are coinciding with advances in other areas, such as particle engineering, which is pretty exciting in terms of their potential," she says.

With insulin, this means that instead of injecting once or twice a day, there will be the potential to make it once a week or even longer, according to DeLuca.

"It could potentially be for any condition where the patient is going to be on medication and it is not something where they have to be monitored in terms of blood levels," he says.

As well as many chronic diseases that require patients to accept a lifestyle of ongoing medication, respiratory and pulmonary conditions such as asthma or chronic obstructive pulmonary disease could also benefit significantly from sustained-release inhalation aerosols directly to the lung. One of the important advantages is reducing the frequency of inhaled dose administration for these chronic pulmonary diseases.

"It can be helpful for patients needing to take a drug for a chronic condition and for which they will need to take it for their lifetime," explains DeLuca. "If you inhale a solution into the lungs, inevitably it is going to clear quite quickly. But if you can incorporate the drug in a nanoparticle and localise it in the lung, it can remain there for a lot longer and will be released slowly. So it may just be, say, one puff a day, which would be a big advantage."

Mansour and DeLuca predict that there will be more research carried out, particularly in the pulmonary area.

"It is easier for the FDA to approve a tablet or a liquid in injectable form," says DeLuca. "But they need to look at the controlled-release form as well. It may be that you must have another clinical trial and that you need to extend the patent base."

From DeLuca and Mansour's predictions, it appears that controlled-release drugs have an exciting future, particularly for the patient, who will be the main beneficiary, with potential for areas such as vaccines or developments that can be used in developing nations. ■