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Drug delivery innovations bring compliance and cost savings

Patient non-compliance places a huge cost on healthcare budgets on a global level. **Peter Thornton** looks at new drug delivery options that could solve this costly problem

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Drug delivery could be one element that saves some much needed pennies and drug technology manufacturers could be the biggest beneficiaries

Patient non-compliance with therapy regimens is often thought to be the single greatest threat to successful treatment in chronic conditions. As one of the most studied indications with regards to the impacts of non-compliance, diabetes provides a good illustration: studies showing that a 25% decrease in compliance in diabetic patients results in an increase in glycated haemoglobin (HbA1c) concentrations. Data from the United Kingdom Prospective Diabetes Study has shown that for each 1% decline in HbA1c concentration there is a risk reduction of 14% for myocardial infarction, 37% for microvascular complications, 21% for diabetes-related deaths and 21% for any diabetes-related endpoint. Low rates of adherence to treatment substantially contribute to increased levels of mortality, as well as accelerated disease progression, which in turn results in hospitalisation or other costly procedures that ultimately place an economic burden on healthcare budgets. And with a number of worldwide economic factors set to cost healthcare systems around the globe more than ever, drug delivery could be one element that saves some much needed pennies and drug technology manufacturers could be the biggest beneficiaries.

In the World Health Organization's 2003 report on patient compliance *('Adherence to long-term therapies: Evidence for action')*, five different aspects that contribute to the multidimensional nature of compliance were detailed, namely: the healthcare system, social and economic factors, patient-related, therapy-related and condition-related.

It is generally acknowledged that patients with asymptomatic disease are most likely to have low adherence rates. Hypertension, for example, is asymptomatic in many patients, yet the side-effects experienced from the treatment regimen can result in potent feelings of ill health. This type of scenario, where the patient feels worse after commencing treatment than they did before, significantly affects their motivation to comply with treatment.

On the other hand, highly symptomatic conditions such as chronic pain typically report higher levels of compliance, given that the patient has a distinct physical incentive to adhere to the treatment regimen. Nonetheless, non-compliance remains a significant problem even in these types of patient, particularly if the possibility of overdosing exists.

The issue of compliance is not limited to chronic illnesses: acute conditions such as bacterial or viral infection also require strict adherence to medication. This is not only beneficial to the individual patient, but also on a wider public health level, as demonstrated by the increasing emergence of microbial drug resistance in recent years, at least part of which can be attributed to the lack of strict adherence to antimicrobial therapy.

Patients become non-compliant when barriers to treatment outweigh the expected benefits. Barriers to patient compliance include aspects from all five of the WHO dimensions of adherence:

- high cost of pharmaceutical drugs
- remembering to take medicines at the right time
- lack of faith in the prescriber or denial of illness
- side-effects
- complex treatment regimens that include several different therapies
- awkward dosing instructions (take standing up, with or without food, for example)

A wealth of evidence points to the fact that poor health outcomes and the associated increase in healthcare costs contribute to a significant unmet need for adequately compliant treatment regimens in all types of disease.

Novel drug delivery systems are being developed to improve patient compliance, an aspect of the WHO's 'therapy-related' dimension of patient adherence. These new systems aim to aid in the more effective and targeted dispensation of optimum therapeutic dosages, thereby potentially reducing side-effects, increasing efficacy, and ultimately impacting in a positive way on patient adherence to the therapy regimen.

ADVANCES IN ORAL DELIVERY

Although the development of sustained-release formulations has allowed for a significant boost to patient adherence, as the dosing frequency is reduced there has been a shift in focus to controlled-release delivery systems. These technologies have allowed for the addition of a large degree of flexibility in the achievable levels of plasma drug concentration. This has resulted in highly specific delivery profiles, often containing a mix of immediate and sustained-release to be achieved which, in certain conditions, has had the effect of significantly better disease control.

Rapidly disintegrating oral formulations, including orally disintegrating tablets and thin films, have seen an unprecedented level of innovation in recent years, driven primarily by advancements in polymer

TABLE 1: MICRONEEDLE TECHNOLOGIES IN DEVELOPMENT, 2011

COMPANY	TECHNOLOGY	INDICATIONS
BD Technologies	**BD Soluvia**	Vaccination
BioChemicas	**mNet**	Undisclosed
BioSerentTech	**Dissolving microneedle chip**	Vaccination, growth hormone deficiency, anaemia
Valeritas	**Micro-Trans**	Undisclosed
Nemaura Pharmaceuticals	**Mycrolator**	Various
FluGen	**Vaccine loaded delivery technology**	Influenza vaccination
Janisys	**Active transdermal microneedle pump**	Undisclosed
Nanobiosciences	**AdminPatch**	Undisclosed
Cosmed Pharmaceuticals	**MicroHyala**	Various cosmetic
TransDerm	**Soluble Tip Microneedle Array**	Delivery of siRNA for various indications
Purdue University	**Microneedle drug delivery patch**	Undisclosed
Nanopass technologies	**Micropyramid**	Cosmetic, diabetes, pain

Source: MedTRACK, company websites

In addition to the development of bioerodible implants, there have been advances made in the development of non-biodegradable implants

and taste-masking technology coupled with the discovery of superdisintegrants, which is likely to make this delivery format increasingly popular. Rapid-release oral transmucosal delivery, which has the advantage of bypassing hepatic metabolism, has seen innovation through the development of mucoadhesive polymers, allowing for low levels of drug with high bioavailability to reach systemic concentrations very rapidly.

Innovation in polymer technology has been the driving force in advancing development in sustained-release delivery systems, to the effect that innumerable drug delivery companies and proprietary technologies offering sustained-and controlled-release profiles are in clinical development.

Technology at the microparticle level, including bioerodible polymer matrices, miniature osmotic pumps and rate-controlling membranes, has revolutionised control over drug release, while liposome technology has offered major improvements in bioavailability and potential for sustained release for both lipophilic and hydrophilic drugs.

PARENTERAL FORMULATIONS

The formulation of injectable drugs that have an increased duration of efficacy for a given dose, thereby reducing the dosing frequency, addresses several important healthcare issues, including fear of needles, which can cause non-compliance. Less frequent dosing offers improvements in patient safety, a reduction of injection site complications, and improved compliance with drug protocols. The repeat dosing of parenteral formulations is accompanied by a burst-release and decay profile that can be significantly enhanced and improved by modifications that allow for a more sustained, constant delivery of the drug. Depot injections and implants are the two key developments in long-term injectable therapy, and there has been considerable R&D activity in this field in recent years.

Immediate-release formulations, particularly for pulmonary administration, have been developed, but the predominant focus of modified-release technology is on sustained and controlled release, which reduce the extent of repeat dosing. One example of a successful technology being applied to allow for sustained-release parenteral drug delivery is microparticulate release. These systems embed the drug either in a matrix or a sphere from which it slowly diffuses. Biodegradable microsphere systems are currently the most commercially successful method of delivering macromolecules (such as proteins) by injection. Examples of these technologies include Durect's Microdur system, Innocore's SynBiosys, and Flamel Technologies' Medusa.

The development of innovative biodegradable polymers has allowed for the emergence of depots and implants as an alternative to standard injectable formulations. Several companies are developing bioerodible implants, including Durect, which is developing its Durin implant for the delivery of first order, zero order, delayed or biphasic drug release profiles. A few companies are working on implants for specific uses. For example, SurModics has developed the I-vation implant for the sustained release of drugs to the back of the eye. In one study (Vincent, P. 1971) it was demonstrated that even when faced with blindness 58% of glaucoma patients were non-compliant, and incredibly 42% of patients who had already lost sight in one eye as a result of non-compliance continued to be non-compliant. The I-vation implant has the potential to improve on this poor level of compliance if formulated for glaucoma or other conditions that are currently treated with regular topical applications of drugs to the eye. Its helical design maximises the surface area available for drug delivery, and ensures secure anchoring of the implant against the sclera, keeping it out of the visual field and facilitating retrieval.

In addition to the development of bioerodible implants, there have been

advances made in the development of non-biodegradable implants. Although these have the drawback of having to be removed at the end of the treatment period, they do offer the advantage of very infrequent dosing as a result of their extended-release profiles. One such implant that is already in use and being developed for several indications is the Duros system from Durect, which uses osmosis to drive a piston that dispenses drug from the end of the implant. One indication in which this device is being developed is type II diabetes, with Intarcia hoping to use it to deliver the GLP-1 analogue exenatide. Exenatide is currently only available as a twice-daily injectable whereas the Duros formulation is designed to be implanted once every three months and has demonstrated favourable clinical results thus far.

TRANSDERMAL ADVANCES

The transdermal route of administration is painless, highly acceptable to patients, bypasses hepatic metabolism and offers a steady state of extended drug delivery. However, there are considerable challenges for the successful delivery of pharmaceutical active ingredients via this route, as the skin, and the outermost stratum corneum layer in particular, poses a formidable barrier to drug penetration. Substantial efforts have been devoted to overcoming the impermeability of the stratum corneum to allow for the transdermal delivery of drugs outside of the naturally absorbable range.

So called 'third generation' transdermal systems are being developed with the potential to deliver a wide array of drugs. There are a variety of technologies being employed in the development of these third generation systems; one of the most interesting is dermal ablation or poration. These technologies selectively ablate the stratum corneum to allow the entry of drugs to the blood stream. Examples include AlteaTherapeutics' PassPort, which uses thermal ablation to create micropores in the skin. This system is being used in the development of transdermal formulations of several molecules including insulin and exenatide, both for the treatment of diabetes and available as injectables.

Another transdermal technology that holds great promise is the development of microneedles,which create larger transport pathways than other novel transdermal delivery systems allowing for the transdermal delivery of much larger molecules than is currently possible. In one study (Cormier et al 2004) the bioavailability of desmopressin delivered via coated microneedles was 79%; this illustrates the possibilities of delivering large molecules with this technology. Microneedle systems typically consist of an array of needles that are between 150 and 200 micrometres in length that are applied to the skin where they penetrate the epidermis and create a physical pathway for drug ingress. Table 1 lists microneedle technologies that are currently in development and the indications they are being developed for.

There are three main types of microneedle – which have their own advantages and disadvantages – these are listed in Table 2.

PHARMA FUTURE

Pharmaceutical devices form an integral part of drug delivery, particularly for the parenteral routes of administration, which generally require a highly specialised administration format in order for the drug to be effectively absorbed.

As technological advances in micro-electro-mechanical systems (MEMS) progress, there will be increased opportunities for biological applications of this technology, not only in oral delivery devices, but for implantable pumps, injectable therapies, transdermal devices, and combinations of administration and monitoring.

Injections will continue to be an essential platform for the delivery of drugs, but device companies will keep striving to develop technologies that reduce the pain, biohazard, cost and inconvenience associated with injections. An increasingly diverse array of prefilled syringes and auto-injectors will enable greater patient choice of device, while novel innovations such as the solid dose injection and infusion pumps will allow for the expansion of patient self-medication while reducing associated hospital or clinician costs.

Technological advances for inhaled pulmonary and intranasal delivery devices will mean increased scope for these routes in the administration of macromolecules, peptides, and biologics, effecting compliance through less invasive routes of administration.

The development of novel formulations and devices that will improve patient compliance presents significant opportunities to the pharma industry for the reformulation of its products. Enhanced compliance can drive improved health outcomes and increased revenues and the developers of these technologies stand to do well as increasing numbers of biologics are approved, and generics players look to differentiate their offerings through the development of supergenerics and the enhanced biosimilar, the biobetter.

So called 'third generation' transdermal systems are being developed with the potential to deliver a wide array of drugs

TABLE 2: COMPARISON OF DIFFERENT MICRONEEDLE TECHNOLOGIES

TECHNOLOGY	ADVANTAGES	DISADVANTAGES
Solid needles	• Relatively cheap to produce	• Require separate patch • May break off in the skin
Hollow needles	• No separate patch required • Broad range of applicability	• Must overcome issues with backpressure • Only small doses can be applied
Drug based needles	• Needle can be left in skin which increases safety	• Prolonged exposure causes skin irritation

Source: Scrip Business Insights