UKICRS

NEWSLETTER 2013

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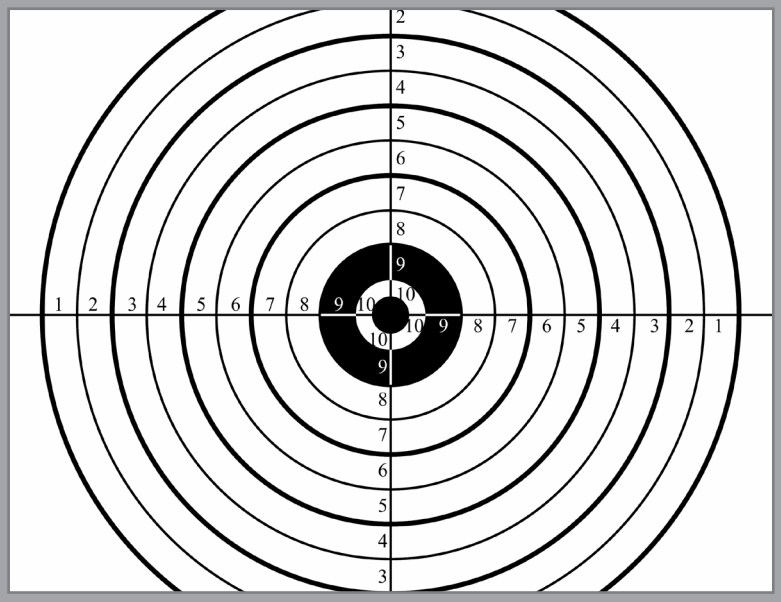

UNITED KINGDOM AND IRELAND CONTROLLED RELEASE SOCIETY

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UKICRS is the leading national organisation in the UK and Ireland for the promotion and advancement of the science of controlled release and drug delivery technology.

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A WORD FROM THE CHAIR

It's been another busy year here at UKICRS! We ran our first ever essay competition, with the top prize of £500 going to James Norman from Georgia Institute of Technology and second place to Sagidi Bibi of Aston University. Both essays are featured in the Newsletter and I'm sure you'll enjoy reading them. We've also started to plan our new summer studentship initiative, and for which we are seeking industrial sponsors to help support up to three 6-week studentships during the summer of 2014. Please e-mail ukicrs@ukicrs.org if you are interested in this scheme.

In April, UKICRS hosted its 20th annual symposium at Reading University. Vitaliy Khutoryanskiy and his team worked extremely hard to make it a huge success. The format was similar to last year, comprising a one–day technical workshop, a symposium dinner followed by a full day dedicated to the scientific presentations. The symposium report is published here in the Newsletter. Well done to all who presented, and especially to the podium and poster prize winners, Giovanna Sicilia (University of Nottingham) and Jit Wilkhu (Aston University), respectively.

UKICRS participated in several other conferences during the year including our 'Bugs and Drugs' sessions at 2012 UKPharmSci and a joint meeting with IChemE. And of course, we are looking forward to this year's UKPharmSci in Edinburgh.

We hope you like the fresh new look for our newsletter. The team has done a superb job in putting together a mix of interesting articles in a highly readable format. Many thank to our sponsors – Stable Microsystems, NanoSight, Surface Measurement Systems, Caleva Process Solutions, Meritics, Fisher Scientific, Presearch, Merrow Scientific and Biopharma Process Systems. Finally, a very big 'thank you' to all our members. Without your interest and support, we wouldn't do what we do!

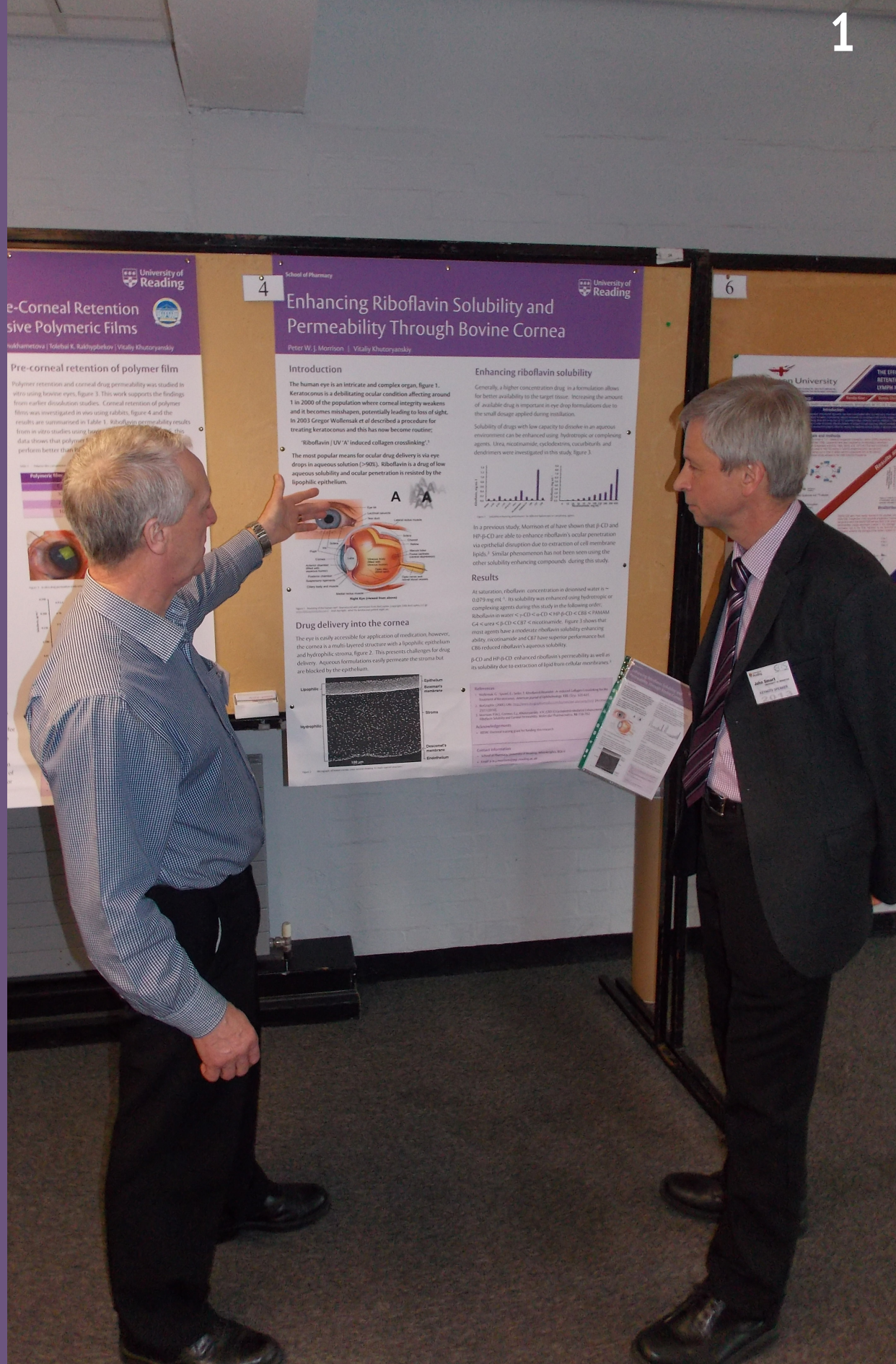
Woei Ping Cheng

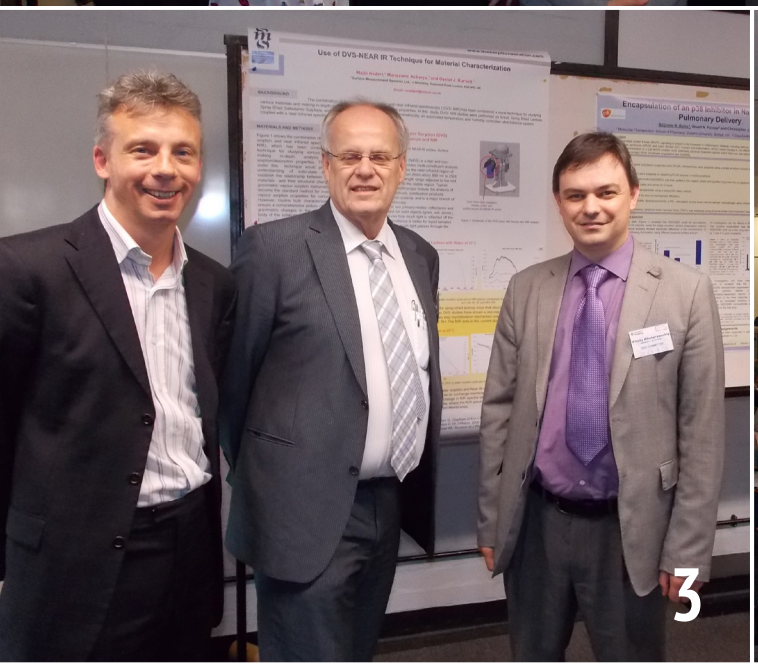
UKICRS **SYMPOSIUM** 2013

This year's annual UKICRS Symposium, entitled 'Future Pharmaceutics – Innovation in Controlled Release', was hosted by the University of Reading 15-16 April 2013. The first day of the symposium was geared towards industrial exhibitors, including Stable Microsystems, NanoSight, Surface Measurement Systems, Caleva Process Solutions, Meritics, Fisher Scientific, Presearch, Merrow Scientific and Biopharma Process Systems, who showcased their products and technologies through a series of short talks and exhibitions.

The scientific programme for the second day included two keynote speakers, eleven talks from postgraduate students and postdoctoral researchers, and 51 poster presentations. Prof Wim Hennink (Utrecht University, Netherlands) kicked off the morning session with a keynote lecture covering aspects of his research on the development of novel biodegradable polymers for protein delivery. He discussed the possibility of using these polymers as in situ gelling temperature-responsive systems for delivery via injections. The keynote lecture was followed by two short presentations from Gayle Wilson (Keele University), speaking about targeted drug delivery via the PepT1 transporter, and Nooshin Daveshpour (Queens University Belfast), focusing on the development of novel sialic acid-coated PLGA nanoparticles for the treatment of acute lung injury.

After the coffee break, three further short presentations were delivered. Jit Wilkhu (Aston University) discussed transit of bilosomes and subunit antigen via the oral route, Dolores Serrano Lopez (Universidad Complutense de Madrid, Spain) talked about novel amphotericin B controlled release formulations and their in vitro/in vivo studies, and Hamid Merchant (University College London) described the application of automatic pH control system to simulate pH along the the entire gastrointestinal tract.





1. Peter Morrison (PhD student, University at Reading) discusses the details of his poster with Prof John Smart (University of Brighton). **2.** Postgraduate speakers and session chairs. **3.** Prof Karl Malcolm (Queen's University Belfast), Prof Wim Hennink (University of Utrecht) and Dr Vitaliy Khutoryanskiy (University of Reading) during the poster session. **4.** Prof Wim Hennink answers questions following his keynote presentation. **5.** A busy poster session!

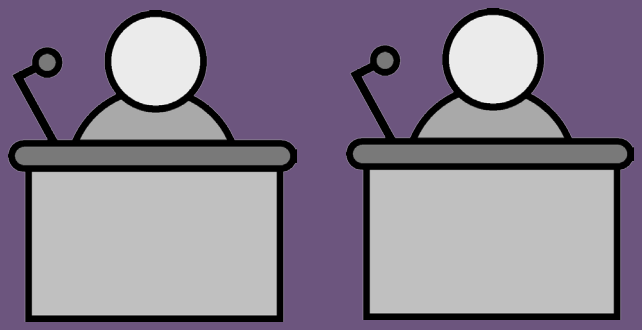
Following lunch and poster presentations, the afternoon session was opened by Prof John Smart (University of Brighton) who provided an excellent overview of drug delivery via the oral cavity, with a particular focus on mucoadhesive polymers. He highlighted the wide range of formulations developed for buccal drug delivery (tablet, patch, liquids and semisolids) over the last 30 years, of which only a small number have found their way on to the market.

PhD student Charlie Chen (University of Cambridge) discussed the application of direct multi-nuclear magnetic resonance imaging for the study of controlled drug release sytems – Charlie has also produced a related article here in the Newsletter (p17) . Giovanna Sicilia (University of Nottingham) presented on the synthesis of a novel dual stimuli responsive polymer-DNA hydrogel, cross-linked via DNA base pairing and disulphide bonds. Samuel Bizley (University of Reading) described the application of layer-by-layer deposition approach for the development of novel enterically coated microparticles. After more coffee and posters, three postgraduate students closed out the final session of the meeeting. Sukrut Somani (University of Strathclyde) gave a presentation on transferrin-targeted dendrimers for gene delivery to the brain. Louise Harris (University of Sunderland) discussed some opportunities in formulating slow release products for farmed ruminants and also talked about knowledge transfer partnership schemes. Fiona McCartney (University College Dublin) described her investigation of sugar esters as novel intestinal permeation enhancers.

The meeting was concluded by the Symposium chair Dr Vitaliy Khutoryanskiy (University of Reading), who announced the winners of the best talk and poster awards. The prize for best oral presentation was awarded to Giovanna Sicilia (University of Nottingham) for her talk entitled 'Reducible polymer DNA-hydrogel as a dual switchable release gate', while the award for best poster was awarded to Jit Wilkhu (Aston University, 'Effect of vesicle size on uptake of bilosomes and antigen by the Peyer's patches').

This meeting report was prepared by Dr Vitaliy Khutoryanskiy.

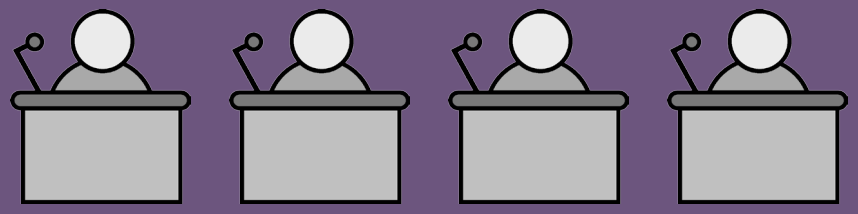
Symposium by numbers ...



Wim Hennink

John Smart

2 keynote speakers

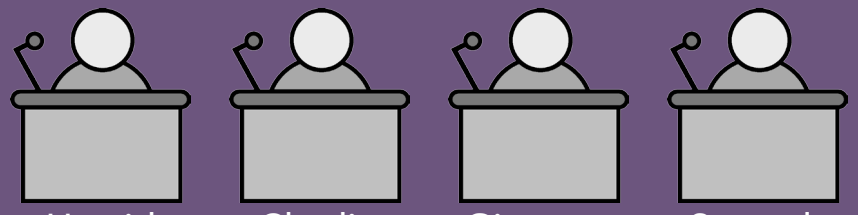


Gayle Wilson

Nooshin Daveshpour

Jitinder Wilkhu

Dolores Lopez



Hamid Merchant

Charlie Chen

Giovanna Sicilia

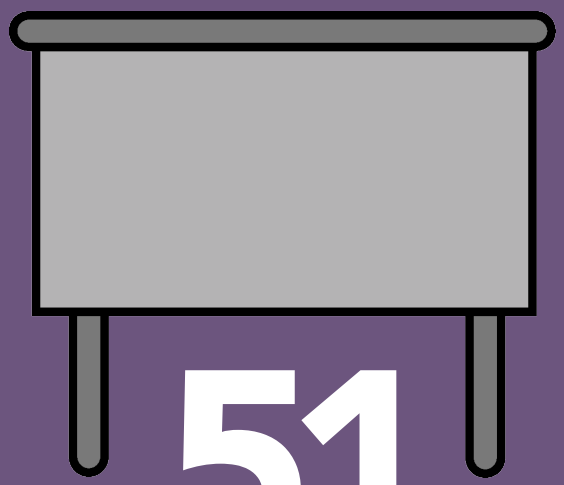
Samuel Bizley

Sukrut Somani

Louise Harris

Fiona McCartney

11 postgraduate speakers



51 poster presentations

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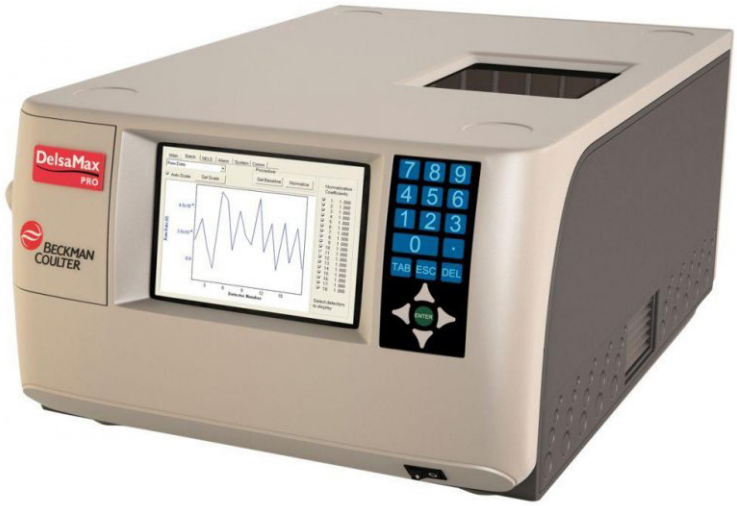

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Visual impairment & Blindness: Treatments, Challenges & Future Developments

Raj Thakur
Queen's University Belfast
E: r.thakur@qub.ac.uk

Visual impairment and blindness are potentially the most devastating health problem worldwide. The World Health Organization estimates that globally about 285 million people are visually impaired; 39 million are blind and 246 have reduced vision.[1] Visual impairment and blindness is one of the major health challenges facing the NHS, which is predicted to cost the UK economy £7.9 billion by 2013.[2] Here, in the UK, every day around 100 people start to lose their sight.[3] As the lifespan of our population and advances in health care improve longevity, there will be an increasing number of people who will be at risk of developing visual impairment, and, therefore, the economic impact of visual impairment will continue to grow.[4]

Most of the eye diseases that cause visual impairment typically originate in the posterior segment of the eye (or back of the eye) and include age-related macular degeneration (AMD) (Fig. 1), diabetic retinopathy (DR), diabetic macular edema (DME), uveitis and retinitis.[5] AMD is the leading cause of blindness among ageing populations (aged 60 and above) in Europe, USA and Asia.[7] Every year nearly 23,000 and 100,000 people lose their vision due to AMD in the UK and the USA, respectively. In the UK, AMD affects more than 600,000 individuals, but with an aging population it is predicted that this figure could rise by a quarter to nearly 756,000 by 2020.[8] The AMD Alliance International research reports the worldwide cost of visual impairment due to AMD alone will be US$343 billion including US$255 billion direct health care costs.[9] At the recent ARVO 2013 conference, a study conducted by researchers from the University of Illinois at Chicago indicated that the patients with AMD are at increased risk of mortality.[10] Additionally, nearly 200,000 individuals in the UK currently experience vision loss as a result of DME and it is estimated that in England every year 4,200 people are at risk of blindness due to DR and there are 1,280 new cases of blindness caused by DR.[11] The number of people with DR and/or DME is likely to increase due to a rise in the number of diabetic patients. Moreover, the growing population affected by sight-threatening eye diseases has resulted in a multibillion-dollar market opportunity with sales for AMD, DME, uveitis/ocular inflammation, DR and glaucoma drugs already surpassing $600 million, $2 billion, $ 500 million, $ 1.5 billion and $5 billion respectively.[12]

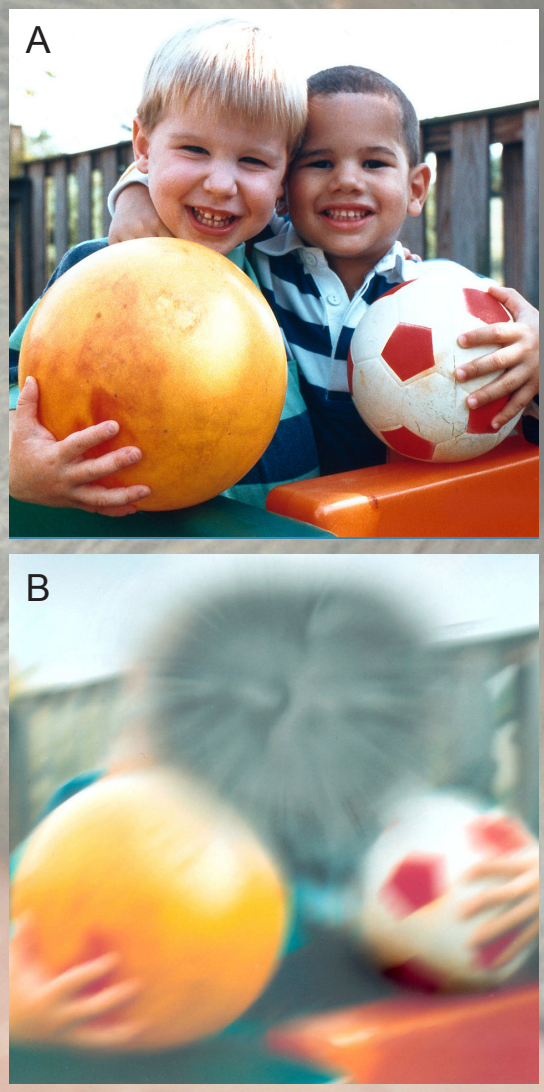

Figure 1. Digital images of (A) normal vision and (B) vision of patient affected with AMD.[6]

Current treatment options and challenges

Delivery of drug molecules to treat visually impairing ocular conditions that originate in the posterior segment of the eye has a major challenge for pharmaceutical scientists and retinal specialists. The difficulties lie with the unique structure of the eye, which restricts the entry of drug molecules to the required site of action and therefore necessitates careful selection of appropriate drug delivery methods. Figure 2 highlights the various methods for delivering drugs to the eye.[13] Topical (e.g. eye drops) and systemic (i.e. oral or parenteral) routes are easily administered; however, drug absorption through these routes is limited due to multiple barriers of the eye. For example, topical administration of eye drops results in low ocular bioavailability (< 5%) therefore necessitating frequent administration and their effective usage may be restricted

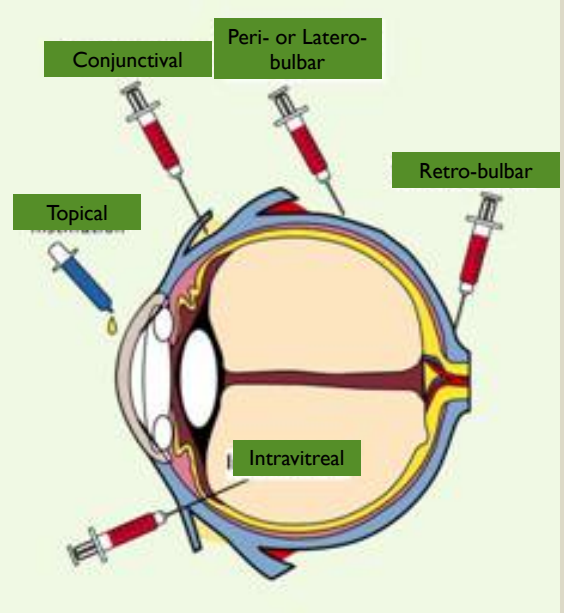

Figure 2. Schematic representation of different routes and methods of ocular drug delivery.[13]

to diseases that affect the front of the eye. Due to these biological barriers, systemic administration is generally given at very high doses with increased potential for systemic toxicity.

Intravitreal and periocular routes are more promising alternatives and have become a standard method of drug delivery to the back of the eye. The intravitreal route involves direct injection of medications into the eye and this method is most commonly employed to treat diseases affecting the back of the eye. Nevertheless, due to the chronic nature of these conditions, patients require frequent injections, performed using conventional needles (e.g. 26 and 27 G needles). Even though intravitreal injections provide direct delivery of therapeutic agents into the eye, this method is invasive and associated with severe side effects, such as high therapeutic dosage-induced ocular toxicity, pain and discomfort, vitreous haemorrhage, elevation of intraocular pressure, retinal detachment, endophthalmitis and cataract development.[14-16] On the contrary, the periocular route that includes retrobulbar, peribulbar, subtenon, subconjunctival, and transscleral routes (Fig. 2) is considered to be less painful and the most efficient route of drug delivery to the posterior segment of the eye that poses reduced risk of endophthalmitis and retinal damage.[17] However, intravitreal injections of anti-vascular endothelial growth factor (VEGF) (e.g. ranibizumab, bevacizumab and aflibercept) and steroids (e.g. triamcinolone acetonide, flunicanolone acetonide and dexamethasone) have remained a common and widespread treatment method for various retinal disorders. For example, Table 1 gives information of commonly used anti-VEGF therapy for patients suffering with AMD. Other modes of treatment in AMD patient include photodynamic therapy and laser photocoagulation. Similarly, steroids and anti-VEGF treatments has been used to treat DME and DR. For example, a non-licensed intravitreal triamcinolone acetonide (Kenalog®, Bristol-Myers Squibb) has been in use, to treat DME, for over 10 years.[18]

A major challenge for pharmaceutical scientists is the development of formulations capable of maintaining drug levels at the target ocular tissues for prolonged periods, thereby reduce the frequency of injections into the eye. Reducing injection frequency and making the treatment minimally invasive are still unmet needs in treating sight-threatening ocular diseases. However, once developed, they will significantly reduce global healthcare costs. For example, currently anti-VEGF therapy of Lucentis®, for a single wet AMD patient, costs £18,300 for 24 injections over 2 years to the NHS in the UK and $23,000 per year for a patient in the USA.[21,22]

With the problems associated with frequent intraocular injections focus has been shifted in engineering sustained-release drug delivery systems, which will improve treatment of back of the eye diseases. To this end pSivida, a global leader in developing sustained release drug delivery products for treatment of back of the eye diseases, has developed three of the only four products approved by either the USA or EU for the long-term sustained release ocular drug delivery systems.[23] Three non-biodegradable products developed by pSivida have been approved by the FDA. Vitrasert® was the first approved sustained release device for the treatment of AIDS-related (Auto immune deficiency syndrome) cytomegalovirus retinitis, in 1996, and is marketed under license by Bausch + Lomb. It contains ganciclovir which is released for 6–8 months.[24] The device is implanted by surgical procedure performed under local anaesthesia that involves a 5.5 mm scleral incision taking a total of approximately 45 min for administration. The total cost of device alone is US $ 4000 in addition to costs of surgery, anesthetic, and operating room fees can add up to approximately $2000 per patient.[25] Retisert® is the world's first approved intravitreal drug implant for the treatment of chronic non-infectious posterior uveitis. It was approved as an orphan drug by the US FDA in April 2005 and is marketed under license by Bausch + Lomb.[24] About the size of a grain of rice, Retisert® contains the corticosteroid fluocinolone acetonide. It is surgically implanted in the eye through a small 3-4 mm incision and sutured to the eye wall to release medication each day for approximately 2.5 years. It costs $18,250 for single implant with registered worldwide sales of US $ 26 million in the year 2010.[26] Iluvien® a most recently approved product to treat DME has received marketing authorization in the UK, Austria, France, Germany and Portugal in 2012.[23] Iluvien® is a tiny rod shaped implant injected into the eye by using an applicator that employs a 25G needle to provide sustained release of fluocinolone acetonide for approximately 3 years (Figure 3). Iluvien® is licensed to Alimera Sciences, Inc. and it is forecast to sell $ 409 m in 2016, with pSividia forecast to collect $45 m in royalties and Alimera $40m from sales outside the US.[27] All three implants require a second surgical intervention either to remove or to be replaced with new implant. Importantly, it will be highly challenging to remove the free-floating Iluvien® implant unlike the sutured Retisert® or Vitrasert® implants. By comparison, Ozurdex® (Allergan Pharmaceuticals) is the only biodegradable implant, approved by the FDA in 2009, which is injected into the eye and releases dexamethasone over a period of up to about six months. Ozurdex® is a costly treatment at £1,044 per implant plus £620 of admin-

Table 1. Intravitreal injections of FDA approved anti-VEGF agents in patients suffering with wet AMD.

Commercial anti-VEGF agents	Treatment strategy
LUCENTIS® (ranibizumab) Genentech, Roche	Monthly injections are given for three consecutive months, and patients should make regular doctor visits to determine further treatments.[9]
EYLEA® (aflibercept) Regeneron, Bayer HealthCare	A 2 mg dose is administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months).[19]
MACUGEN (pegaptanib sodium) Eyetech Pharmaceuticals, Pfizer	Giving every 6 weeks for up to 2 years has been shown to significantly reduce the risk of moderate vision loss in patients with all types of wet AMD.[20]

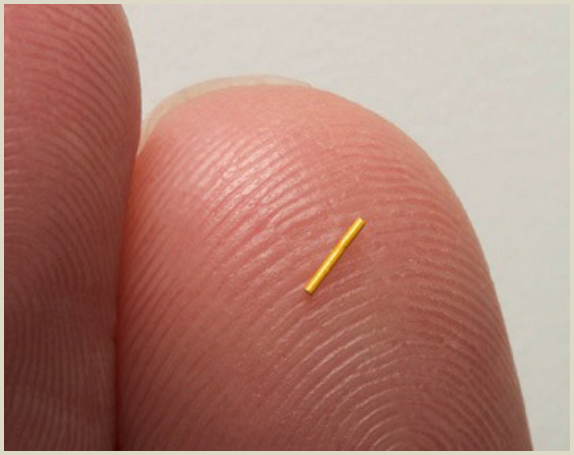

Figure 3. Iluvien is an injectable, non-erodible, fluocinolone acetonide releasing intravitreal implant for the treatment of DME.

istration costs. The maximum cost per patient per annum is an estimated £6,600.[28] Worldwide sales of Ozurdex® were observed to be $56.5 million in 2011.[29] Despite many appealing features of these devices they are associated with a greater burden of adverse effects, many of which are transient, mild, and self-limiting. However, of greater concern is an increased incidence of cataract and raised intra-ocular pressure compared with placebo. In addition, some patients will require bilateral treatment with an attendant increase in cost.

Future Developments

Currently, there is growing interest among pharmaceutical industries and retinal surgeons to deliver drugs in non-invasive or minimally invasive approaches. This delivery method will significantly improve patient compliance, reduce operation times and overcome disadvantages associated with current implants and/or intravitreal injections. To this end three non-invasive iontophoresis-based devices namely EyeGate® II (Eyegate Pharmaceuticals, Inc, USA), Ocuphor™ (Iomed Inc., USA) and Visulex® (Aciont Inc., USA) are under investigation for trans-scleral drug delivery. Aciont Inc., USA has proposed that the Visulex® device, for treating uveitis, can generate approximately $200 million within first five years.[12] However, limitations of ocular iontophoresis are potential discomfort to patients, longer wear time of the device e.g. 5 to 20 min, inadequate and sustained drug delivery of selected therapeutic agents. Furthermore, due to the chronic nature of eye disorders such as DE, AMD and uveitis, frequent use of iontophoresis is required. However, its safety in prolonged usage has yet to be established. Other non-invasive techniques undergoing research include, electroporation, electrophoresis, and photoacoustic delivery systems. Although, these non-invasive techniques can enhance patient compliance; disadvantages such as cellular damage, safety for long-term application, sustained drug release capacity, and the costs of the final device need further consideration. On the other hand, minimally invasive microneedles, which are mostly commonly applied in delivery of medications across the skin, are now under investigation in ocular delivery of medications. In January 2012, a newly formed ophthalmic pharmaceutical company i.e., Clearside Biomedical, Inc. received $4 million in venture capital funding for their research using microneedles for microinjection of drug solutions or nanoparticles into the eye, proposed to treat a range of eye diseases.[30] Other ocular drug delivery devices that are currently undergoing clinical studies include I-VationTM (Surmodics Inc - a non-biodegradable titanium implant), Rh CNTF (Neurotech Pharmaceuticals - a genetically modified human cell implants), VerisomeTM (Icon Bioscience, Inc - injectable gel-based implant).

Conclusions

It is now clear that the ocular drug delivery holds a huge market potential and with a growing ageing population this is expected to grow tremendously in the next two decades. Increasing demand for sustained drug release devices is being driven by its potential for enhanced patient compliance and reduced financial burden on healthcare system. Even though intravitreal injections currently remain in standard clinical practice, increasing demand for sustained release devices will further drive the ocular drug delivery market. However, sustained release of biologics, such as anti-VEGF agents, still remains a major challenge.

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Dr Raj Thakur is a Lecturer in the School of Pharmacy, Queen's University Belfast. His research interests are in development and evaluation of novel in situ forming controlled release implants, ocular and transdermal drug delivery using novel minimally-invasive devices.

A Brief History of the Pharmaceutical Industry

Laura M Mason, Formulation Insights, School of Pharmacy, University of Nottingham, University Park, Nottingham, UK.

The origins of pharmacy

The roots of the Pharmacy profession are traced back to 4000 BC when medicinal plants were prepared to treat the ill in Iraq. In the Antiquity and Middle Ages in the UK, chemists and druggists would prepare their own medicines based upon historical recipes. However, there was no evidence of efficacy other than what the chemist had seen work previously. Knowledge management was an ongoing concern even in the Middle Ages!

The origins of medicines

In the 1600s, there was a new trend for branded products known as 'patent medicines' which were heavily advertised and promoted as medical cures.[1] These were not patented products, but rather original recipes which the manufacturer kept secret to protect their product. Although some of these were the ancestors of medicines in use today, such as Vicks VapoRub and Phillips' Milk of Magnesia, most had no medical effect and their sellers were exposed by journalists as 'quacks'. The passage of the Pure Food and Drug Act of 1906 in the US meant that whilst patent medicines containing dangerous drugs such as opiates, alcohol and cannabis could still be sold, they had to be labelled correctly. This led to a reduction in misleading and overstated claims, as well as a decrease in sales.

The birth of the pharmaceutical companies

Some pharma companies were born out of patent medicines, such as Beechams (later GSK) who marketed the efficacious Beechams Pills Laxative until the 1950s. Eli Lily was started in 1876 when a pharmacist aimed to develop high quality medicines after observing the poor quality of the patent medicines used in the American Civil War. The vast majority of large pharmaceutical companies were originally chemical (Pfizer, Merck, Roche, Abbott) or dyestuff factories (Bayer, Novartis) in the Victorian era. The industrial revolution led to an increase in availability of chemicals, which when combined with an increased focus on science in the latter half of the 19th century resulted in the application of chemistry to help human health.

The changing face of pharmaceutical regulation

The pharmaceutical industry was largely unregulated until the 1960s,

Patent medicines: cocaine-laced toothache remedy aimed at children from 1885 (www.colorantshistory.org).

when the thalidomide crisis led to a critical rethink in the safety of medicines.[2] Thalidomide was first marketed as an anti-nausea and sleeping tablet between 1957 and 1962. It was subsequently withdrawn after being found to be a teratogen. Over 10,000 children were born with deformities after their mothers took thalidomide for morning sickness. At the time, use of medications during pregnancy was not regulated, and drugs were not thoroughly tested for potential harm to the foetus.

Before thalidomide, pharmaceutical manufacturers only had to control the quality of their medicines; there was no obligation to assess their clinical safety or efficacy. After the thalidomide disaster, the Declaration of Helsinki was published outlining standards for clinical research and requiring manufacturers to show efficacy before a medicine could be approved for clinical use. Eventually, this led to the passing of the Medicines Act 1968.

The age of the blockbuster and boom

Towards the end of the 1970s, there was a boom in the pharmaceutical industry as companies were able to patent their medicines and their methods, and a race developed to bring the next blockbuster drug to the market. Advances in technology, such as high throughput screening and molecular modelling, brought the ability to rapidly screen for potentially efficacious and pharmaceutically suitable molecules. The majority of pharmaceutical compounds were

Children with phocomelia as a result of exposure to thalidomide in-utero (http://www.thetimes.co.uk/tto/news/world/australia-newzealand/article3479163.ece).

small organic molecules, with favourable BCS classification allowing rapid development of suitable formulations. Mergers and acquisitions became common place as companies continued to expand. The industry was focused on generating big products with big profits to drive future development.

The changing face of new chemical entities

In recent years, there has been a shift in the balance of R&D pipelines from conventional small molecules to biologics, including antibody therapy and peptide chemistry. Some would say the age of the blockbuster is over. It is certainly true that companies are relying upon orphan diseases and products with smaller returns to sustain their portfolio. Future research is likely to be driven by industrial support of academia and the industry is moving back to using smaller outsourced companies with specialist knowledge of their field. Companies have needed to rationalise the products they develop, with the consequence that there is underinvestment in those research areas that generate low revenue, such as infectious diseases. This has arguable been spurred by increased manufacturing of generics driving down the cost of current therapeutics and the limited time a manufacturer has to generate a return on their research investment.

Mega-mergers and consolidation

Pharmaceutical companies have always merged in order to sustain growth. Historically, this has involved a larger company taking over a smaller one to expand the areas of expertise. However, the need to reduce rising R&D costs has led to mega-mergers where major international pharmaceutical companies, such as Pfizer and Wyeth, and Merck with Schering-Plough (both in 2009), have joined forces.

Future of the pharmaceutical industry

The pharmaceutical industry faces a new challenge moving forward. The industry relies upon medical use of its new products, with approval by bodies such as NICE in the UK being an important in recouping R&D investment. As such, there is intense secrecy to protect research results as private intellectual property (IP) until they have achieved a marketable compound. A by-product of this is an inability to share research results with each other, even within a single company, with around 50% of clinical trials data not being published. The *AllTrials* group are campaigning for all clinical trials data to be made public, irrespective of the results; currently the only pharmaceutical company to back this is GSK.[3]

The ongoing clash between privately funded companies, which rely on the generation of profits, and the public sector (NHS and government) who require efficacious medicines for the most common conditions at the lowest price, is something that the pharmaceutical industry is going to have to resolve in order to maintain growth.

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3. http://www.alltrials.net

'Keep Science Public' placard at Science is Vital Rally, 2010. Photograph: Alice Bell (www.guardian.co.uk).

Controlled release at the interface between food, pharmaceuticals and agrochemicals

November 2012 Meeting Report ● by Sam Pygall

UKICRS have a strong ethos of reaching out and collaborating with other organisations having a common interest in the science underpinning controlled release. In November 2012, UKICRS co-hosted a scientific meeting aimed at reviewing the science and technology involved in controlled release systems employed in the food, pharmaceutical and agrochemical industries. The one day meeting, organised by Serafim Bakalis (University of Birmingham) and Sam Pygall (MSD) on behalf of the Food & Drink, Particle Technology and Pharma Subject Groups of the IChemE and UKICRS, was intended to cross historical boundaries and encourage attendees to learn from the different approaches applied to common challenges accross the diverse range of industries. The event was kindly supported by MSD who hosted the event at the Discovery Centre at the MSD Head office in Hoddesdon, Hertfordshire.

The event attracted 30 delegates including a good number of postgraduate students from a variety of universities, industrialists and academics across the three sectors. Several of the postgraduate students and the industrialists (Ashland and Colorcon) took up the opportunity to bring along posters highlighting their work. These provided a useful topic of conversation during the breaks throughout the day.

Following some opening remarks from Sam Pygall (MSD and UKICRS committee member), the session kicked off with an excellent presentation by Colin Melia (University of Nottingham) which focused on controlled release in the context of the pharmaceutical industry. The session provided a comprehensive review of historical approaches used by the industry to deliver controlled release from oral solid dosage forms, including matrix, pellet and osmotic systems. There was then a shift in gears to consider future technology that may be used by the industry moving forward. In addition, Dr Melia provided an overview of his group's contributions in the oral CR area, particularly the work of Hywel Williams on the direct food effects on HPMC matrices.

Without any delay, we switched industrial sectors and focused on controlled release in the context of agrochemicals. David Stock from Syngenta provided an overview of how key elements of controlled release can be applied to the formulation design with the goal of crop protection.

Following quickly from the opening session, it was a great opportunity to see the overlap with pharmaceuticals and highlighted the value of the meeting. An illustrative slide from the talk shows the elements that needs to be considered for agrochemical formulation design.

The next talk saw UKICRS committee member Vitaliy Khutoryanskiy (University of Reading) take the podium to provide a cross-disciplinary talk on the microencapsulation for probiotics.

Blurring the lines between the pharmaceutical and food industries, the excellent talk gave some insight into the issues that need to be overcome to get probiotics effectively delivered via the oral route. The organisers (Sam Pygall and Serafim Bakalis) then closed out the morning session by providing an

industrial and academic flavoured overview of multicomponent CR systems for the pharmaceutical and food industries. Neatly summarising and reinforcing the message communicated through the earlier talks, it was clear that the issues that need to be overcome in order to develop robust CR formulations are common to all three industries.

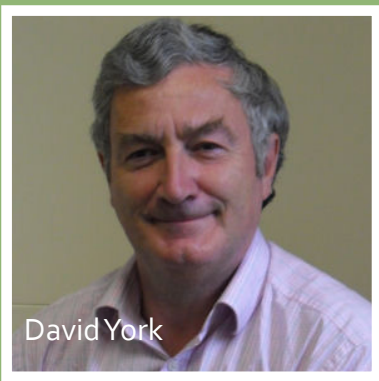
After a welcome lunch and an opportunity to view the wide range of posters on display, David York (University of Leeds) gave an overview of controlled release capsule design and manufacture. It was a great coup to secure David as a speaker for the event, given his 35 years as a research process engineer at Procter and Gamble where he has worked on a wide range of processes, mostly associated with particulates. He has extensive experience in taking projects from upstream conception through pilot plant to plant start up and production trouble shooting. His talk gave a snapshot of some of his experiences and provided great inspiration to delegates on the routes that can be taken for the practical application of lab-based science in supporting the development of commercial products.

Like the UKICRS's annual symposium (see page 4 of this newsletter), this meeting sought to provide a friendly and supportive environment for emerging young scientists in the area of controlled release to present their work to a wider audience. Abstracts from Yewande Oni (University of Nottingham), Peter Morrison (University of Reading) and Marijana Dragosavac (Loughborough University) were selected from those submitted to the meeting for focused 15 minute podium presentations on their postgraduate work. These postgraduate-led sessions were highly interactive, with questions and contributions from the entire audience.

Overall, the meeting was a huge success and helped to foster greater links with industries having a common interest in the underpinning science of controlled release. The organising committe offer their sincere thanks to MSD, the speakers and the delegates who all contributed to the success of the meeting.

As an organisation, UKICRS are very keen to seek similar opportunities for co-support future meetings in this or other areas of controlled release. If this is something you or your colleagues are interested in, please do get in touch with UKICRS (ukicrs@ukicrs.org) and we can explore the possibilites together.


David Stock

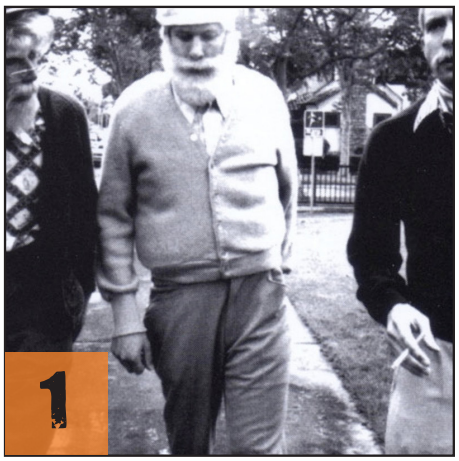

David York

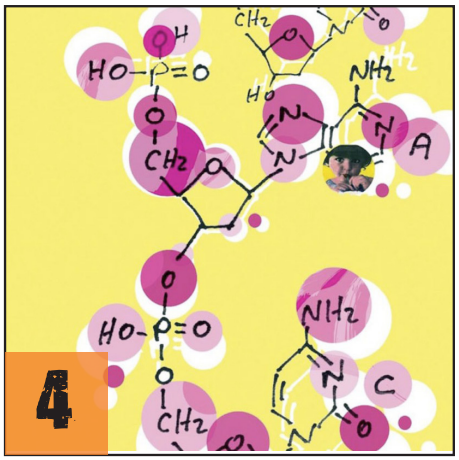

Colin Melia


Vitaliy Khutoryanskiy

9.00	Registration & coffee
9.30	Opening session: overview of controlled release in pharmaceuticals - current status and future opportunities / *Colin Melia, University of Nottingham, UK*
	Session 1
10.20	Delivery approaches for crop protection chemicals: optimising location and time of delivery / *David Stock, Syngenta Formulation Technology Group, UK*
10.55	Microencapsulation and controlled release of probiotic bacteria / *Vitaliy Khutoryanskiy, University of Reading, UK*
11.30	Coffee break
11.45	Design, manufacturing and processing challenges for multi-component CR systems / *Serafim Bakalis & Sam Pygall, University of Nottingham, UK*
12.45	Lunch / poster viewing
	Session 2
14.00	Practical considerations in the design, but more importantly the manufacture, of controlled release capsules / *David York, University of Leeds*
14.45	Coffee break
15.00	PhD student presentations / *Yewande Oni (University of Nottingham), Peter Morrison (University of Reading), Marijana Dragosavac (Loughborough University)*
16.00	Closing remarks

UKICRS Competition





The nine images show part of the cover artwork for an album, EP or single, each having some association (however tenuous) with science. Simply name the artist AND the song/album for each image. First email submission (ukicrs@ukicrs.org) with all nine correct answers wins a £100 prize. UKICRS decision is final. Competition is open to anyone and everyone ... except UKICRS committee and graduate network members.

ukicrs@ukicrs.org

Controlled release testing...

Stable Micro Systems

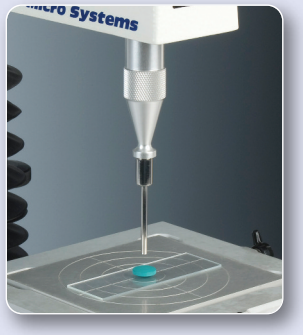
Stable Micro Systems' texture analysers open up a whole new world of advanced testing possibilities...

- *MUCOADHESION*
- *TABLET SWELLING*
- *BIOADHESION*
- *TABLET DISINTEGRATION*
- *GEL PROPERTIES*
- *TABLET STRENGTH*
- *FILM PROPERTIES*
- *FRACTURE OF MICROSPHERES*

- *RESEARCH*
- *QUALITY ASSURANCE*

- *TENSILE*
- *COMPRESSION*
- *SHEAR*
- *EXTRUSION*
- *FRICTION*
- *3 POINT BEND*

Mucoadhesion
Mucoadhesion measurement of solid dosage forms, semi-solids and even systems which solidify on contact with the target organ can be performed.



Tablet swelling
By means of a small cylinder penetration this test allows determination of dimensional changes associated with matrix hydration and swelling.

Bioadhesion/ transdermal
The peel strength of films or patch formulations can be investigated using porcine or synthetic skin secured to a sliding platform of a 90 degree Peel Rig.

Tablet/'Fast Melt' disintegration
This test can provide a simple means by which to establish onset, rate and time of disintegration of fast dissolving tablets or wafers.

Gel properties
Typical measurements include gel strength, Bloom strength (according to ISO standard), rupture force, adhesiveness, gel forming points and elasticity/ brittleness.

Tablet strength
While this device enables testing for bilayer tablet separation, it is just one of a number of attachments specifically designed for assessing tablet strength.

Film properties
Burst strength of thin, film-like pharmaceutical products may now be rapidly and accurately measured, along with resilience and relaxation of other films.

See our Controlled Release Testing Applications video...

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Multi-nuclear Magnetic Resonance Imaging Studies of Controlled Release Systems

Charlie Chen, LF Gladden, MD Mantlem, Department of Chemical Engineering and Biotechnology, University of Cambridge, CB2 3RA, United Kingdom, E: cc610@cam.ac.uk

Introduction

The use of magnetic resonance imaging (MRI) as a tool in pharmaceutical dissolution research is now well established.[1-2] The non-invasive and non-destructive nature of MRI enables the investigation of structural, chemical and dynamical processes in many optically opaque systems at the microscopic level. Spatial maps of water penetration, tablet swelling and dissolution, as well as the mobilization and distribution of drug products can now be quantified and visualized.[3-4] In addition, the hydrodynamics within a USP recommended flow-through dissolution apparatus can also be visualized by MRI.[5] Such comprehensive information is essential in pharmaceutical research for: (i) the correct interpretation of conventional drug dissolution testing profiles and (ii) the optimal design (QbD) of controlled release formulations.

MRI principle

Magnetic resonance images of a sample are reconstructed from a nuclear magnetic resonance (NMR) signal, which is generated by certain nuclei (e.g. ^{1}H, ^{19}F) when subjected to a strong external magnetic field, B_0 (e.g. 9.4 Tesla) and subsequently irradiated with radio frequency (r.f.) pulses. A spatially encoded NMR signal, i.e. an image, is generated by the application of RF pulses and additional magnetic field gradients of much smaller magnitude. The spatial image can then be obtained via Fourier transformation of the raw data. Figure 1 depicts the setup of a vertical MRI magnet and USP-IV dissolution cell. By tailoring the timings of the r.f. pulses and magnetic field gradients, the MR images can be weighted to show different information such as molecular species composition and concentration, spin-lattice relaxation time (T_1), spin-spin

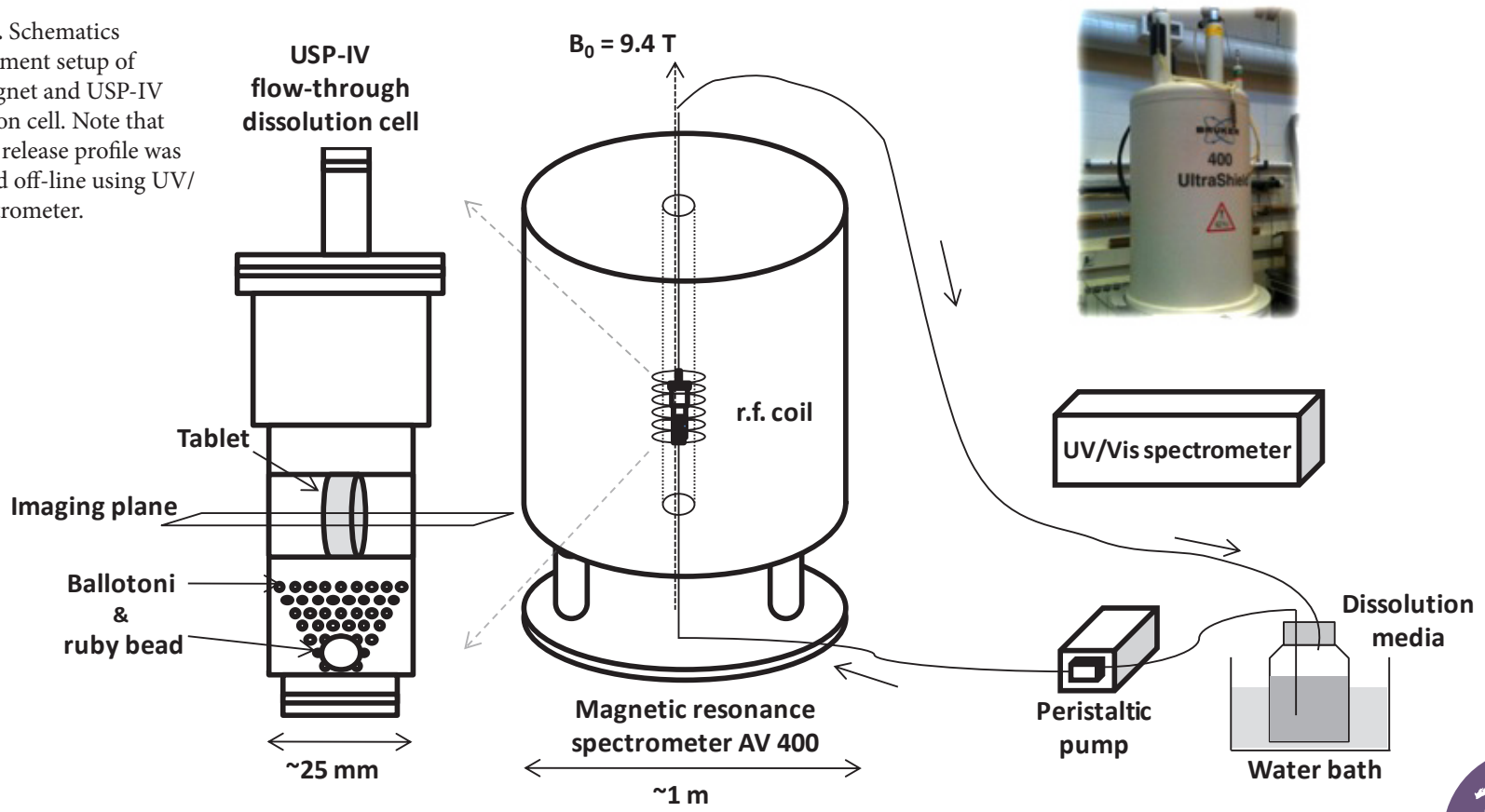


Figure 1. Schematics of experiment setup of MRI magnet and USP-IV dissolution cell. Note that the drug release profile was measured off-line using UV/Vis spectrometer.

relaxation time (T_2), and molecular self-diffusion coefficient, as well as the velocity of flowing dissolution media within the dissolution apparatus.[3-6]

Quantitative information

The 'quantitative' nature of magnetic resonance is one of the defining beauties of MRI. The acquired signal, in theory, is proportional to the number of nuclei of interest in a particular sample. Thus MRI tells us 'how much' of a particular substance we have in a particular system.[1,3-4] For example, we can spatially map the concentration of water in a swellable polymeric hydroxylpropyl methylcellulose (HPMC) based tablet (Figure 2). In addition to 'how much', MRI data can be also be acquired and manipulated to give quantitative information regarding 'how fast' the molecules of interest move.[1,3-5] For example, of particular interest within the pharmaceutical research community is being able to: (i) quantify the rate of ingress of dissolution media into swellable matrices (water diffusivity map) and (ii) quantify the rate of formation and expansion of gel layers (indirect polymer mobility map) (Figure 2). Hence by using the comprehensive ^{1}H MRI information of the water behaviour during the tablet swelling and dissolution process (Figure 2), it is in turn possible to quantitatively evaluate the polymer behaviour. For example, we have found that two distinct regimes exist in the 'gel' region, namely the 'swollen glassy layer' and the 'gel layer'; these are based on the correlation between the absolute water concentration, Cwat and T_2 relaxation time image obtained by ^{1}H MRI (Figure 3).

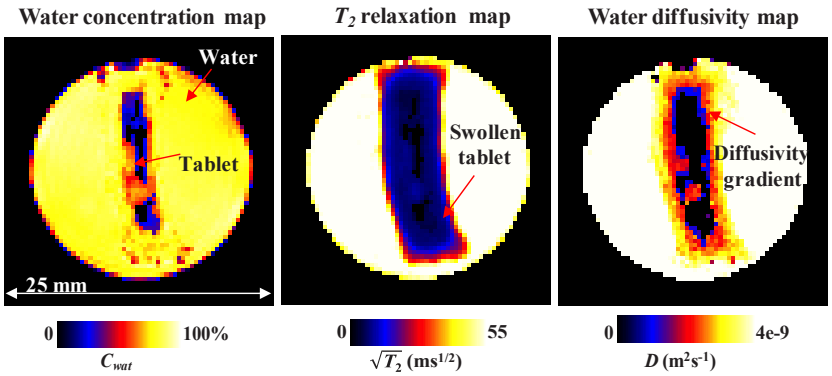


Figure 2. Water concentration map, indirect polymer mobility map (water T_2 relaxation time map) and water self-diffusivity map of the model tablet (70% HPMC K4M; 30% trifluoperazine dihydrocloride, TFDH) after 1 hr upon dissolution in USP-IV dissolution cell under pharmacopeial conditions. Field of view = 25 mm × 25 mm, pixel resolution = 391 μm × 391 μm, slice thickness = 1 mm, temporal resolution = 3 min per image.

Visualization of the drug distribution and mobilization

The majority of the existing studies in this research area have used 1H MRI to acquire signals from water molecules within a pharmaceutical tablet during the dissolution process. In contrast, very few studies have investigated directly the behaviour of the active pharmaceutical ingredients (APIs),

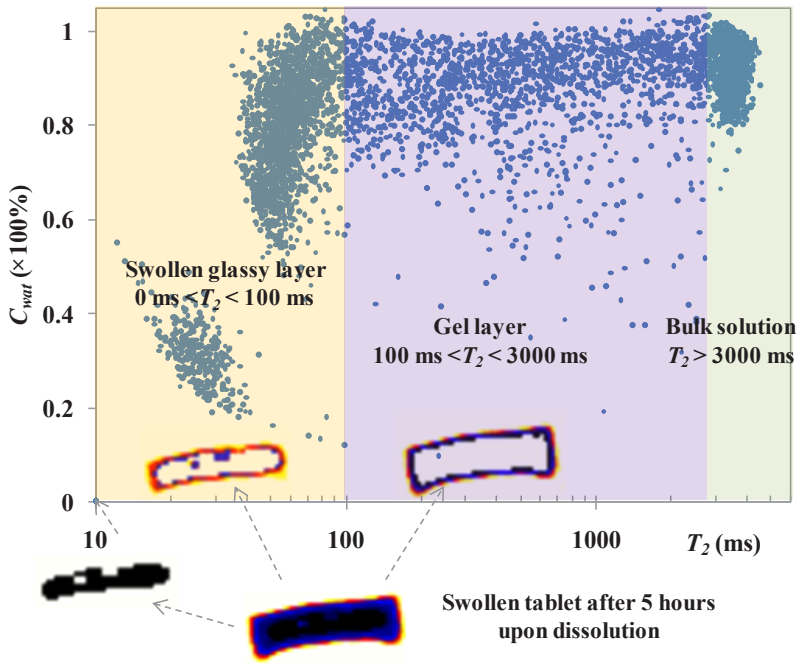


Figure 3. C_{wat} and T_2 relaxation time correlation of model tablet (70% HPMC K4M, 30% TFDH, w/ bloomfieldpresbyterian.org w). Data points were collected from series of water concentration maps and T_2 maps over 19 hr of dissolution. Three regimes (dry core, swollen glassy layer and gel layer) within the swollen tablet were separated by their T_2 values.

since the ^{1}H signal from API is normally obscured by the huge 1H signal associated with the water based dissolution medium. In fact, due to the nuclear specific and non-invasive nature of MRI, the API can be tracked using signatory atoms it possesses, e.g. ^{19}F. Thus, MRI shows great potential in revealing the distribution and evolution of APIs at a local level within the tablet or dosage form under in vitro pharmacopeial dissolution conditions.[3]

^{19}F is very promising candidate for API screening due to its close relevance in the pharmaceutical industry. Approximately 20% of the new drugs introduced to market since 1957 are fluorinated

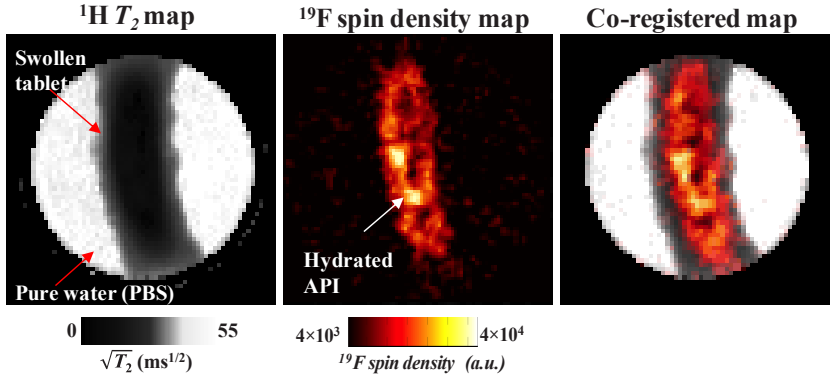
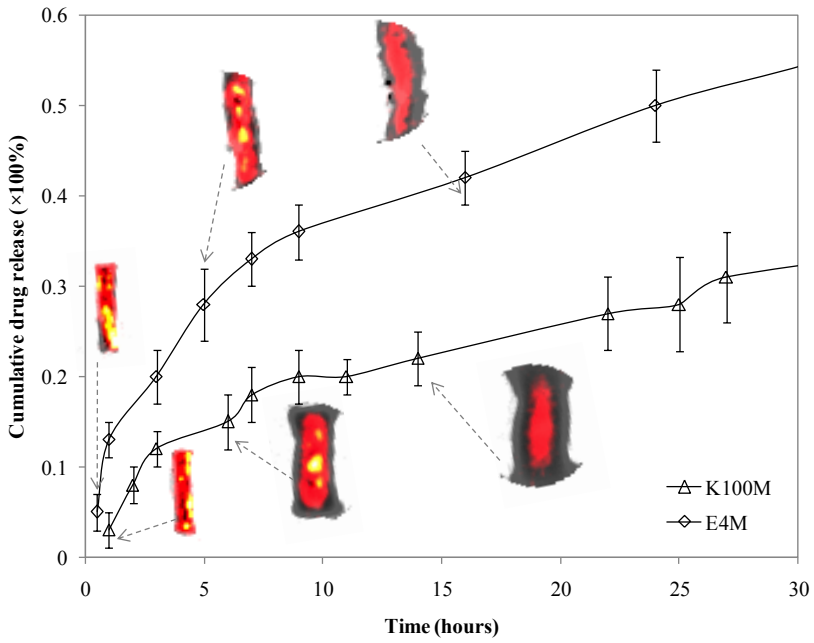


Figure 4. Co-registration of quantitative ^{1}H T_2 images and ^{19}F spin density MR images from the model tablet (70% HPMC K4M, 30% TFDH, w/w) after 9 hr upon dissolution.

drugs.[7] In this study, we report preliminary findings from a ^{19}F-1H co-imaging method to visualize both the dissolution medium ingress and drug mobilization during the tablet swelling process. By correlating ^{19}F images of the API and quantitative ^{1}H images, the evolution of drug distribution within the swelling polymeric system is visualised (Figure 4). Such information is essential to aid our interpretation the conventional drug release profile as monitored by UV-Vis spectroscopy. Figure 5 shows that the rate of release of TFDH from two HPMC based polymeric matrices with different molecular weights follows the trend: E4M > K100M, where E4M has a molecular weight that is approximately 25 times lower than that of K100M. The traditional drug release kinetic curves of these two systems can be explained in detail by the ^{19}F and 1H MRI results which show that the gel layer of the K100M system is larger than the E4M system. The larger gel layer hinders the diffusion of TFDH through it, resulting in the slowest release rate. In contrast, the limited swelling behaviour of E4M results in the fastest release rate. This behaviour is not obvious from optical observation within a working dissolution apparatus.



Type of HPMC	E4M	K100M
Methoxyl content, %	28.8	22.6
Hydroxypropoxyl content, %	9.3	10.5
Viscosity of 2% solution in water, mPa·s	3887	118951

Figure 5. Drug release profile of TFDH from the polymeric matrix K100M and E4M (70% HPMC, 30% TFDH, w/w) obtained by UV spectroscopy and ^{19}F and ^{1}H co-registered MRI images of the tablets. Error bars on the UV data were derived from three repetitive measurements.

Conclusions

Quantitative ^{1}H magnetic resonance imaging was used to investigate the swelling and dissolution process of HPMC based tablets. Quantitative maps of absolute water concentration, spin-spin relaxation time and water diffusivity were obtained in less than 3 min each, allowing a thorough overview of tablet dissolution process. ^{19}F MRI techniques were developed to evaluate the local drug release process within tablet formulations containing 19F API. The ^{19}F nucleus offers important advantages of high sensitivity and zero background. Co-registration of ^{1}H and ^{19}F MRI enables the visualization of drug egress from and water ingress into the polymer matrix simultaneously. Drug diffusion and distribution within the swelling system can now be tracked.

The drug distribution information may then be used to interpret traditional drug release profiles obtained by the UV-Vis spectroscopy. It is therefore possible to correlate the drug release, drug diffusion and polymer matrix swelling and dissolution. Collectively this represents a significant improvement towards a comprehensive understanding of the drug dissolution process.

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Acknowledgements

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4 ways open access enhances academic freedom

by Curt Rice / curt-rice.com

Are politicians stealing our academic freedom? Is their fetish with open access publishing leading to a "pay to say" system for the rich? Will the trendy goal of making publicly financed research freely available skew the world of scholarship even more in the direction of the natural sciences? I don't think so. But it took me a while to get there.

The freedom to choose

Academic freedom lets scientists choose the research questions they want to ask. They can pursue their hypotheses however they like. Their results and reasoning can be discussed without any fear of reprisals from governments or universities. The frontiers of knowledge move forward without political interference or personal risk because of academic freedom.

Can open access policies violate academic freedom?

The Norwegian government recently wrote about open access publishing as a potential threat to academic freedom.

"All research that is publicly financed should be openly accessible. This principle, however, must not hinder the academic freedom researchers enjoy to choose their preferred channels of publication."

How could academic freedom be impeded by a requirement to publish in open access journals? Doesn't it seem just a bit too luxurious to turn this principle into something about the business model journals use? Maybe. But experts writing about academic freedom recently asserted a right "to decide how publication shall happen." This, I think, is where academic freedom and open access policies may collide.

The cost of knowledge

The possible conflict becomes clearer if we turn the question around. Could a researcher refuse to publish in for-profit journals? Thousands just have: Elsevier's excessive profitability triggered the Cost of Knowledge protest. Do professors with academic freedom have the right to boycott a publisher? What if a government supported the boycott and refused to let publicly funded research appear in Elsevier's journals? This would prevent researchers from publishing in The Lancet or Cell, to mention two of their most important titles. Would that prohibition violate academic freedom?

If you answer yes to these questions — as I do — then we must also accept the idea that there could be a conflict between a requirement to publish in open access journals and academic freedom.

Open access policies

Important policies have emerged from the National Institutes of Health, the European Commission and the Research Councils of the UK, to mention a few prominent examples. As far as I can see, not one of these mentions academic freedom — in contrast, for example, with Communia's progressive recommendations about open access policies.

The Norwegian Ministry of Education and Research therefore deserves praise for raising the issue. The power of funding alone should not be enough to override academic freedom. The route to enhanced use of open access, in other words, is not exclusively through compulsion.

Enhancing academic freedom

How can universities and governments nudge their researchers forward? Is there no carrot

that can help? I think there are carrots, and here are four examples of ways in which open access publishing enhances academic freedom.

1. Copyright — In open access journals, authors retain copyrights while in the traditional system, they must sign over the copyright to the publisher. Professor Stuart Shieber at Harvard elaborates:

"Traditional publishing infringes academic freedom. Authors assign copyright to publishers as part of the publication process. With this control, publishers can and do limit access to the scholar's writing. Scholars are therefore not free to disseminate their academic work in the broadest way."

2. Interference — Open access journals can be cheaper to run, which can increase editorial independence, say Stanford's John Willinsky and his colleagues in Doing Medical Journals Differently: Open Medicine, Open Access and Academic Freedom.

"Open access enables a new journal to become part of the larger academic community immediately, without first having to convince a major corporation or organization to sponsor it or having to assemble sufficient resources to sell initial subscriptions through some combination of advertising and agents. (One estimate sets the price of securing 500 subscribers at roughly US$50,000)."

3. Citations — There is a growing literature suggesting that open access articles are read and cited more. This enhances academic freedom by allowing you to better fulfill the responsibilities that go with it — especially the obligation to put your work in front of others.

Increased citation also enhances your academic freedom through its quality control function — the use and evaluation of your work by others will give you a sturdier basis for determining what questions to ask next.

In short, the connection is tight between visibility, academic freedom and its concomitant duties. (I leave aside here the challenges traditional publishing models are facing as they lose their grip on quality control, cf. Why you can't trust research: 3 problems with the quality of science.)

4. Archiving — A bizarre consequence of for-profit digital publishing is that the responsibility for archiving scientific articles has de facto been transferred from libraries to publishers. A library that subscribes to an electronically published traditional journal cannot simply keep an archive of what it subscribes to.

The publisher does that. At least until it decides not to. Or goes out of business.

With open access publishing, archiving becomes possible for independent non-profit institutions wanting to take on that responsibility. A natural extension of the notion of academic freedom is the right to have your published work remain available. This is part of the ongoing debate and quality control process that pushes science forward.

In fact, the archiving issue represents the very core of the distinction between traditional and open access approaches to publishing, namely accessibility. Surely scientists concerned about academic freedom agree that the longer their words are accessible, the greater their potential contribution and impact. And isn't this, after all, exactly what academic freedom is intended to facilitate?

There is a connection between open access policies and academic freedom. It's subtle and it requires our reflection. From my perspective, the balance tips strongly in favor of open access when we ask which model strengthens academic freedom. I hope ministries and research councils soon will make this case, too.

About the author: Curt Rice works as the Vice President for Research & Development (prorektor for forskning og utvikling) at the University of Tromsø. Please note that the views expressed in the article of those of the author, and are not necessarily those of UKICRS.

Open-access journals are scholarly journals that are available online to the reader without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. Some are subsidized, and some require payment on behalf of the author. Subsidized journals are financed by an academic institution, learned society or a government information center; those requiring payment are typically financed by money made available to researchers for the purpose from a public or private funding agency, as part of a research grant. There have also been several modifications of open-access journals that have considerably different natures: hybrid open-access journals and delayed open-access journals.

Open-access journals (sometimes called the "gold road to open access") are one of the two general methods for providing open access. The other one (sometimes called the "green road") is self-archiving in a repository. The publisher of an open-access journal is known as an "open-access publisher", and the process, "open-access publishing".

In successively looser senses, open-access journals may be considered as:

- Journals entirely open access
- Journals with research articles open access (hybrid open-access journals)
- Journals with some research articles open access (hybrid open-access journals)
- Journals with some articles open access and the other delayed access
- Journals with delayed open access (delayed open-access journals)
- Journals permitting self-archiving of articles

interview ...

with Paul Smith (Colorcon, UK)

Karl @ UKICRS
Paul, you've recently joined the UKICRS committee. You work for Colorcon - where are you based and what do you do?

Paul @ Colorcon
I work at Colorcon's European HQ in Dartford, Kent. My job title is Formulation Technologies Manager.

Karl @ UKICRS
Give us a quick summary of your education ...

Paul @ Colorcon
Biochemistry at the University of Liverpool and then a PhD in Molecular Biology from the University of Edinburgh.

Karl @ UKICRS
Did you move to Colorcon straight after your studies?

Paul @ Colorcon
No, my early career was spent as a research scientist in the biotech industry, in both the UK & US. It was quite a different environment to the pharma excipient industry.

Karl @ UKICRS
So why the move to the pharma industry?

Paul @ Colorcon
Although I really enjoyed my time working at the bench, I wanted to work in a more commercial environment (although still in a technical role). I was offered an opportunity by an excipient supplier, and then 8 yrs ago moved to my current role at Colorcon.

Karl @ UKICRS
So, what exactly does a 'Formulation Technologies Manager' do?

Paul @ Colorcon
I technically support and promote our tablet core excipients & modified release coating systems.

Karl @ UKICRS
Presumably, the vast majority of your work is focused on human pharmaceutical formulations?

Paul @ Colorcon
Yes. I work with pharmaceutical and some nutraceutical companies on both immediate release & modified release formulations.

Karl @ UKICRS
What's new and exciting in the world of excipients?

Paul @ Colorcon
There's a lot of focus currently on Quality by Design (QbD), ensuring that the formulator fully understands the impact of excipient quality and variability on final product performance.

Karl @ UKICRS
What exactly is 'Quality by Design'?

Paul @ Colorcon
QbD has many different elements. One aspect is ensuring that the performance of your formulation is not affected by normal variability in the specifications of the raw materials. Much better to design a robust formulation, rather than risk out-of-spec product.

Karl @ UKICRS
I suspect many scientists don't think too deeply about excipient selection and testing. Is this true in your experience?

Paul @ Colorcon
It can be. Sometimes the full impact of an excipient on the performance of the final formulation is not fully considered. Especially with modified release formulations.

Karl @ UKICRS
How does this play out in practice? If I was developing a modified release tablet using an excipient with relatively large variability in specification, how can a robust formulation be assured?

Paul @ Colorcon
It's important to use good quality excipients, and follow best practice guidelines. For example, a low polymer conc. in an ER matrix may give the desired release profile, but could lead to variability.

Karl @ UKICRS
How do you test or quantify a formulation's robustness?

Paul @ Colorcon
One approach is to test performance of the formulation using three random batches of excipient. A better strategy is to test using batches at the extremes of specification for key parameters. Some excipient suppliers now offer such "QbD library" samples.

Karl @ UKICRS
What do you like best about your job?

Paul @ Colorcon
I really enjoy working with our customers, whether it be brainstorming formulation approaches for a new project, troubleshooting a problematic process, or presenting at an educational seminar.

Karl @ UKICRS
And what aspects of your job do you not like so much?

Paul @ Colorcon
My role involves a lot of travel, and I really enjoy that; but spring and autumn times are very busy with travel. I sometimes wish that the split between office and travel was more even throughout the year.

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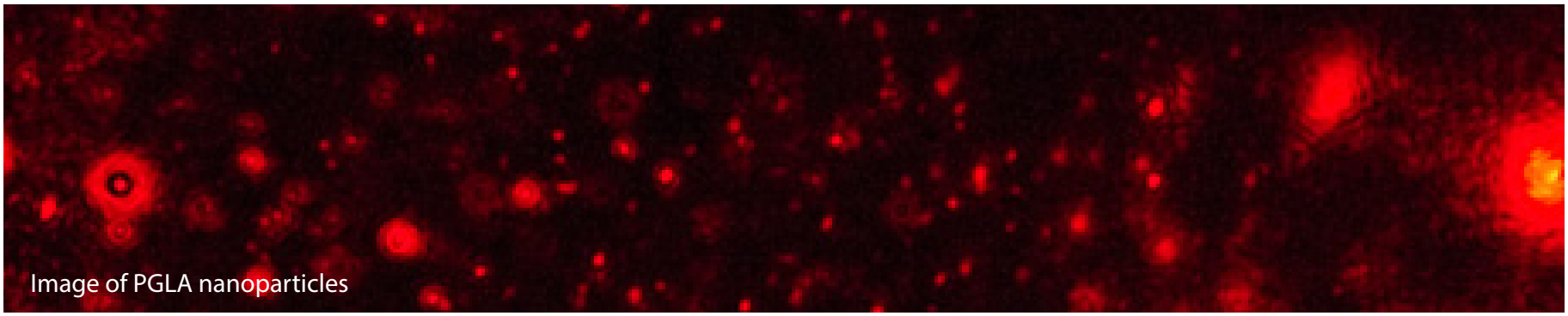

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WHY CAN'T I USE BACON FAT IN MY DRUG PRODUCT FORMULATION?

by Bruce Rehlaender, Ph.D., PharmaDirections, Inc.

IF there were a bar where all of the hip drug product formulators hung out at the end of a hard day of formulating, two things would be certain – the beers on tap would be from breweries like Avery, Greenflash, and Dogfish Head rather than Coors, Miller, and Anheuser Busch, and all of the jokes would be about discovery guys. We formulators would pick on the discovery guys in part because deep down inside we realize they are smarter than us and get more dates than we do and in part because they make our lives miserable, and they think that DMSO is a formulation. Just as likely in this bar is that no one would dare challenge out loud the sanctity of our bible, the FDA Inactive Ingredients Guide, for fear of being beaten up out back by a bunch of hooligan formulation zealots.

Just in case there are any discovery guys reading this, the Inactive Ingredients Guide (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm) is a list of (supposedly) all excipients used in marketed drug products listed by route of administration and level in the formulation. For a long time this was a pdf document that hadn't been revised since 1996, but more recently, the Agency has maintained it as a searchable database that is presumably updated as new drug products are approved. We rely on it to know what has been safely done already so that we don't come up with a formula that provides great solubility, stability, and bioavailability but does irreparable damage to the patient. And just as importantly, we rely on it so that when our boss or sponsor asks us if that excipient is precedented, we can point to the list and say "there it is; FDA said it's okay."

While the Inactive Ingredients Guide is certainly a useful reference, and we can be grateful to the Agency for providing it to us, there are a number of pitfalls with relying on it too heavily, and without trying to pick a fight, I want to point some of these out.

First and foremost, the guide is only a list of excipients that have been used and not a list of excipients that are allowed in a particular type of dosage form. If an excipient is not on the list, it may mean that it is harmful, but it more likely means that no one has had the guts to venture off The List and use it. For example, anyone who has ever worked in inhalation can tell you, sometimes rather emphatically, that phosphate buffer cannot be used in nebulizer formulations, but I have yet to find anyone who can tell me why not. Even the pulmonary division at CDER may be unclear on this point, as I have seen phosphate buffered saline used as a nebulized placebo in some FDA-approved clinical trials.

Just as importantly, the fact that an excipient is on the list for a particular route of administration does not necessarily mean that it is safe. Paclitaxel has been formulated with high levels of the PEGylated surfactants, Cremophor EL and Polysorbate 80, both of which are known to cause anaphylaxis in susceptible humans and in pretty much all dogs. The FDA accepted these formulations because they were the only thing that worked for a drug that isn't used unless it is the only thing that works. It doesn't mean you can go crazy with the Cremophor in an injectable formulation of ibuprofen.

Even if a drug is on the list for a particular route of delivery, the details of administration never seem to match the target at hand. Looking up an excipient in the database is just the first step in assessing whether it is precedented. One need next dig out package inserts for the actual drug products it is used in and determine whether the level of the excipient and the site, rate, and duration of administration as well as the dosing frequency and period of dosing are sufficiently similar to the intended use at hand. Since the names of the drug products are not listed (or even hinted at) in the database, this is best done by

searching the name of the excipient and thom or Drugs.com. If you are doing anything more complicated than a bolus injection or an IR tablet, don't count on finding an exact match to what you want to do.

Since the list includes only approved products and since it takes so long to get a product approved, the fact that an excipient is not on the list does not mean that it has not undergone extensive clinical testing and been found to be safe. Only a few years ago many of our clients shied away from using hydroxypropyl-beta-cyclodextrin (HPBCD) even in Phase 1 formulations since the only two cyclodextrin-based formulations on the list used the sulfobutyl ether (Captisol®). The four HPBCD-containing products currently on the list would likely have been through most or all of their Phase 3 trials at the time.

Contrary to what some may believe, the database is not complete. When performing the abovementioned searches on package insert websites I almost always come up with a few drug products that are not included on the FDA list.

Another more trivial concern with using the database is that you really need to be sure that you know the correct name of whatever you are looking for. For example, if you do a search on ethanol, you will come up with a relatively short list of ethanolamides and ethanolamines but nothing that would taste good in your punchbowl. You need to search on alcohol if you want to know where the strong stuff is.

What are the disadvantages of using an excipient that is not precedented? From the regulatory perspective, the FDA is only interested in whether the overall drug product is safe and efficacious and well enough controlled to be consistent from batch to batch. They are not the ones telling us we can only use what is on their list. Nonetheless, besides pleasing your boss, there are some distinct advantages to sticking to what is tried and true: (i) the prior use of an excipient in a similar formulation amounts to a clinical history, just as a drug that has been used before has a clinical history that it allows it to slide through on an ANDA or 505.b.2. Every drug product is its own entity and is judged on its own merits regardless of what excipients it contains, but having a precedent substantially reduces the risk of an unanticipated problem and makes for easier writing in the Pharmaceutical Development section of an NDA; and (ii) the fact that an excipient has been used for the same route of delivery in an approved product means that there is a Drug Master File on it as well as a supply that is appropriate for the use. A little carnauba wax might be just the thing to brighten up your injectable formulation, but you might be hard pressed to find an endotoxin-tested grade.

The main reason we formulators have such a hard time getting dates is that we are inherently boring people. While the discovery guys are creating spanking new molecules for novel targets, we are stuck in our dingy labs searching the shelves for those same old bottles of HPMC or PEG or lactose. We tend to blame our conservative ways, directly or indirectly, on the FDA, but it is really not they who are holding us back. In most cases it makes sense to stick to what we know, but I wonder how often safer or otherwise better formulations have been overlooked simply because they were not sufficiently similar to what had been done before.

Some final advice for my fellow formulators:

1. Never forget that all those sexy discovery, pre-clinical, and clinical people are useless without us.

2. As to the title of this piece, I would certainly not advise you to try bacon fat as an excipient, especially if you are trying to reformulate Lipitor, but if there were a demonstrated safety or efficacy advantage and you had a well-controlled supply, there is no legal reason you could not throw in a bit.

3. If you are thinking about a novel excipient, be bold and stand your ground. Don't let anyone tell you that you can't use it just because it is not on some list. Go ahead and throw in a sodium rather than a potassium salt or a sulfate rather than a chloride. Be the first on your block to put whatever crazy new thing Gattefosse comes up with into an injectable. Use phosphate in a nebulizer or black pepper extract in a nasal spray. Whatever you put in, I promise I will find a way to use it too. Once you get it on The List.

Bruce Rehlaender is Principal of Formulation Development at PharmaDirections, Inc.

DRUG DELIVERY IN A DIVERGING SOCIETY: PREDICTIONS FOR 2050

James Norman, PhD, Georgia Institute of Technology

UKICRS Essay Competition 2013 Winner

Drug delivery is a pragmatic field motivated primarily by the needs of society. Luckily, this simplifies the prediction of its future course. One only needs to track the changes in society and extrapolate them to forecast mid-century drug delivery needs.

Three key forces shaping our society today are technology, income inequality, and environmental degradation. Technological advance is apparent with the acceleration of computing power and biological knowledge. Income inequality is with us due to regressive taxation, population growth, urbanization, and stiff competition among workers in a global economy - soon to be compounded by displacement of skilled workers by robots and algorithms[1]. The environmental pressures of climate change, deforestation, and invasive species also represent a great challenge leading into 2050.

With these forces, my bold prediction for society is that by 2050, the wealthy and impoverished people of the world will be diverging past a point of return. A "hyper-modern" group will reap the benefits and consequences of unprecedented wealth and technology. A larger "post-modern" group, displaced by industrial society, will have to reinvent their lives with vast knowledge available on the internet but limited material resources[2]. The remainder of this article will examine how the divergence of these two groups will shape drug delivery by 2050. The article first looks at the major afflictions of 2013 and then moves to discussing emerging problems for 2050.

Predictions about 2013's afflictions

First World Problems in 2013

In the United States, a developed country by all accounts, the current top 10 costliest medical conditions are heart disease, cancer, mental disorders, trauma, arthritis, COPD, hypertension, diabetes, back pain, and hyperlipidemia[3]. These are the conditions of an aging, sedentary society. In the hyper-modern world of 2050, an ever older and more sedentary society, expect these costly conditions to have and even greater grip. Treatments will be more aggressive, personalized and expensive. Personalized therapies may utilize personalized drug delivery systems rather than personalized drugs. Cellular and tissue engineering therapies, another form of personalized therapy, will likely be profitable for drug delivery researchers. A demand for top-notch, aggressive therapy could also involve risky implanted drug delivery systems. These conditions of age and sedentary lifestyle should be far less prevalent in a labor-intensive, vegetarian-by-necessity post-modern world. Moreover, since an ounce of prevention is worth a pound of cure, people unable to afford a pound of cure will gravitate towards low-cost preventative interventions like diet and exercise.

Infectious Disease in 2013

Looking at world as a whole in 2013, the top two causes of disease burden – and 6 of the top 12 – are infectious diseases[4]. Infectious diseases are most prominent in lower-income countries. By 2050, there will likely be vaccines (or

more precisely: immunotherapies) for all of these diseases thanks to reverse vaccinology, systems vaccinology, and their integration with drug delivery. Additionally, due to extraordinary humanitarian effort combined with easily administered thermostable vaccines, polio will surely be eradicated with measles soon to follow. By mid-century in the hyper-modern world, drug delivery will probably enable elderly-specific vaccines and immunotherapies to slow immunosenescence.

Emerging Topics for 2050

Infectious Diseases

Two threats emerging as the infectious killers of today recede are antibiotic resistance and a catastrophic worldwide pandemic. Authorities today are sounding the alarm:

- The World Health Organization[5]: "More and more essential medicines are failing. The therapeutic arsenal is shrinking. The speed with which these drugs are being lost far outpaces the development of replacement drugs."

- British physicist Martin Rees[6]: "By 2020, bioterror or bioerror will lead to a million casualties in a single event."

- The British Medical Journal[7]: "Intensive farming practices, environmental degradation, and processes related to the mining industry could all increase opportunities for infectious agents to breech the species barrier; some of these infections may have epidemic or pandemic potential in humans."

For antibiotics, I predict that by 2050, all will use some form of cellular[8] or colony-specific[9] targeting with many antibiotics using heat or irradiation rather than biochemical methods for annihilating their targets[10]. Concerning worldwide pandemics, broad spectrum antivirals[11] and inexpensive immunotherapies are in development. It is the responsibility of drug delivery to reduce the cost of stockpiled drugs, to ensure effectiveness using the lowest dose and simplest administration possible.

Food, Water, and the Environment

Driven by curiosity and human need, I believe drug delivery researchers will venture out of traditional healthcare, applying their techniques to nutrition and environmental management. Monitoring hyper- modern children's gut microbiomes will become commonplace, using nutrient delivery to prevent disease and target certain behavioral traits[12]. Additionally, some hyper-modern families enabled by smart-phone-like apps will follow personalized diets[13] that include controlled release nutraceuticals.

Delivery needs related to food and water in the developing world will concern efficiency more than self-optimization. It is conceivable that most food and drink will be prepared in ways to optimize nutrient uptake. Similarly, inexpensive drugs may be available for delivery that aid water and nutrient absorption and slow excretion. Controlled release should continue to benefit agricultural yields, and may well have applications in advanced aquaculture and farming on the continental shelf.

Regarding the environment, it is notable that the Controlled Release Society has an inaugural session on controlled release for the energy industry at the society's annual meeting in 2013. Beyond work in energy, much opportunity exists in environmentalism. Three ways drug delivery could help maintain our ecosystem are by delivering agents to invasive species, protecting pollinator and insect-eating species which are on the brink of collapse[14], and facilitating the regrowth of forests to capture CO_2. Controlled release may also factor into geoengineering as a method for controlling climate change: enhancing plankton blooms to capture CO_2, for example. If we do control climate change and ecological disruption by 2050, I imagine the drug delivery and controlled release will be an integral part of the solution.

Changes to Manufacturing

I foresee two critical changes for the drug and device industries. First, great concentrations of wealth and power in the hyper-modern world will likely lead to half-hearted or non-existent regulation similar to what was seen in the Gilded Age of the United States. Barrier to entry on the market will be nonexistent, leading to great innovation and an entire new field of health for cleaning up after mishaps. The second great change is for the post-modern world. I anticipate nearly all health manufacturing will centralize to enormous facilities to achieve the greatest economy of scale, much like Avarind and the Serum Institute in India. Few specialized devices will be able to be produced in this atmosphere.

Trans-Humanism

What prediction of the future is complete without people genetically modifying themselves and linking up with the

internet? If regulation does erode and trends in biomedical innovation continue, this experimentation with humanity is practically inevitable. I envision drug delivery researchers will be involved, conducting highly controversial research outside any traditional authority[15]. Examples include genetic modification of fetuses, attempts at neural enhancement and immortality, and the introduction of long lasting brain-machine interfaces. A brave new world for drug delivery.

Conclusions

Drug delivery mirrors society. There are transformational schisms underway such that life in 2050 depends more on the influences of the humanities than it does on technology. Regardless of society's path, drug delivery and controlled release are powerful tools that will remain mainstays of engineering.

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2. This post-modern group is already cropping up in small pockets across the world. Two of the most influential sources for this prediction are the innovative informal settlements of the world (aka "slums") and the village of Gaviotas in Columbia. For more on informal settlements: http://www.cooperhewitt.org/exhibitions/design-other-90-cities. Gavoitas is a planned community in one of the least hospitable places of Columbia. Through the ingenuity of its residents, this village achieved such sustainability and health that a doctor assigned to the village had to find another occupation. For more on this remarkable place, see Gaviotas: A Village to Reinvent the World by Alan Weisman.
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15. This parallels malaria therapy of the early 20th century where a doctor gave patients febrile malaria to treat syphilis and won the Nobel Prize.

James Norman is a postdoctoral researcher at Georgia Institute of Technology, USA.

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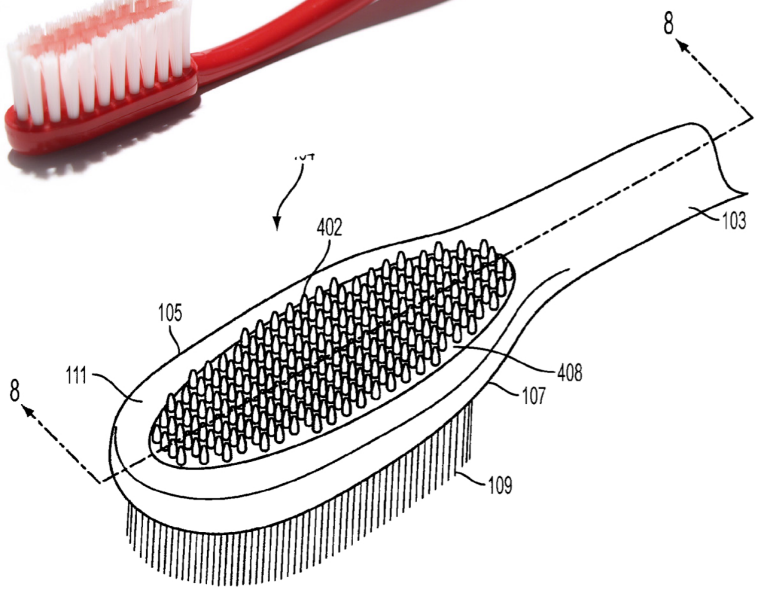
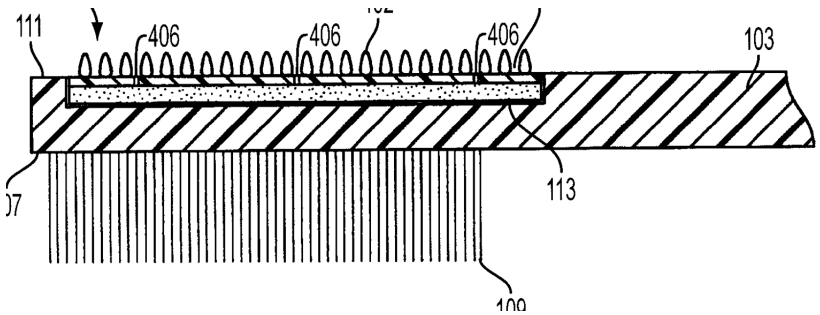
PATENT CONTROLLED RELEASE WATCH





Patent Application No: US2013/0048020 A1

Publication Date: Feb 28 2013

Title: Oral Care Implement

Assignee: Colgate-Palmolive Company, New York, US

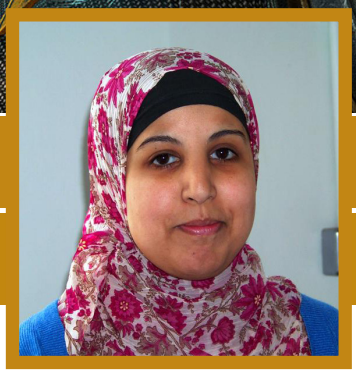
Abstract: An oral implement includes a releasable sensory material that invokes a sensory response when in contact with tissues or surfaces on a mouth of a user. In one embodiment, an element is provided that is visually indicative of the sensory response. The oral care implement may also include a soft tissue cleaner provided with the sensory material.

In English: Basically, an advanced toothbrush design that offers the potential to release chemicals into the mouth during use. Chemical examples include benzocaine, caffeine, aspirin or appetite suppressants.

Drug Delivery Scientists in the Year 2050: The Force is With Us!

Sagida Bibi, Aston University

UKICRS Essay Competition 2013 Runner Up



Will the year 2050 be a post-apocalyptic world, with mankind numbering so few that Will Smith is the only person you will recognise (I am Legend)? Will cyborgs have taken control (Terminator 1, 2 and 3) or worse still, will the decepticons have destroyed all the autobots (Transformers)?

Perhaps a large asteroid wipes out a significant part of the population (Armageddon and Deep Impact) because Bruce Willis was too old to lead a team to save us? The population of the earth is thus reduced to only a select group of people (I doubt this includes drug delivery scientists) that have survived in specially built underground bunkers (Deep Impact again!) because global warming has advanced more rapidly than anyone could have predicted ('The day after Tomorrow'). There are many who would link the inevitable demise of mankind to a more intelligent and highly advanced species, 'War of the Worlds', 'The Matrix' and of course 'Men in Black'. This view is further supported by scientologists (not to be confused with scientists!). Maybe we should not be so pessimistic; after all, Sir Isaac Newton did not believe the world would end until 2060, which gives us another decade.

We can choose to divert from the depressing Hollywood notion of what may await us in the year 2050 and take a more resilient attitude from the inspirational words of Mikey, "Goonies never say die". More realistically as scientists we would be more inclined to agree with the Nobel Laureate Joshua Lederberg who said: "The biggest threat to man's continued dominance on this planet is the virus." (As a female, I particularly lean towards this theory.) But when looking into the future, are we really going to see significant developments in terms of health care with Star Trek style tricorders being carried by all doctors as a matter of course? Well, not if the Klingons have anything to do with it!

It was in the early 1960's that Sir Alec Bangham inadvertently discovered liposomes (lipid based bilayer vesicles enclosing an aqueous compartment). However, in terms of drug delivery, the most significant development emerged with the proposal by Gregory Gregoriadis (1971) that these vesicles could be used as a delivery system for drugs, proteins, anti-tumour and anti-microbial agents. In just over half a century an idea is transformed into licensed liposome based products which have treated and continue to treat millions worldwide. Just like Inspector Gadget, drug delivery scientists are 'on the case', and continue to strive harder and further to achieve the delivery systems of the future. Visudyne® was the first licensed photo-triggerable drug delivery system and is currently used for the treatment of age related macular degeneration. Thermodox (liposomal doxorubicin) is a triggered release PEGylated formulation composed of DPPC, monosteroyl PC (MSPC) and PEG2000-DSPE of liposomal doxorubicin used for treatment of primary liver cancer (hepatocellular carcinoma) and also recurrent chest wall breast cancer. These liposomes have been formulated to release their contents

upon the application of heat and this is done with the use of radio frequency ablation (RFA). Thermodox is currently in phase III clinical testing.

So now it's that moment in the 'The Matrix' when Neo is given a choice by Morpheus: "You take the blue pill, the story ends, you wake up in your bed and believe whatever you want to believe. You take the red pill, you stay in Wonderland, and I show you how deep the rabbit hole goes." No, I am not taking you into the matrix or even a rabbit hole, but it's worth building up the suspense as we venture into some possibilities by the year 2050. The first of these scenarios begins with a tumour which is difficult to treat because it is small and in a delicate area where surgery is dangerous. A marker is delivered which is targeted directly to the tumour with targeting proteins selected to bind in the region of the micro-environment surrounding the tumour and using a handheld device (of course, we annihilated the Klingons!) the doctors are able to image exactly where the tumour is. The targeted liposomal delivery system is then given to the patient and this also carries a marker and sophisticated drugs to destroy the tumour. Once the liposomes are in the area of the tumour (they can also now be visualised by the Doctor), the liposomes are then triggered to release their contents by heat, ultrasound or even light. Radiation therapy will become obsolete. Even a cursory glance at scientific literature related to liposomes and triggered release will make you realise that, far from being implausible, such a reality can be achieved.

Not many of us can claim to have the pain threshold of William Wallace. In fact, for some of you even the thought of a travel inoculation is enough to make you slightly nervous. For the young baby taken by its parents for the first set of vaccinations there is trepidation as they enter the room; there is that underlying hope that their child recovers quickly from the shock of that 'sharp pinch' and for their young child, it is that moment of betrayal of being delivered into the hands of a smiling nurse only to have pain inflicted on them. Or, take the all-too-familiar scenario of a visit to the dentist for a simple check-up that quickly spirals into the removal of a tooth, the dentist wielding an injection for local anaesthetic like Tom Cruise with his sword in 'The last Samurai' causing you to firmly grip the side of the chair as your utmost effort is placed into not flinching as it is delivered. By the year 2050 such scenarios will become obsolete, as needleless delivery systems become the established procedure for all vaccinations and injections. No child will associate vaccinations with pain and adults everywhere will rejoice at the abolition of needles to deliver local anaesthetics elevating drug delivery scientists everywhere to celebrity status (well maybe not quite; but like Po (Kung Fu Panda), scientists will just have to be content with their 'awesomeness'!). But the fact is that such advances will make significant impacts on the delivery of vaccines and medications.

It is unrealistic to assume by the year 2050 that many of today's diseases and disorders will be completely resolved, but easing the treatment of patients and increasing compliance is achievable. Is it possible that specialised controlled delivery systems will be tailored for patients so that a single patch placed on their arm in the morning can deliver multiple drugs, at the correct concentrations and at the right time throughout the day? For a seven year old patient with end stage renal disease this could have a significant impact on quality of life. Patients that are on warfarin treatment have their international normalised ratio (INR) levels monitored regularly which involves a trip to the hospital; this is an important test used to monitor blood clotting and the risk of bleeding as a result of treatment and the dosage is varied depending on the value. An implant that is able to monitor the INR and immediately release the correct amount for the day would bring significant ease for the patient and bring down costs for hospitals. The real challenge for drug delivery scientists is tackling diseases that don't necessarily have immediate cures and although continuing to find the 'cure' is essential; the journey for the patient whilst this is achieved should be eased and by the year 2050 significant advances will have been made.

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Movie quotes referred to in the text are all classics…if you haven't seen them, it is your duty to rectify this as soon as possible.

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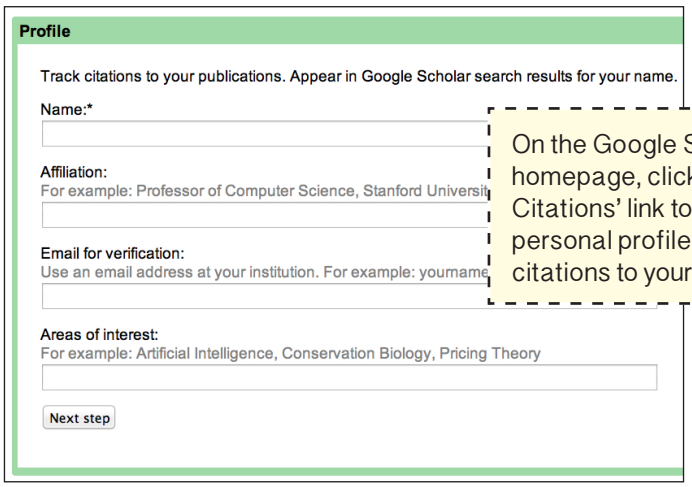

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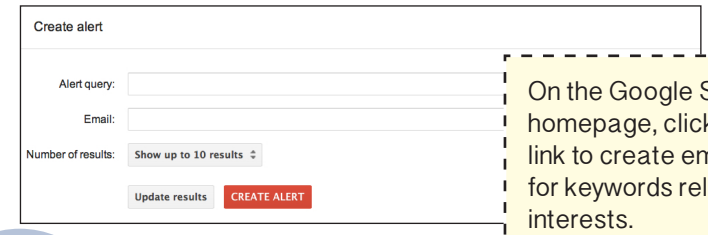

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THE H

Despite having a high value Scrabble, the letter *h* is suprisingly common. In fact, it's the eighth most common letter in the English language, mostly because it is often paired with other consonants like *wh*, *ch*, *sh*, and *gh*. However, *h* has recently made a move for independence, shirking off the vowels and consonants that tag along like lost puppies. The *h-index* is here.

The h-index is a new quantitive tool being used to measure how good we are as scientists. In an era consumed by metrics, we are constantly striving to find new and improved methods for assessing scientific performance and thus providing suitable systems for the rational selection of appropriate candidates for academic positions and allocation of grants by funding bodies. In addition, metrics may be used to 'effectively' monitor/manage academic performance with a view to improve research impact. In this sense, the h-index is providing a means by which we can compare the the quality of two scientists in a chosen field. The h-Index, first proposed by Professor Jorge E. Hirsch at the University of California at San Diego, is a simple bibliometric method to quantitatively analyse scientific output of scientists[1]. It is defined as the number of papers with a citation number ≤ H. Rather than using common indicators such as (i) total number of papers, (ii) total number of citations and/or (iii) citations per paper, the h-index measures the importance, significance and broad impact of an individual's cumulative research contributions, thus avoiding common disadvantages associated with other methods. For example, it is claimed that the h-index can be used to compare the productivity of

INDEX

by Gavin Andrews

Quantifying the cumulative impact of scientific research output

two different researchers, even if their total number of papers or citations is different.

As a concept, the h-index is pretty simple. You first determine the number of papers you have and the number of citations you have received. You then need to rank your papers from most cited to least cited. Your h-index is equal to the number of papers that have received at least h citations.

By way of example, a scientist with a h-index of 14, has 14 papers with at least 14 citations. Hirsch suggests that 20 years of research, should result in a h-index of 20 for a good scientist and 40 for an outstanding scientist. Nobel prize winners often have h-indices greater than 60.

One of the key advantages of the h-index is that it combines productivity (in terms of paper count) and impact (number of citations) in a single number, meaning both are required for a high h index. Therefore, neither a few highly cited papers or a long list of papers with a small number of citations will yield a high h-index.

Although a useful metric by which scientific performance may be measured, there are some important caveats in using the h-index as a single 'bean-counting' measure to judge scientists. Importantly, the h-index is dependent upon the chosen field of study and it does not take into account the number of authors on a paper. Also, it is known that the h-index of early career scientists is much lower than more senior colleagues (see box below). When considering the use of the h-index one must also remember that review articles have a greater impact on the h-index than research papers since they are usually cited more frequently.

Although the h-index is a useful metric, we must be careful in gifting it too much significance. The h-index of Nobel Prize winner Kary Mullis (he of PCR fame) is only 19, much lower than the 'typical value' for a 'successful' scientist. Should we really question the impact of Mullis' work due to lack of peer recognition and thus a h-index that does not exceed 20?

The h-index depends on how citations are counted, and there are various online tools to calculate citations. Unsurprisingly, the results obtained depend upon the method used. Recognising this anomaly, the UK REF2014 exercise has selected SCOPUS as its official tool to calculate citations - check it out for yourself, it's very easy to use. Alternatively, you can use Google Scholar, which upon registration and login with a Google mail account, provides a user-friendly interface for monitoring citations and h-factor. Google Scholar also provides useful updates on your homepage which matches articles similar to your own and finds papers that you may have otherwise missed using traditional web-based publication searches.

UKICRS @ PharmSci 2012

by Ambreen Khan and Woei Ping Cheng

Chair and speakers for the morning session. L to R - Dr Woei Ping Cheng, Robyn Fowler, Dr Alexander Edwards, Dr Tony Worthington and Prof Les Baillie

Overview

The UK PharmSci Conference is the leading Pharmaceutical Sciences Conference in the UK. An interesting and insightful PharmSci 2012 conference entitled 'Science of Medicines' was organised by the Academy of Pharmaceutical Sciences (APS) and took place at the East Midlands Conference Centre. The conference was a platform for academics, industrial scientists and postgraduate students to showcase their research and to learn about the latest innovations and developments taking place within their discipline. There were presentations from prominent leaders and young scientists on various sessions including 'Polymeric and self-assembled delivery systems', 'The future of in-vitro drug release testing approaches in product development', 'Bugs and drugs', 'Medicinal chemistry', 'Biopharmaceutics', 'Paediatric drug delivery and Inhaled product development', 'Tackling counterfeiting by formulation and processing approaches', and 'Green formulations and processes'.

Bugs and drugs

This year UKICRS organised and chaired two sessions on 'Bugs and drugs'. The sessions were well attended by an enthusiastic audience interested in the anti-infective field. The opening presentation was delivered by Professor Les Baillie from School of Pharmacy, Cardiff University. He presented an interesting talk on 'Bacillus anthracis: how to stop the bad guys from killing us all'. Anthrax is a disease caused by the bacterium B. anthracis. He provided insights on how to decontaminate anthrax if a site is being exposed. Firstly, environmental friendly ways of decontamination of anthrax e.g. sprays with biocides like paraacetic acid. Secondly, bacteriophage based decontamination and finally the use of vaccines to prevent anthrax infection. He also highlighted the new fact that beer can be a potential cure for tuberculosis and anthrax and that polyphenols found in green tea can kill bacterium *B. anthracis*. Professor Les Baillie talk was followed by Dr Tony Worthington from Department of Microbiology, Aston University. He talked about novel strategies in infection control of *Clostridium difficile* (CD). The CD spores are resistant to routine cleaning methods and hospitalised patients might accidentally ingest these spores leading to infections. He focussed on the development of new non-hazardous ways to improve CD infection control. He revealed a panel of amino acids such as glycine, arginine and sodium taurocholate encourage germination of CD spores. Once the CD spores germinate, routine cleaning solutions can be applied to kill the bacteria.

The third talk, presented by Dr Alexander Edwards from University of Reading, was entitled 'Oral drug delivery to breast feeding infants using a modified nipple shield'. The idea was to safely and efficiently deliver anti-viral drugs to the infants in developing countries. The approach appeared to be simple and convenient and it enabled administration of drugs to infant via breast feeding. Dr Edwards' talk was followed by a postgraduate speaker, Robyn Fowler, from the University of Nottingham who presented on the elucidation of the transport mechanisms for vitamin B12 conjugated polystyrene nanoparticles across CaCo2 cells. She demonstrated that the intracellular uptake and trafficking of Vit B12 conjugated nanoparticles was different from both soluble B12 ligand and unmodified nanoparticles. Her result showed that vitamin B12 conjugated nanoparticles were taken up via caveolar pathway and avoided lysosomal

Chair and speakers for the afternoon. L to R - Farzad Ahmad Khayrzad, Prof Marc Brown, Steven Fallows, Prof Colin McCoy, Prof Karl Malcolm

degradation.

Biofilms

After returning from lunch, Prof Colin McCoy from the School of Pharmacy, Queen's University Belfast opened the session with a talk entitled 'Biofilms on medical devices: strategies for prevention and cure'. He highlighted major problems with medical devices which are susceptible to biofilm formation and he focussed on designing biomaterials that are resistant to infections. He talked about stimuli responsive drug eluting materials that can be designed to release a drug on demand upon light activation. To employ this approach, the drug needs to have photo labile groups. The next invited speaker was Professor Marc Brown from MedPharm. He presented a talk on 'The topical treatment of onychomycosis: As hard as nails'. He talked about the recurrence and relapses of nail infection following oral treatment and highlighted the fact that topical therapy would overcome the adverse events and drug interactions of orally administered antifungal drugs. However, successful topical therapy is facing challenges due to the very low permeability of drugs across the nail plate. He discussed and provided an overview of the strategies for improving fungal drug delivery and fungal permeation enhancers.

The next speaker was Farzad Ahmad Khayrzad, a postgraduate student from School of Pharmacy, University College London. He highlighted the challenges with the use of antimicrobial peptide (AMPs) which have short serum half-lives and prone to enzymatic degradation. He talked about site specific conjugation of poly(ethylene glycol) (PEG) to AMPs and his result showed that PEGylated AMPs has lower microbial activity compared to native AMP but suggested that this can be compensated by the prolonged in-vivo half-life. The final speaker was Steven J. Fallows from Queens University Belfast. His title of presentation was 'Iontophoretic hydrogel delivery systems for photodynamic treatment of wound infections'. Using aqueous blends containing poly(methyl vinyl ether-co-maleic acid) (PMVE/MA) and polyethylene glycol 10kDa (PEG 10,000), he fabricated electrically-responsive hydrogels for incorporation of two photosensiters. He demonstrated a significant increase in the rate of drug release when an electric current passed through the hydrogel, demonstrating the potential use of this hydrogel for the photodynamic treatment of infected wounds.

PharmSci 2013

UKICRS is organising three sessions at this year's PharmSci conference in Edinburgh.

Tuesday 3 September / Session 2.21
10.25 am – David Jones, 'Engineering solidstate properties through polymer processing'
11.05 am – Afzal Mohammed, 'Molecular, micro, nano analyses: diagnostic investigations to de-risk development of compressed orally disintegrating tablets'

Tuesday 3 September / Session 2.22
2.15 pm – Francisco Diaz-Mitoma
2.45 pm – David Brayden, 'Oral vaccines using nanoparticles - the enigma of the Peyer's patch'

Tuesday 3 September / Session 2.23
4.20 pm – Randy Mrsny, 'Overcoming biological barriers for the delivery of biopharmaceuticals'
4.50 pm – Ijeoma Uchegbu, 'Peptide nanofibres - Efficient brain delivery systems for plasma labile peptides'

The Effect of Bilosomes and Vesicle Size on the Oral Biodistribution of a H3N2 Subunit Antigen

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Introduction

Bilayer vesicles are currently recognized for their efficacy as drug delivery systems either by encapsulation or surface adsorption of the active compound to vesicles.[1] For example bilosomes, which are vesicles formed from non-ionic surfactants have been investigated as vaccine delivery systems.[2,3] Whilst the oral route offers a range of advantages including ease of administration, patient compliance and a non-invasive route of delivery; few vaccines can be administered orally due to their degradation in the harsh gut environment and their poor uptake by appropriate target sites, namely M cells located in the Peyer's patches, which are responsible for secretory IgA and other mucosal responses.[4] Therefore within this work we have considered the use of bilosomes to enhance the protection and delivery of sub-unit vaccines.

Experimental methods

Bilosome vesicles were prepared by heating the surfactants monopalmitoyl glycerol (MPG), cholesterol and dicetyl phosphate (DCP) in a 5:4:1 molar ratio. Sodium bicarbonate buffer was then added to the molten mixture and homogenised for 3 minutes at 50°C. Bile salt was added to the solution and it was homogenised for a further two minutes prior to the addition of an antigen solution (H3N2). The mixture was continuously homogenised for 5 min and then left to cool to room temperature. Vesicle size was reduced by an optimised sonication cycle.

The antigen was radiolabelled using iodine-125 (125I). To achieve this, 40 µg of antigen was placed into an iodination tube (Pierce Biotechnology) with 2 Mbq of iodine for 1 hr and subsequently separated from non-labelled antigen by column chromatography.[5] Biodistribution studies were carried out in

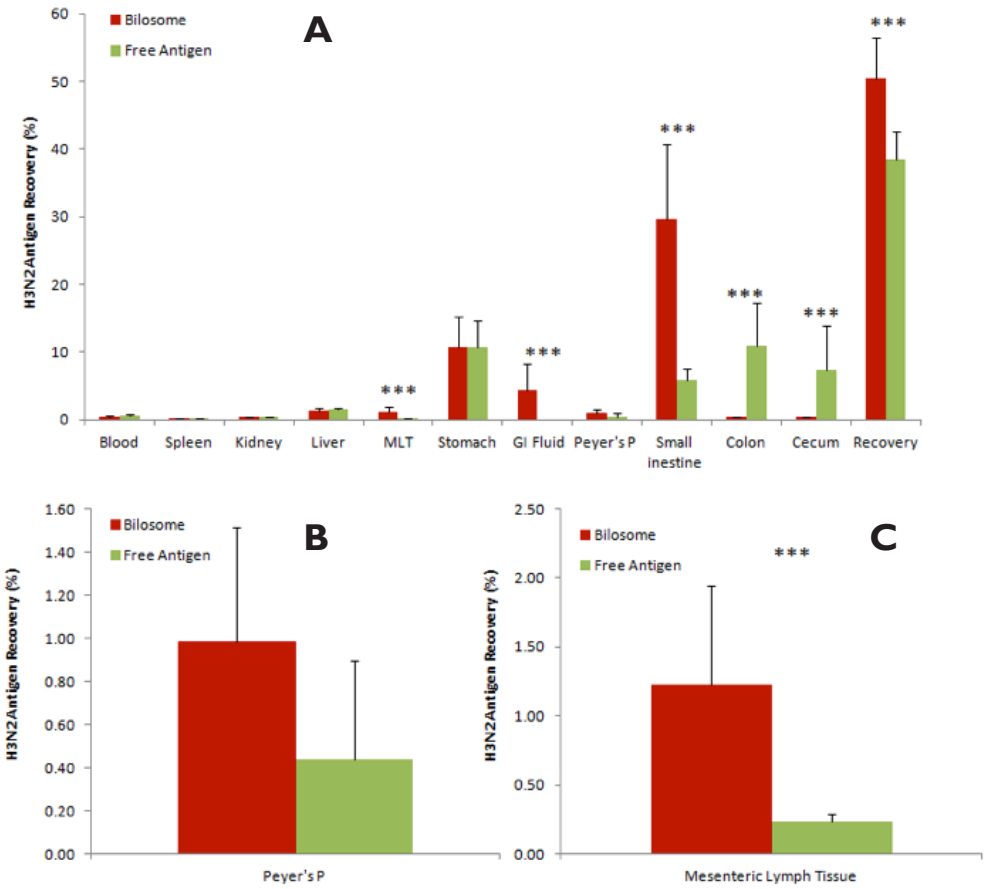

Figure 1. (A) Antigen recovery within organs at time point 1 hr after administering antigen only dose or antigen associated with bilosome vesicles. (B) Antigen recovery at the Peyer's patches. (C) Antigen recovery at the Mesenteric lymph tissue. Results represent mean ± SD; n =4. (*=significant p<0.05 using ANOVA and Tukey's post-hoc analysis).

Balb-C mice (6-8 weeks old) and were dosed via oral gavage. Experimentation adhered to the 1986 Scientific Procedures Act (UK) and was subject to ethical review.

Results and Discussion

H3N2 antigen was radiolabelled with I-125 isotope and was then entrapped into bilosome vesicles prepared using the homogenisation melt method. Results show that trace amounts of antigen were recovered in the blood, spleen, kidneys and liver, with the majority of the antigen being located in the stomach, small intestine, colon, and cecum (Figure 1A).

Antigen incorporation in bilosomes (6 μm) resulted in a statistically significant ($p < 0.05$) increase in antigen recovery in the small intestine, however significantly less in the colon and cecum (Figure 1A). Of the dose administered, in general significantly ($p < 0.05$) more antigen (50.5%) was recovered when formulated with bilosome vesicles compared to the free antigen dose (38%) (Figure 1A). In terms of the antigen reaching the site of action, the results demonstrated that delivery using bilosome vesicles resulted in a higher recovery of antigen within the Peyer's patches (Figure 1B), and significantly higher ($p < 0.05$) levels of antigen within the mesenteric lymph tissue (Figure 1C).

Following the biodistribution study, two bilosome preparations of vesicle size 2 μm and 6 μm were prepared and another biodistribution study was carried out to determine the effects of vesicle size on translocation of antigen and vesicle via the oral route (Figure 2). In this study the bilosome vesicle was radiolabelled with tritium.

Reduction in vesicle size did not result in a statistically significant enhancement in the recovery of either the bilosomes or associated antigen (as measured using radioabelled trackers) in the Mesenteric lymph tissue (Figure 2). However, when comparing recovery within the Peyer's patches, whilst there was no significant difference in localisation of antigen, there was a greater recovery of bilosomes within the Peyer's patches of the normal size (6 μm) ($p<0.05$) in comparison to the 2 μm size reduced vesicle formulation. This would suggest that it is advantageous to employ the larger vesicle sized formulations as they offer the prospect of increased retention time and hence stimulation of the dendritic cells to produce the effective immunity. This trend has also been observed by other studies where, Ebel, 1990 investigated the uptake of polystyrene latex beads of 9 μm and 2 μm via the Peyer's patches and Mesenteric lymph nodes. The results showed that the larger particles were retained within the Peyer's patches with no presence in the mesenteric lymph nodes, whereas the smaller particles were more noticeable in the mesenteric lymph nodes.[6]

Conclusion

In conclusion, there is an advantage of associating the H3N2 antigen with the bilosome vesicles as it increases the percentage of antigen recovered within the target site. In terms of vesicle size, results show increased recovery of larger (6 μm) vesicles within the Peyer's patches, highlighting the potential to offer a greater chance to increase mucosal

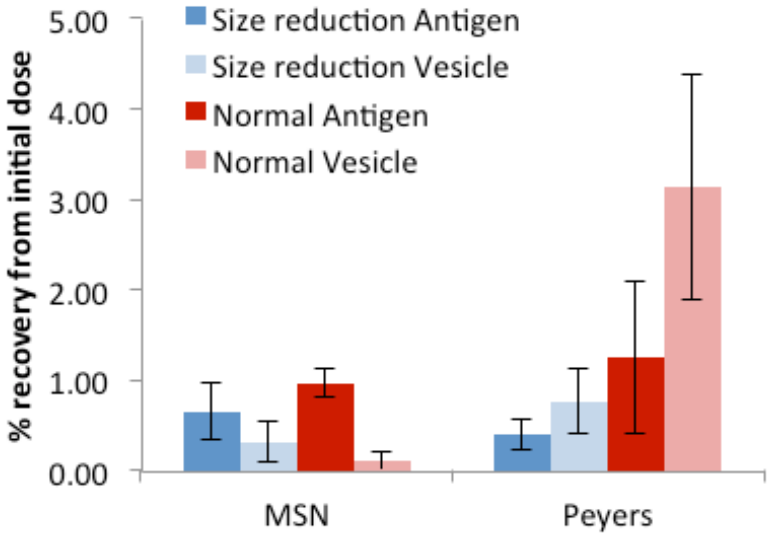

Figure 2: A closer look into the Mesentery (MSN) and Peyer's patches for the size reduced (2 μm) vesicle formulation and for the normal sized (6 μm) formulation. Darker bars represent antigen radiolabelled with 125I and lighter bars represent vesicle carrier radiolabelled with Tritium.

immunity. Studies into their potential to stimulate immune responses continue.

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Acknowledgements

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AMORPHOUS SOLID DISPERSIONS

YIWEI TIAN • QUEENS UNIVERSITY BELFAST

Solubility issues in the pharmaceutical industry

Over the last 40 years, high throughput screening tools have been implemented in the design and development of new chemical entities (NCEs). These methods were introduced to reduce the cost of finding lead compounds for a specific pharmaceutical target, thus permitting faster optimisation in the generation of candidate drugs. One of the principle drawbacks of this approach has been the generation of molecules that have limited solubility in gastrointestinal fluids[1]. It is estimated that 40% of new chemical entities are poorly water-soluble, leadsing to incomplete absorption and low, or highly variable, bioavailability. Solubility is one of the most important physicochemical properties of a drug. The determination of drug solubility and ways to alter it, are essential components of pharmaceutical development. Drug molecules are required in a dissolved form, in order to be absorbed and have a therapeutic response. Therefore, low aqueous solubility can either delay and/or limit drug absorption and hence reduce therapeutic efficacy. Moreover, drug solutions are often preferred for other pharmacological, toxicological and pharmacokinetic studies during development. There are many methods that can be used to tackle the issue of poor water solubility, including identification and selection of stable pharmaceutical salts[2], particle size reduction, formation of nano-sized suspensions[3], complexation[4], solubilizing excipients[5], cocrystals and amorphous dug dispersions.

Amorphous pharmaceutical solids

Amorphous or glassy solids, also known as disordered or frustrated systems, can be prepared by increasing the temperature beyond melting point followed by rapid cooling. If cooling rate is sufficient to negate nucleation, the material will enter its supercooled liquid state (amorphous phase). As the temperature drops, the increased viscosity and decreased molecular mobility will restrict the freedom of the molecule, forming an amorphous solid. Amorphous solids normally exhibit a higher aqueous solubility than their crystalline counterparts. Given that the oral absorption of BCS class II drugs is dependent upon the solubility, using a high-energy state amorphous solid form is a powerful way to improve solubility and drug absorption. It has been reported that the solubility advantage of an amorphous drug form may be 10 and 1600 fold higher than its most stable crystalline counterpart[6].

An amorphous drug has a higher free energy, enthalpy and entropy than a crystalline drug. This energy difference is the reason why it is possible to achieve higher solubility in gastrointestinal fluids. However, amorphous drug forms present a significant challenge to commercial application due to poor physical stability and a tendency to recrystallise. Only a small number of pharmaceutical products have been successfully marketed having enhanced bioavailability and acceptable physical stability[7,8]. The limited commercial success reflects the difficulty in stabilising the amorphous form for industrial mass production.

Amorphous solid dispersions

Amorphous solid dispersions describe a group of dosage forms in which the drug is dispersed, in an amorphous form, into another hydrophilic amorphous carrier in the solid state[9]. A crystalline carrier may also be considered. However, in amorphous drug-crystalline polymer solid dispersion systems, drug compounds typically have a higher tendency to phase separate due to rapid recrystallisation of the polymeric carrier, thereby negating the advantages of amorphous drug forms. If the drug is dispersed and/or dissolved into the polymeric matrix at the molecular level, its aqueous solubility may be preserved and/or further enhanced relative to the solubility of pure amorphous drug. This is because drug is incorporated into a hydrophilic, dispersing polymer and thus drug

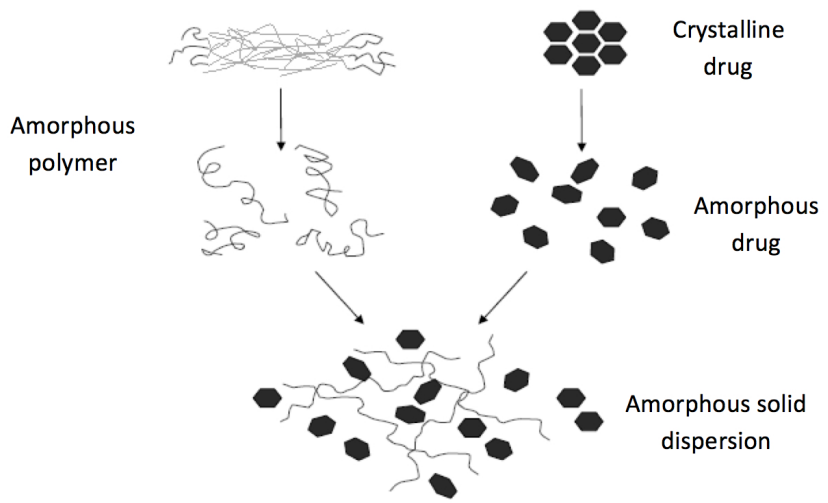

Figure 1. Schematic representation of amorphous drug formation.

presented to dissolution fluid with polymer. This improves wetting and may reduce agglomeration in the dissolution media[10]. Amorphous solid dispersion systems are currently receiving considerable attention both in industry and academia. The number of publications and patents associated with these systems has increased extensively over the last decade[8]. An illustration of the formation of an amorphous solid dispersion is shown in Figure 1.

Apart from the normal considerations in selecting a polymer for formulation purposes, a number of challenges need to be considered in implementing this technology to enhance the aqueous solubility of a crystalline drug.

1. *The recrystallisation of supersaturated drug during dissolution* – Since the solubility of a poorly water-soluble drug in amorphous form is much higher than in crystalline form, a supersaturated drug solution is normally generated during the dissolution. The supersaturated drug molecules may recrystallize. Therefore, a sharp increase and gradual decrease in the apparent drug concentration may be observed which is often referred to as 'spring and parachute' dissolution profile[11]. Consequently, selection of a suitable polymer carrier is crucial for the generation and maintenance of the metastable supersaturation state. Cellulose derivatives (HPMC, HPMC-AS), methacrylate group (Eudragit®) and vinyl-pyrrolidone group (PVP, PVPVA) polymers can maintain the supersaturated drug concentrations during dissolution[12-14].

2. *The kinetic restriction of dispersed amorphous drug from phase separation and crystallisation* – The glass transition (Tg) is normally used to evaluate the stability of amorphous solid formulations. In this case, a polymer carrier with a higher Tg is likely to be employed to increase the physical stability of the system. It is well known that both chemical and physical instability of the amorphous system are more pronounced at temperatures exceeding the Tg[15]. However, exceptions have been reported on certain drugs[16-18]. It is very important to understand that, despite the general acceptance of using Tg as a description of amorphous system stability, the correlation between physical stability and temperature relative to Tg is not often predictive.

3. *Thermodynamic miscibility of drug and polymer* – Although the kinetic restriction of the amorphous drug molecules should prevent phase separation, it is not the case for long-term stability. The degree of supersaturation of drug in a polymer matrix is of significant importance. Consequently, it is extremely important to understand the thermodynamic miscibility of drug and polymer molecules in amorphous solid dispersion systems[19, 20]. Furthermore, molecular interactions between drug and polymer must also be probed so that specific interactions which may play an important role in dictating phase miscibility and possibly, physical stability, may be better understood[19, 21].

4. *Manufacturing process and the impact on the properties of amorphous solid dispersion* – Preparation of amorphous solid dispersions commonly involves thermal fusion methods, such as melt extrusion or solvent methods such as spray drying[22,23]. The manufacturing techniques and process parameters are very important for the physical stability and dissolution performances of amorphous solid dispersions[24, 25].

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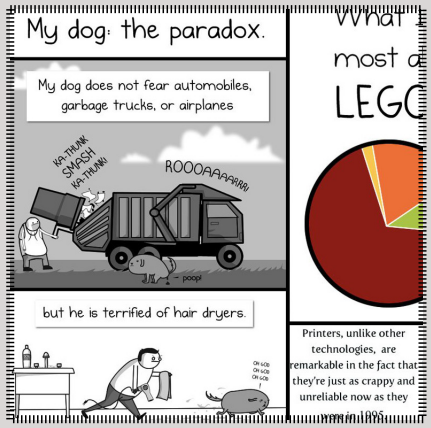

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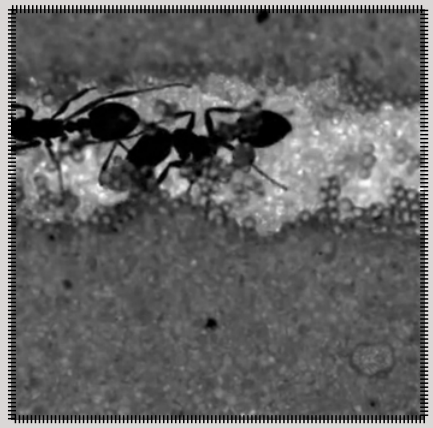

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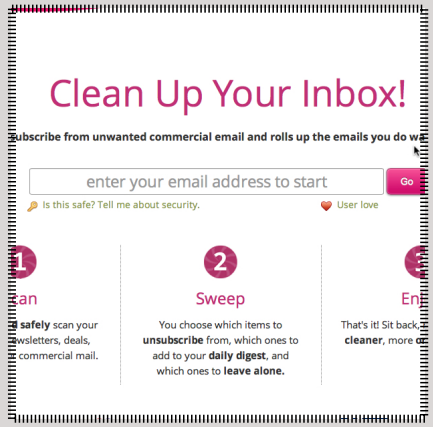

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UKICRS

Summer Studentship Initiative 2014

As part of a new initiative, UKICRS are seeking industrial sponsors to help support up to three 6-week summer studentships during the summer of 2014. It is anticipated that the general research topic will be selected by the industrial sponsor. Applications, including a one-page outline proposal relevant to the topic, will be invited from students entering the penultimate or final year of their undergraduate education in any university within the UK and Ireland. The applicant must have the support of an academic supervisor and the institution in order to apply.

Winning applicants will be selected by a panel comprising UKICRS committee members and representatives from each industrial sponsor. The key criteria for assessing the applications will include project feasibility, novelty, and the previous academic performance of the applicant.

UKICRS will contribute £500 to each project with a further £1000 coming from the industrial sponsor. The money will be used to pay the student a bursary of £200 per week and to contribute £300 to laboratory consumable costs. UKICRS will administer the payments.

The winning applicants and their industrial sponsors will be featured in the 2014 UKICRS Newsletter. Also, the applicants will be expected to write a short article describing their summer project for inclusion in the 2015 UKICRS Newsletter.

If your company would like to be involved in this exciting new initiative, please email Paul Smith (UKICRS Committee Member, ukicrs@ukicrs.org).


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