DDT Vol. 8, No. 21 November 2003

Controlled release technologies for drug delivery

David J. Brayden, Faculty of Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland; tel: +3531 7166013, email: david.brayden@ucd.ie

With an attendance of >2000 delegates, the 30th Annual Meeting of the Controlled Release Society (CRS) (Glasgow, UK, 19–23 July 2003; http://www.controlledrelease.org) addressed key issues in the formulation and targeting of molecules that are normally difficult to deliver. The Society's major goal is to promote new technologies with which to achieve optimal plasma profiles of established and novel drugs. New drug delivery technologies enable drugs to be more effective and, therefore, have an important niche in treatments. Remarkably, drug delivery is still considered a poor relation to drug discovery; >95% of all new potential therapeutics have poor pharmacokinetics. The lack of promotion of drug delivery and controlled release was illustrated perfectly by the honest admission of a plenary speaker, Sir George Radda (former Head of the UK's Medical Research Council), that he was unaware of the existence of the CRS before this conference.

Rationale for controlled release

Linda Hakes (Schwarz Biosciences, http://www.schwarzpharma.com/) presented an elegant set of arguments that addressed why we should continue to consider controlled release. Medicines need to be as effectively administered as possible to enhance compliance and efficacy. For example, drugs with short half-lives delivered by multiple injections or tablets each day are less attractive to patients than the same chemicals delivered by sustained release from a once-a-day oral formulation, a six-monthly implant or three-day skin patch. So much is the inconvenience, in fact, that efficacy is reduced because most patients tend to miss doses if required to adhere to complicated dosing regimes.

Sustained plasma levels are typically preferred to the peak-and-trough plasma profile that is normally associated with oral and injected delivery. Furthermore, if the maximum plasma drug concentration (Cmax) is associated with side effects, then sustained release can improve the benefit:risk ratio. Hakes presented the potential advantages of a once-a-day transdermal patch containing a novel dopamine agonist for the treatment of Parkinsonism that is currently being developed by Schwarz. In this case, a sustained plasma profile from a once-a-day patch can offset the dyskinesia and rigidity that accompany the undulations in plasma levels that are produced by oral delivery. This example proves that a modified release formulation meets a real patient need and that the 'convenience' argument promotes improved therapeutic efficacy. It is worth noting that Schwarz's development approach (i.e. producing a transdermal formulation with a novel agent) is associated with a higher risk of adverse effects than are other approaches; all currently approved patches consist of pre-approved drugs. As justification, the laudable point was made that patients benefit more from optimization of a new drug formulation at the outset, rather than in later-generation products. From an economic viewpoint, such optimized formulations can lead to reduced hospital stays and additional savings to health services.

Oral delivery: linking biology to formulation

Of the 100 top-selling drugs in America, 76 are available as oral formulations. There is no doubt that the oral route is preferred by patients and that it still dominates controlled release research. From a personal review of 30 years of delivery research, Bob Davis (University of Nottingham; http://www.nottingham.ac.uk) presented some highlights that have had a major impact on this field. He asserted that advances are made when formulation and cell biology or gut physiology are studied in parallel. In the 1970s, little was known about processing times in different regions gastrointestinal (GI) tract. Pioneering the technique of gamma scintigraphy, Davis' group concluded that transit time in the colon could be upto 20 hours and could, therefore, be a potentially attractive delivery site for drugs. This spawned the field of colonic targeting using biodegradable particles, azo-polymer prodrugs, chitosan bioadhesives and pH-sensitive coatings. Gamma scintigraphy underpinned the establishment of Pharmaceutical Profiles (Nottingham, UK), a company specialising in tracking the movement of devices and formulations along the human GI tract.

 PII: S1359-6446(03)02874-5

This type of approach relates to the oral delivery of peptides, an area of research where practical advances have not matched the hype of the early 1990s. Davis argued that an extended colonic residence should permit adequate contact time with the large intestinal wall, assuming that the peptide remains intact (i.e. in a protected formulation). Use of absorption enhancement technologies, such as bioadhesives, surfactants and tight-junction-openers has not yet produced reproducible, safe and adequate plasma levels for many peptides tested in clinical trials, the exception being the oral microemulsion formulation of cyclosporine (Neoral®, Novartis; http://www.novartis.com). Furthermore, Davis explained that the proliferation of conjugated peptide technology might not be the ideal alternative approach, considering the difficult regulatory hurdles that lie ahead for such new chemical entities. Instead, he favoured the more traditional approach, of maintaining the peptide in native form but in novel carrier formulations.

The difficulties associated with oral delivery of complex formulations might not be as limiting for localized indications as they are for systemic indications; oral delivery of topical coating formulations to the luminal surface of the distal ileum and colon to treat inflammatory bowel disease appears more achievable.

In reviewing the promise of oral delivery of vaccines in biodegradable microspheres, Davis described a study in which the uptake of fluorescent particles by human colonic Peyer's patches in 20 hemi-colectomized patients undergoing surgery was negligible by comparison with rodent data (unpublished data). The study entailed administration of latex microparticles to patients by intubation before surgery, followed by assessment of particle uptake by the colonic tissue that was discarded in the operation. Davis suggested that M cell-targeted vaccine-loaded particles might be a way to improve Peyer's patch uptake [1], with an expectation that this would lead to an enhanced and durable mucosal immune response. In pursuit of this aim, he advocated the further discovery of novel human M cell apical membrane-specific receptors that interact with ligands from infectious pathogens, such as polio, reovirus and *Yersinia*. Imitation of nature might prove fruitful in the study of targeting M cells. A simpler pharmaceutical solution, however, might be to avoid a requirement for targeting, by increasing the concentrations of localized particles in ileal and colonic regions.

Targeting folate receptors in cancer and inflammatory diseases

The benefits produced by the targeting of specific receptors in the body in selective cancer chemotherapy are a good example of improved risk–benefit profiles of drugs with narrow therapeutic indices. Philip Low (University of Purdue; http://www.purdue.edu/) described how the folate receptor is currently being used in a double-pronged approach to the diagnosis of serious cancer and subsequent receptor-targeted therapy [2].

The folate receptor is overexpressed on malignant cancer cells; a fact that Low's group have used to develop diagnostic screens with indium-linked folate conjugates, coupled to *in vivo* imaging. Normal tissue clears folate rapidly but stage 3 ovarian cancers take up the 'label' selectively. This approach can be extended to localized chemotherapeutic treatment because folate can be conjugated to haptens, such as fluorescein, in combination with IL-2 or gamma interferon. Successful delivery of folate antibody-linked conjugates in mice has already led to complete cures for murine cancers and human studies are set to begin. New data presented at the meeting showed that other types of diseased might also express folate receptors to a higher level than normal. Activated macrophages in rheumatoid joints take up folate conjugates especially well and this, therefore, might open potential avenues for localized therapies with lower systemic toxicity. Activated macrophages are also seen in Crohn's disease and atherosclerosis and perhaps folate-linked therapies can be targeted to prostaglandin- and type-1 cytokine-secreting cells.

Treating CNS diseases: targeting

Owing to the relative inability of most drugs to cross the blood–brain barrier, novel methods are needed to enhance the pharmacokinetics of therapeutics for the treatment of brain diseases. Ulrike Bickel (University of Amarillo; http//www.ama.ttuhsc.edu/) described how recent advances have been made in the harnessing of physiologically-expressed receptors on blood–brain barrier endothelia. He reviewed the failure, thus far, of efforts to pharmacologically regulate the barrier by manipulating capillary endothelial cell tight junctions, the inefficiency of delivery from the nose-to-brain route and the impractical nature of intracerebral implants.

Bickel then turned to the targeting of transferrin and insulin receptors on the barrier using streptavidin-linked antibody chimeric peptide conjugates. Of particular interest were the impressive rodent brain delivery data with OX26-avidin-brain derived neurotrophic factor and vasoactive intestinal peptide chimeric conjugates; however, there has been scepticism about the economic feasibility of such an approach. In opposition to this, Pardridge and co-workers have recently demonstrated that

OX26-transferrin-targeted PEGylated immunoliposomes carrying expression plasmids for the gene for tyrosine hydoxylase are an effective treatment for a rat ablation model of Parkinsonism [3]. Gene delivery for multiple brain diseases using targeting methods might, therefore, hold great potential. Bickel also highlighted the fact that gene chip and proteomics work is beginning to elucidate the physiology of known and unknown receptors on the blood–brain barrier endothelia; he suggested that transferrin and insulin receptors might be the trail-blazers for CNS delivery targets in the future.

Conclusions

Several key points emerged from the highlighted talks at the 2003 CRS meeting. There is a real patient need for more-effective modified release of newer drugs, using established delivery platforms, such as transdermal patches. Enhanced delivery systems will improve therapy and reduce side effects as a result of more appropriate plasma profiles. Oral delivery of vaccines remains elusive and is compounded by a poor understanding of the relationship between Peyer's patch uptake and mucosal immunity. Overall, however, developments within drug delivery and controlled release are encouraging; the scope for future advancements is immense and ranges from the therapeutic targeting of solid tumours, to accessing the CNS and elements of the immune system.

References

1 Clark, A. *et al* (2001) Targeting polymerised liposome vaccine carriers to intestinal M cells. *Vaccine* 20, 208–217

2 Yu, Y. and Low, P.S. (2002) Folate-mediated delivery of macromolecular anti-cancer therapeutic agents. *Adv. Drug Del. Rev.* 54, 675–693

3 Zhang, Y. *et al* (2003) Intravenous non-viral gene therapy causes normalization of striatal tyrosine hydroxylase and reversal of motor impairment in experimental parkinsonism. *Hum. Gene Ther.* 14, 1–12

Multiple Drug Resistant Bacteria

Editor: Carlos F. Amábile-Cuevas, Horizon Scientific Press, 2003, (182 pages, hardback, GB£80; US$160), ISBN 1-898486-45-X

The steady rise in the global burden of antibiotic resistance has received a lot of attention recently and belief is growing that we are losing the battle against bacterial infections, particularly in our hospitals. The introduction of a new antibiotic, a rare event in itself, is invariably followed, sooner or later, by the emergence of bacterial resistance to the agent. Accumulation of resistance genes in bacterial pathogens has been accelerated by the over-prescribing of antibacterial agents, by the transfer of resistance genes amongst bacteria and by the epidemic spread of resistant strains among patients. The emergence of multi-drug resistant Gram-positive pathogens, such as methicillin-resistant staphylococci (MRSA) and vancomycin-resistant enterococci (VRE), as a fundamental cause of hospital-acquired infections is a major concern; the isolation of the first vancomycin-resistant MRSA strain last year, from a catheter exit site, broadens the spectrum of infections that are untreatable with currently available antibiotics. Over the past ten years, many books have been published on the subject of antibiotic resistance and this volume now joins the list, with the aim of focusing on the problems caused by multi-resistance. The contributors review multi-resistance in a broad context, considering the biological, social and economic forces that have influenced the emergence of the multi-resistant genotype.

The book consists of seven chapters, charting the rise of antibiotic resistance, describing the processes by which Gram-negative and Gram-positive bacteria accumulate resistance genes on single genetic elements and in single bacterial cells, reviewing recent research on the roles of regulation of the stress response and efflux mechanisms in Gram-negative bacteria and taking a detailed look at VRE and MRSA infections. The final chapter examines the evolution of horizontal gene transfer in relation to the selection of antibiotic resistance. Most of the contributions are from internationally recognised experts in the field and are, therefore, authoritative tracts; much of what is covered has, however, been recently reviewed by others and hence, the informed reader, at which the book is aimed, will be familiar with the material. The usual argument, that rapid evolution of antibiotic resistance is not only making our current antibiotic solutions useless but is compromising our future efforts to control infections through chemotherapeutic intervention, is discussed in a refreshingly broad context: the role of non-antibiotic agents that are known to select or induce resistance phenotypes is covered in depth, and the contribution of the public, physicians, hospital personnel, veterinarians and the pharmaceutical industry are given appropriate

  PII: S1359-6446(03)02859-9