UKICRS Newsletter

United Kingdom & Ireland Controlled Release Society http://www.pharmweb.net/ukcrs.html
Editors: Marianne Ashford & Clive G. Wilson No.4 September 1998

Welcome to the Fourth UKI Controlled Release Society Newsletter. The local chapter has expanded to incorporate the Republic of Ireland and the new title and logo acknowledge our growth. New Events are planned for 1999 and 2000 in the face of stiff competition (everyone wants a millenial conference!). The UKICRS Committee has had an injection of new blood and there have been the inevitable committee changes. If you would like to hear the latest news about the UKICRS why not join our Internet mailing list, information of which is in this Newsletter (UKICRS on the Internet).

Contents

A Message from the Chairman

Arrangements for the incorporation of Ireland into the local chapter and the change of articles in our constitution to allow us to represent the enlarged organisation are complete. A new member, Dr David Brayden, of Elan pharmaceutical technologies has joined the committee and is charged with increasing our membership in Ireland and of course, organising joint meetings. David is already busy within UKICRS and is working with Alan to organise a two day meeting in Dublin in January 2000. The theme of the meeting will be novel vaccines, and an exciting line-up of speakers have agreed to contribute. Saghir is busy organising the January 99 meeting at Aston – see the report in this issue.

Three members of the committee left this year – Mike Tobyn to concentrate on his constituency (or should that be consistency) Mark Roberts to keep track of his sanity and Anya to a new job in Madrid. Anya was a particularly enthusiastic member of the committee, keen to host a meeting at Brighton, although we never did. Perhaps Spain will be an even more tempting venue… Anyway, we wish both Anya, Mark and Mike well and thank them for their valued contributions to the society.

It's autumn again (where was summer?), and we have the pleasure of contributing to the British Pharmaceutical Society at Eastbourne. Marianne and Anne have been very busy ensuring that the joint CRS – Pharmaceutical Sciences Group Committee integrates into the programme. This year, we have decided to have a stand at the meeting and Andy Francis of Skyepharma has kindly donated a portable display which we will use at future meetings. Many thanks to Jane and Andy for an extremely useful piece of publicity kit. Last year's symposium 'New Approaches to Drug Delivery' at Scarborough was a great success and the invite to repeat the experiment a testimony to the good will between the societies. Let's keep up the momentum !

Clive Wilson, Chairman of UKICRS

The UKICRS Committee

The UKICRS Committee has changed dramatically in recent months with several new faces joining. A short biography is presented of the current members.

Saghir Akhtar - Organiser 1999 Meeting

Address: Department of Pharmaceutical and Biological Sciences, Aston University, Aston Triangle, Birmingham B4 7ET
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Saghir Akhtar is Reader in Pharmaceutical Sciences at The University of Aston. He received his PhD in polymeric drug delivery systems from the University of Bath in 1990 and did his post-doc. at the University of North Carolina School of Medicine at Chapel Hill where he studied the cellular uptake mechanisms of antisense oligonucleotides. In 1991, Saghir moved to The Department of Pharmaceutical and Biological Sciences at Aston University. His current research interests include the cellular delivery and biological evaluation of antisense oligonucleotides and ribozymes as novel therapeutic agents for anticancer and antiviral applications.

Marianne Ashford - Secretary

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Marianne is currently working in Pharmaceutical Research at Zeneca Pharmaceuticals. After, completing a PhD at the University of Manchester on oral drug delivery to the colon, Marianne joined Zeneca. She still maintains an interest in oral controlled release delivery systems. Marianne's current position is leading a team which is responsible for providing the biopharmaceutical support to drug discovery projects.

Anne Brindley - Programme Organiser 1998 Meeting

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Anne is a Team Leader at Astra Charnwood. After graduating from the University of Bath with a degree in Pharmacy, Anne worked for Glaxo Group Research, on the formulation of solid dosage forms. Anne then left Glaxo to undertake a PhD at the University of Nottingham on the site-specific delivery of polymer colloids. After completing her PhD, Anne returned to Glaxo at Ware, working on the development of dry powder inhalers and then metered dose inhalers. Anne joined Astra Charnwood in 1996 where she currently works on metered dose inhalers.

Alan Coombes - Programme Organiser 1999/2000 Meeting's

Address: Aston University, Aston Triangle, Birmingham B4 7ET
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Alan studied material science at the University of Nottingham and received a PhD in polymer physics from the University of Bristol. Research in bioengineering at University College London was followed by two years at the University of Texas working on biodegradable polymer implants for bone repair. In 1990 he took up a position as a research fellow in the Department of Pharmaceutical Sciences at the University of Nottingham working on microparticulate systems for drug delivery, vaccine development and controlled release of proteins and peptides. Recently he rejoined academia and has the dubious pleasure of working with Saghir !

Tony D'Emanuele - External Relations

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Tony is a senior lecturer in the Department of Pharmacy at the University of Manchester. After graduating from The School of Pharmacy, University of London, Tony undertook a PhD at the University of Bath on responsive electrophoretic drug delivery. Tony took up his current appointment after an eighteen month postdoctoral fellowship at the Massachusetts Institute of Technology where he investigated the use of ultrasound to modulate drug release from biodegradable implants. Tony is currently researching pulsatile and responsive delivery systems, biodegradable polymeric systems, and the delivery of genes into cells by means of sonication.

Hiep Huatan - Organiser 1998 Meeting

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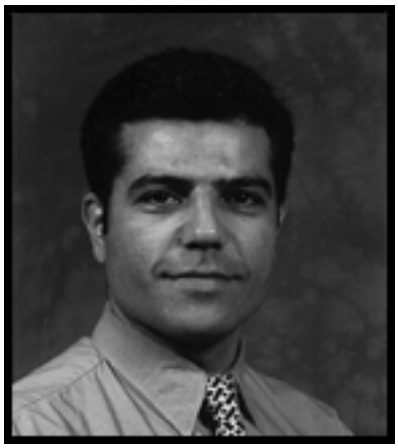
Hiep is a Research Scientist in the Exploratory Drug Delivery Group, Pfizer Central Research. After graduating from the University of Nottingham, Hiep undertook a PhD at the University of Manchester on the characterisation of multicomponent polymeric drug delivery systems; an area of research which he maintains an active interest. In his current position, Hiep is involved in the provision of biopharmaceutics support for a number of human medicinal and animal health discovery projects. More recently, Hiep has also been involved in product enhancement initiatives at Pfizer.

Ali R. Rajabi-Siahboomi - Academic Liaison



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Ali is a lecturer in the School of Pharmacy and Chemistry, Liverpool John Moores University. After graduating in Pharmacy from Nottingham University, Ali undertook a PhD at Nottingham University on HPMC in hydrophilic matrix dosage forms. Ali's current research interests include: formulation and characterisation of oral controlled release matrices and lymphatic drug delivery.

Peter Scholes - Programme Organiser 1998 Meeting

Address: 3M Healthcare Ltd., Conventional Drug Delivery, Morley Street, Loughborough, Leicestershire LE11 1EP

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Peter is currently working within the Conventional Drug Delivery Department at 3M Healthcare in Loughborough. After graduating in Pharmacy from the Department of Pharmaceutical Sciences at the University of Nottingham, Peter returned there to complete a PhD on the development of a biodegradable microsphere carrier system for site specific drug delivery. His current position at 3M is as the liquids and creams development section leader with responsibilities for both new product development and also the provision of technical support to existing marketed products.

Clive Wilson - Chairperson

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Clive is the current J P Todd Professor of Pharmaceutics at Strathclyde having taken up the post from Professor Sandy Florence in 1992. He admits an origin from strange backgrounds (physiology, biochemistry, parisitology) which probably does not account for his interest in pharmaceutical sciences. During his years at Nottingham Medical School, he helped develop scintigraphic techniques used in formulation evaluation in man. In Scotland, he has continued his interest in ophthalmic and gastrointestinal drug delivery and in newer methods of non-invasive drug monitoring.

Jane Worlock - Treasurer

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Jane joined the international operations department of SkyePharma AG to work on European business development from her base in South West France. Skyepharma specialises in oral drug delivery with it's Geomatrix® and inhalation technologies, and is an enthusiastic supporter of the CR.

Dr David Brayden

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David obtained a first class honours in Pharmacology from University of Dublin, Ireland (1984). His Ph.D in Pharmacology was from the University of Cambridge (1988), and he was then appointed as a Post-Doctoral Research Fellow at Stanford University (1989). He joined Elan Corporation (1991) to set up Elan's *In Vitro* Pharmacology Laboratory in Trinity College Dublin. He was made Senior Scientist, Section Head in Biology and is currently Elan's Project Leader in Vaccines. He is the author or co-author of 50 original publications and was Guest Editor of the Journal of Controlled Release Special Issue on Peptide Delivery arising from CRS Ireland Conference in Dublin in 1995. He has been invited to speak at IBC, AIC, AAPS, and Management Forum conferences. He is a member of the British Pharmacological Society, the New York Academy of Sciences, the AAPS and the CRS. He also acts as a reviewer for EU Framework Programmes and for leading journals in the field of drug delivery.

Report on the 4th Annual UKICRS Symposium - London

4th United Kingdom-Ireland Controlled Release Society Symposium on:

"Continuous v Discontinuous therapy - Current Perspectives"
6th January 1998, School of Pharmacy, University of London

Professor Sandy Florence welcomed around seventy delegates to the 4th UKICRS National Meeting which despite severe storms off the south west coast, gales preventing ferry sailings from Ireland and a snow fall in the Midlands took place in almost balmy weather conditions in the capital. Professor Clive Wilson, chairman of UKICRS delivered the opening address, outlining the broad aims of the society to link academia and industry, to provide interesting scientific

meetings and funds for young scientists to attend conferences in the UK and abroad. An important goal, achieved in 1997, was the linking of Ireland to UKCRS to form a new UK-Ireland local chapter. Dr Anne Brindley, the meeting organiser, then thanked committee members, Peter Scholes, Hiep Huatan and Saghir Akhtar for assistance in particular and acknowledged the generous sponsorship of Astra Charnwood, 3M Healthcare, Pfizer Central Research, Jago Pharma AG, Polymer Laboratories, Faulding Pharmaceuticals and Bristol Myers Squib.

Dr John Devane, from Elan Pharmaceutical Technologies opened the scientific proceedings with a talk on Continuous versus Discontinuous Therapy : Drug Delivery and Therapeutic Issues. The central tenet settled on the growing recognition, through the study of chronotherapeutics, that variable or mixed drug exposure was optimal. Intensive study of natural biological patterns had revealed strong links over a 24 hour period with the pattern of activity and associated symptomatology of the diseased state. The combination of chronotherapeutics with chronopharmacokinetics (variation of drug kinetics with the time of day it is administered) and chronopharmacodynamics (variation of biological responses with the time of day) has resulted in the ability to define optimal drug exposure/time profiles. This in turn has created major challenges but also opportunities for drug delivery to meet new and complex therapeutic regimens. One intriguing response involves the integration of biosensor technology and feedback drug delivery technology to produce individualised 'smart pills' .

Dr Rob Horne, senior lecturer in Health Psychology and Pharmacy Practice at Brighton quickly grabbed attention when he revealed that £2 billion of UK health resources is wasted per year due to unused medication. This is occasioned by a 30-50% non-compliance rate with most patients being non-compliant some of the time. Psychological research has shown that patients form their own 'common sense' models of their illness and evaluate health advice in a 'risk-benefit' analysis before responding to recommended treatment. In a significant number of patients, beliefs that medicines were oversubscribed or were essentially harmful and addictive presented barriers to taking medication. Thus non-compliance may be a logical attempt to moderate the perceived risks by taking less. Compliance may be improved if patient and doctor engage in a more open dialogue about the nature of the illness and treatment to lower 'motivational barriers' alongside making the regime simple and convenient to follow.

Professor Peter Redfern from the School of Pharmacy and Pharmacology at Bath returned to the subject of chronotherapy - the influence of time of day on drugresponse - with a talk on circadian rhythms (CR) in physiological processes. Rhythms in blood pressure, temperature, and hepatic metabolism for example respond both to the biological clock residing in the suprachiasmatic nuclei of the hypothalmus and the 24 hour day-night pattern of the environment. Circadian periodicity can influence the 1) symptomatology of the disease process over 24 hours 2) the pharmacokinetics of drugs (eg due to the variations in physiological processes responsible for absorption) 3) altered afficacy. Thus we should aim to deliver drugs such as cytotoxic agents according to the rhythmic variation in biological processes (the principles of chronotherapeutics). Difficulties in applying this strategy include a deficiency of knowledge of circadian periodicity in physiological processes, an often small amplitude of the CR, significant inter-individual variation and alteration of the normal CR by disease. A major challenge to drug delivery technology lies in provision of a delivery profile which varies reliably and reproducibly over 24 hours.

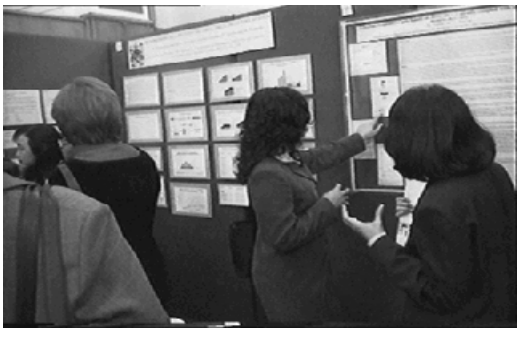
Lunch provided attendees with the opportunity to view the poster exhibition, renew aquaintances and

establish new contacts. Nineteen posters were submitted all being automatically entered in the competition for two prizes of £500 which are awarded annually to the winning post graduate students to help attend the CRS international meeting.

The first talk of the afternoon session was given by Professor Philip Home of the Human Diabetes Research Institute, University of Newcastle on the subject of 'Restoring Physiological Insulin Delivery'. Professor Horne's first salient point was that insulin is still injected 75 years after its discovery. A tendency for the peptide to hexamerise, its acid solubility and surface adsorption coupled with a widely varying physiological requirement, slow and erratic absorption from the subcutaneous site and poor bioavailability (insulin has a half-life of approximately 5 minutes in the) underline the challenges inherent in delivering insulin effectively. Control of insulin delivery via glucose sensors is desirable but indwelling sensors present biocompatibility problems. Implanted insulin pumps have suffered from long-term incompatibility of insulin with pump surfaces. Promising advances have however been achieved in design of insulin molecules to prevent hexamer formation and improve absorption rate or to prolong absorption time to mimic basal insulin delivery between meals. Not surprisingly, Professor Horne's specification of an ideal insulin delivery device : diameter 10μm, 107 per person, multiple inputs, fast response, no calibration, lifespan 70 years, powered by the measured (glucose) molecule fitted the Islet B-cells of the pancreas and turned attention once more to the potential of cell encapsulation technology.

Dr David Chaplin from the Gray Laboratory, Cancer Research Trust described the opportunities for targeting tumour epithelium so as to cause shut-down of the tumour vascular function leading to secondary tumour cell death. Significant selectivity between tumour and normal tissue response is the key to effective targeting. Combretastatin (A-4 disodium phosphate) was found to cause vascular shut-down at 1/10 the maximum tolerated dose and short in vitro drug exposure resulted in long-term anti-proliferative/cytotoxic effects against proliferating but not quiescent endothelial cells. The potency of combretastatin A-4 was convincingly illustrated by an impressive video recording of progressive vascular shut-down and tumour necrosis in vivo in experimental models.

The coffee break provided valuable extra minutes for Dr Friederick Rudenbekke to reach the lecture theatre after flying in from Germany as a late replacement for Dr DeGrande of 3M. The talk on novel transmucosal (TMD) and buccal drug delivery systems centred on the advantages of 3Ms 'Cydot' adhesive patch devices which are positioned on the gingiva of the gum. The system has been used to deliver melatonine, buprenorphine and low Mw heparin and can provide rapid or sustained delivery, good dose response and reproducibility. Other advantages include low inter-subject variability and avoidance of first pass liver metabolism. An intriguing future prospect raised by Dr Rudenbekke involved TMD of therapeutic proteins and peptides.



The scientific session was brought to a close by Dr Glynn Wilson of Access Pharmaceuticals who described some of the challenges facing the development of novel polymer therapeutics. In particular, polymer conjugates as pro-drugs or as components of particulate systems had been shown to provide a number of opportunities for improving drug efficacy by exploiting disease-related physiological changes (eg 'leaky' tumour endothelium) and specific drug release mechanisms. However the successful translation of innova-

tive research into commercial products necessitated integration of basic research with essential development activities. These included detailed safety assessments, patent protection, pre-clinical and clinical testing and education of industry and clinicians.

An extremely interesting meeting, notable for the high level of audience participation through enthusiastic questioning of the speakers, was closed by Professor Wilson. The two winners of the £500 prizes for best posters were Aminul Islam from the Dept. of Pharmaceutical and Biological Sciences at Aston for 'Studies on uptake and sub-cellular trafficking of antisense oligodeoxynucleotides using self assembling cationic lipids as delivery systems' and Alison Potts from the Dept. of Pharmaceutical Sciences, University of Strathclyde for ' In vivo determination of the oesophageal retention of smart hydrogels'.

Alan Coombes

Report on the 5th International CRS Symposium in Las Vegas

The society celebrated its' 25th year at the Mirage Hotel in Las Vegas on June 21st, combining with the 1st Consumer and diversified products conference. Keynote addresses were given by Eigler, Shaw and Anderson to the largest audience the CRS meetings have attracted so far. The CRS this year released the proceedings on CD and book. CD is a great idea if you really want to lug a portable around with you. Anyway, just a few pearls from the sessions I attended in between losing money on the machines.

Jane Shaw of AeroGen in California addressed the growth of small companies and identified future challenges for the relationships between small companies and the larger risk-averse pharmaceutical company. In her analysis, the average small company holds two platforms, which if they have sufficient possibility for diversity, fuels development and the energy hump for capitalisation. Overall, she was fairly upbeat about the future for small pharmaceutical companies, provided that appropriate niche markets could be identified.

A collaboration between Purdue University and Cedars-Sinai Medical Center has focused on coated metallic scaffolds (stents) in a novel delivery of antiproliferative agents. Professor Eigler reviewed developments in angioplasty, a technique for revascularisation of stenosed coronary arteries, 20 – 50% of patients require surgical intervention within the first 6 months to address restenosis. Restenosis is partially prevented by placement of stents in the vessel lumen. The long term aim is to reduce restenosis by local delivery of antiproliferative agents targeted against proliferating vascular smooth muscle cells. Eigler and colleagues have examined the delivery of exogenously synthesized ribozymes (RNA with endonuclease activity) targeted to enzymatically cleave cell cycle regulating cycline mRNA. This will prevent growth of vascular smooth muscle cells occluding the artery. The alternative approach, also under investigation is to deliver the gene cDNA that encodes for the in vivo synthesis of specific ribozymes. The authors have prepared the cDNA of pig PCNA ribozyme and have demonstrated transfection of pig coronary arteries with locally delivered constructs. The team plans to compare ribozyme delivered directly by stem vs. local catheter delivery.

As usual, transdermal delivery attracted a significant session at the conference and Dr Elias of the Department of Dermatology at UCSF opened the session with a consideration of the structure of the stratum corneum. This barrier is a two- component system of lipid-depleted comeocytes embedded in a multi-lamellar, lipid-enriched extracellular matrix. Formation of this matrix is a multi-step

sequence, beginning with the synthesis of the three lipids, cholesterol, ceramides, and fatty acids. This is followed by packaging of these lipids as their precursors, along with catabolic enzymes, within lamellar bodies. Each step of the sequence is tightly regulated by alterations in barrier requirements allowing for rapid restoration of barrier homeostasis after most types of acute perturbation. The regulatory signals that link the SC with the nucleated layers, thereby driving the epidermal metabolic apparatus, are beginning to be characterized. Considerable evidence suggests that they may reflect epidermal injury as an inevitable accompaniment of barrier disruption; i.e. neither epidermal hyperplasia nor inflammation are prevented by occlusion after barrier disruption. Thus, barrier-derived signals can initiate pathophysiological alterations and perhaps recruit disease-specific inflammatory components.

In vivo biocompatibility studies play an important role in determining the safety and efficacy of devices. Professor Anderson, a pathologist who advises the FDA, addressed issues on the biocompatibility, efficacy and safety of implanted controlled release systems. He approached the topic with a review of the inflammatory and wound healing responses. Inflammation, wound healing and foreign body responses are generally considered as parts of the tissue or cellular host responses to injury. Injury is initiated by the injection, insertion or implantation of materials. Reaction is tissue and organ specific and varies between species. Unravelling these factors is important in understanding the biocompatibility of materials and physical trauma has to separated from chemical injury. Dimensions are important – for example injectable systems with dimensions < 10 μ may undergo phagocytosis by macrophages in the granulation tissue and foreign body reaction; whereas larger microspheres may initiate a foreign body reaction with macrophages and foreign body giant cells on the surface of the particles. At the other extreme, larger devices may have a foreign body reaction similar to larger microspheres plus a surrounding fibrous capsule consisting of fibroblasts and collagen. The development of delivery systems for peptides, proteins and other may affect the structure or function of the immune system. As a result of these and other types of devices which may potentially exhibit immunotoxicity, an adverse effect adverse if it impairs humoral or cellular immunity. Regulatory agencies have focused on identification of immunotoxicity as a component of biocompatibility or safety evaluation, and this aspect of the device (dimensions and materials) has to be considered at an early stage of development.

Clive Wilson

UKCRS joins with Pharmaceutical Sciences Group……

The first symposium held jointly between the UKCRS and the Pharmaceutical Sciences Group (PSG) was a great success. The 1 day symposium discussed some of the new methods of drug delivery and outlined some of the problems of moving from the laboratory to a fully-fledged product. It was held last September in Scarborough and was part of the "new look" British Pharmaceutical Conference. The symposium took the form of invited speakers from all parts of the Globe and a poster session. The symposium was jointly chaired by representatives from both the PSG and UKCRS. It was well attended by both recognised scientists and younger researchers. A full report is available in The Pharmaceutical Journal, Vol 259, p 553 -555.

We look forward to our next joint symposium with the PSG (this time as the UKICRS) - "New Strategies for Formulation and Delivery - From Concept to Clinic" to be held in Eastbourne on 9 & 10th of September this year as part of the 135th British Pharmaceutical Conference. The symposium has been extended to 2 days to allow younger presenters the opportunity to present some of their work orally. It, again, promises to be an interesting and exciting two days with a range of international speakers discussing some of the hot topics in controlled release.

Let's hope the weather and social is as good (or better than) Scarborough as well!!!
(Both the Cavalier and Buccaneer, a stone's throw from the Conference centre, are highly recommended….- keen tennis players should bring their rackets and test their game on Devonshire Park's world famous grass courts which include the old Wimbledon No. 1 court……!!??.)

Marianne Ashford

5th Annual UKICRS Symposium - Aston 1999

The fifth anual meeting will be held in the School of Pharmacy at Aston University on Jan 8th, 1999. The theme of the meeting will be "Polymeric drug delivery into the next millenium". The local organisers: Dr Saghir Akhtar and Dr Alan Coombes, have arranged a star studded cast so it should be an excellent meeting. Remember to get your students to come along. As last year, we will be giving travel prizes for the best posters - the CRS fee for the Boston meeting will be waived for the winners, so it's a subsidised trip to the States. Further details will be available very soon.

CRS Poster Prize Winners

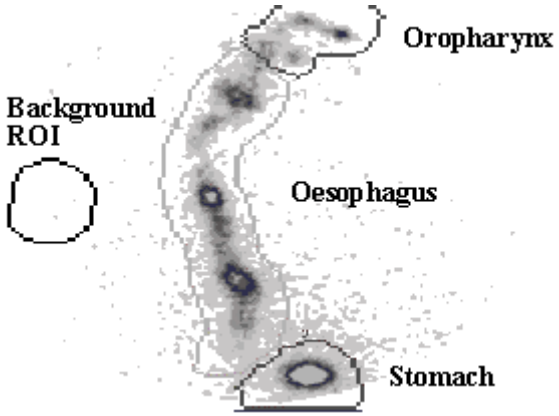
The two winners of the poster prizes were Alison Potts of the Department of Pharmaceutical Sciences,Strathclyde and Aminul Islam of the Department of Pharmaceutical Sciences, Aston. The prizes were free registration for the Las Vegas meeting and £500.,towards travel costs. The posters are featured in the following articles

Alison Potts and colleagues 'In vivo determination of the oesophageal retention of smart hydrogel', Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, Scotland

Gastro-oesophageal reflux is an extremely common disorder affecting an estimated 30% of the general population at some time in their lives. Current therapies primarily address the problem by reducing the acidity of the refluxed material, or by forming a floating "raft" on the gastric contents which acts as a mechanical barrier to reflux. These agents have varying degrees of success. The concept of coating the damaged oesophagus with a material, which is resistant to acid damage, to our knowledge has not previously been explored. This study examined the potential of a hydrogel, which has the property of temperature-dependent gelation, to adhere to the oesophageal mucosa.

Experimental methods
Smart Hydrogel (MedLogic Biomaterials Inc USA), a block copolymer (poly(oxyethylene-b-oxypropylene-b-oxyethylene)-g-poly(acrylic acid)) was used in this study. The polymer was radiolabelled by inclusion of ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). Simple viscosity studies demonstrated that the labelling procedure did not affect the viscosity of the gel. 5mls of the radiolabelled hydrogel was administered to the mouth of each subject using a dosing syringe whilst seated by the gamma camera. As the subject was instructed to swallow, dynamic imaging of the head, oesophagus and upper stomach was performed. Immediately following administration, approximately 65% of the hydrogel was seen to pass into the stomach within 5 seconds. 15% of the administered dose displayed prolonged retention in the oesophagus. The mean value for the retained fraction after 10 minutes was 13% of the administered dose.

Figure 1. Scintigraphic image of the ^{99m}Tc-DTPA labelled formulation in the oesophagus, ten minutes after dosing in one subject.



This pilot study successfully highlights the potential role of the temperature sensitive gel as both a drug delivery system and as a protective oesophageal coating. Extended retention within the oesophagus would be of great value as a platform for a localised drug delivery system, giving a new target for controlled release therapies.

Aminul Islam won the other prize for his poster entitled "Cellular uptake, sub-cellular trafficking and efflux of antisense oligonucleotides using self-assembling cationic liposomes as delivery systems'. A precis of the article follows:

Antisense and gene therapies represent formidable tools for the treatment of serious and incurable diseases in the near future. Dr Islam's work has mostly involved the use of antisense oligodeoxynucleotides (ODNs). These are short single strands of DNA which are sequence-specific inhibitors of gene expression. Antisense molecules are currently undergoing evaluation for the potential treatment of several forms of cancer and viral diseases. However, several limitations to the development of ODNs as inhibitors of gene expression in the clinic have become apparent. These include poor biological stability, a failure to elucidate the mechanism of action, and their inefficient delivery to target cells.
ODNs are reported to enter cells predominantly by fluid-phase endocytosis. These routes of cellular entry are generally highly inefficient, typically yielding very low intracellular concentrations. Furthermore, these uptake mechanisms usually lead to accumulation within endosomal/lysosomal compartments which prevents much of the administered ODN dose from reaching the desired genetic targets in the cytosol and/or nucleus. Delivery strategies such as the use of self-assembled cationic liposomes (phospholipid vesicles) have been employed in an attempt to enhance both cellular selectivity and uptake of antisense ODNs. Cationic liposomes which consist mainly of a positively charged lipid with a neutral lipid at a certain weight ratio form stable complexes by intercalating with ODNs; the interaction involved is of an electrostatic nature involving the negatively charged sugar phosphate backbone and the surface of the liposome. Using a combination of fluorescence microscopy, electron microscopy and efflux studies with radiolabelled ODNs, the group has shown that cationic lipid (Lipofectamine)-ODN complexes alter the intracellular trafficking and biodistribution of PS ODNs in cultured C6 glioma cells. Lipid-ODN complex at a 1:1 charge ratio caused the greatest increase in cellular association while at a charge ratio of 1: 8 and 1: 10 the complex produced the poorest cell association. On examining the physicochemical parameters such as surface charge and particle size of the Lipid-ODN complexes, it was evident that uptake was dependent on the charge ratio of the complex. Particle size measurements indicated that optimal cellular association occurred with those complexes which exhibited a larger diameter of between 200 to 500nm. However there was little correlation between zeta potential measurements and cell association efficiency. Perhaps a mixed population of

complexes, with differing physicochemical and cell association potential, may be present in the various charge ratios and measurement of the zeta potential only reflects their overall properties, and not necessarily those of the population causing efficient cell association.
Intracellular distribution and trafficking of ODNs was monitored using Transmission electron microscopy. Biotinylated PS-ODNs were incubated with C6 glioma cells and detected by immunolabeling with gold-tagged anti-biotin-antibodies. The TEM analysis confirmed the presence of free PS ODN within vesicular bodies thought to be either endosome or lysosome like structures. Free PS ODN was shown to escape by a mechanism involving membrane disruption which is dissimilar to that suggested for complexed PS ODN, thus proposing the existence of specific mechanisms of endosomal release for each species i.e. free and complexed ODNS. Further studies in understanding the uptake and trafficking of nucelic acids will have important implications in relation to developing an optimised self assembling liposomal delivery system for potential use of ODNs as both biological tools and clinical therapeutic agents.

Role of local chapters

At the international CRS meeting in Las Vegas, representatives of the local chapters met to share experiences on the role of the local chapters in the CRS and methods of increasing membership. The organisation continues to grow globally, with creation of new chapters in Scandinavia and the former Eastern European countries (Slovenia). Not to be left out, the first student-based CRS organisation was created in the U.S. at Purdue University. These developments fuel the engine by which the society evolves and each few years the society undergoes a reappraisal of the conference and it's activities. The current Board of Governers are keen to signal to Professor Tom Kissel (the incoming president of the sociey) of possible directions which the society should take. Many feel that the conference is too intense and compact and the conference should be extended to three and half days.

As expected, the Las Vegas meeting attracted a record number of posters and the committee is now considering methods of keeping this under control. Interesting suggestions include restructuring the symposium to allow more time for poster-viewing, selecting posters for podium discussion and of course, establishing a more rigorous policy for accepting contributions.

More colloboration across local chapters was raised at the Stockholm meeting, and sure enough, some of the organisations have taken the hint. Most of the established local chapters are now active, like ourselves, in raising awareness of the CRS activities by contributing to national symposia with like-minded organisations. Some chapters are looking for even tighter links and in October 1999, the CRS local chapters of the mediterranean countries (Greece, Israel, Italy, Spain, Portugal, Slovenia) will organise a symposium entitled 'Drug Delivery for the third millenium' This is viewed with some apprehension by the parent organisation, as such meetings will be of a size and near enough in scheduling to the annual meeting of the CRS to compete for scientists (and perhaps, advertising revenue).

Tom Kissel has signalled very clearly that he expects more control at the grass-roots level which means that local chapters will have a say in the activities of the society. Our meetings do give the committee an opportunity to identify future speakers for the international meeting and make our American colleagues cognisant of European Science. Opportunities for extending the number of speakers at the national conference will be provided by establishing mini-symposia - let's make sure UKICRS is adequately represented.

Clive Wilson

UKICRS 2000 Winter Meeting In Ireland

The first conference of the merged UKI-CRS to be held in Ireland has been provisionally set for January 10th-11th, 2000. This will be the first conference under the auspices of CRS to be held there since the memorable CRS Ireland meeting in 1995. The conference will take place at historical Trinity College Dublin, in the heart of Dublin City, a location which doubles as the research home of Elan Pharmaceutical Technologies. The theme of the meeting will be "Novel Vaccine Formulations and Delivery Systems," and the organisers and co-chairs are Dr. David Brayden (Elan) and Dr. Alan Coombes (University of Nottingham). As in the case of the CRS Ireland 1995 conference, the organisers plan to publish a book of articles from the invited speakers and abstracts from all contributors. Details of the programme, housing and transport will be advertised and sent to all members of UKI-CRS in early 1999. We can already assure prospective attendees that we can guarantee some big name speakers even at this early stage. And of course it goes without saying that the social side of things will be a very high priority !

Boston Meeting 1999

The 26th Annual meeting will be held at Boston Marriott Copley Place, Boston, Massachusetts, USA. Dates for your diary : Symposium and Exhibit: June 21-23; Workshops: June 24-25. The meeting will be cochaired by Vladimir Torchilin, Massachusetts General Hospital, USA and Francesco Veronese, University of Padova, Italy

PLENARY LECTURES

Rakesh Jain, Harvard Medical School, USA
Role of Physiology in Drug Delivery into Tumors

Robert Langer, Massachusetts Institute of Technology, USA
Polymeric Biomaterials: From the Laboratory to the Clinic and Future Challenges

Nicolai Platé, Russian Academy of Sciences, Russia
Polymeric Hydrogels as Matrices for Drug Targeting

Helmut Ringsdorf, University of Mainz, Germany
Polymer Therapeutics and Supramolecular Systems Toward the Millennium

MINISYMPOSIUM

Minisymposia run parallel with podium sessions and are comprised of lectures given by invited speakers. The lectures vary from 45 to 60 minutes each and include an opportunity for questions and answers. The topics this year are:Vaccines, New Materials and Vehicles for Controlled Delivery, Gene Delivery and Gene Therapy

There will be a couple of new features this year including the Capsugel Graduate Student Minisymposium: Innovative Aspects of Controlled Drug Release and the soapbox session. The soapbox session will run on Sunday afternoon, June 20. There will be many company executives

presenting their technologies, products, ideas, suggestions, services, etc., limited to the field of controlled release. Space is limited! Contact CRS for more information.

WORKSHOPS

Cancer Therapy and Drug Delivery Systems
Chair: Alberto Gabizon, Hadassah Hebrew University Hospital, Israel

Development of Products for the Delivery of Protein and Peptide Drugs
Chair: Mark A. Tracy, Alkermes, Inc., USA

Controlled Release Technology for Veterinary Products
Co-chairs: Susan Cady, Hoechst Roussel Vet, USA;
Michael J. Rathbone, InterAg, New Zealand

UKICRS on the Internet

In addition to being the first pharmaceutical organisation to develop a web site, the UKICRS can also take pride in being the first organisation to broadcast a pharmaceutical conference live on the Internet (see report of the January 1998 meeting). The UKICRS web pages have recently been updated and include all the latest UKICRS news. Information on the 3rd and 4th UKICRS meetings in Manchester and London are also available. A new mailing list has also been created for those of you interested in the activities of the UKICRS. To join the list simply go to our web page and select the mailing list. You can join/leave using a simple on-line form.You will be kept informed of UKICRS and CRS activities. There is also a controlled release discussion group available through the UKICRS site. The **NEW** URL (address) of the UKICRS page is:

http://www.pharmweb.net/ukcrs.html

Annual CRS Symposia Dates

June 20th - June 25th, 1999, Boston, Massachusetts, USA, 26th International Symposium on Controlled Release of Bioactive Materials

July 7th - July 13th, 2000, Paris, France, 27th International Symposium on Controlled Release of Bioactive Materials

Other Meetings

Fourth European Congress of Pharmaceutical Sciences,
Milan, Italy, 11th - 13th September 1998

Pharmaceutical Water Systems: Principles in Practice,
The St George Swallow Hotel, Harrogate, UK, 5th - 8th October 1998

5th EUFEPS Conference: Optimising Drug Development: Fast Tracking into Human,
Kurhaus, Wiesbaden, Germany, 7th - 9th December 1998

2nd Congress of Pharmaceutical Sciences,
Faculdade de Ciências Farmacêuticas de Ribeirão
Preto, Universidade de São Paulo, Brazil, 27th - 31st March 1999

59th International Congress of FIP,
Barcelona, Spain, 5th - 10th September 1999

Millenial World Congress of Pharmaceutical Sciences,
San Francisco, California, USA, 16th - 20th April 2000

Information on these and other conferences relevant to the field of controlled release may be found on the PharmWeb pages on the Internet at the following URL:

http://www.pharmweb.net/conferences.html

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Joining the CRS

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