UKICRS Symposium 2011

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Postgraduate Symposium

Wednesday 13 April 2011

Great Hall, Lanyon Building
Queen's University Belfast
Belfast, Northern Ireland

WELCOME!

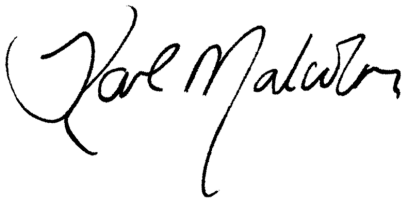
Dear delegate,

A very warm welcome to the 2011 UKICRS Symposium! The committee are delighted to to be hosting the event in Belfast once again, following our last successful meeting here back in 2003. Unlike previous UKICRS symposia, this year's programme is aimed primarily at encouraging participation from UK postgraduate students, postdoctoral researchers and early-stage industrialists working in the general field of drug delivery. We do hope that you appreciate the change in emphasis, and, if successful, we plan to run similar events in future years.

We're delighted to welcome Prof Vladimir Torchilin and Prof Morgan Alexander to the symposium as our keynote speakers. Both have a reputation for excellence in their respective research fields and we are privileged to have them present their work to us.

At the core of any scientific meeting are the opportunities to formally present research results and ideas to a wider audience, and UKICRS have been careful to ensure that as many attendees as possible are afforded this opportunity through the oral and poster sessions. However, the real measure of a successful scientific meeting lies in the degree and quality of the engagement and interactions between people. We encourage you to take the time to ask questions, to discuss your research with your peers, and to make new friends and collaborators.

Enjoy the symposium!



Karl Malcolm & G a v i n Andrews
2011 UKICRS symposium organizers

PROGRAMME

8.30 am	Registration / Poster Setup
9.30 am	**Prof Sean Gorman** / **Dr Karl Malcolm** (Queen's University Belfast) Welcome & Opening Remarks
9.40 am	**Prof Vladimir Torchilin** (Northeastern University) 'Nanomedicines'
10.25 am	**Robyn Fowler** (University of Nottingham) 'Morphological and permeability characteristics of Caco-2 and Calu-3 layers: A Comparison'
10.40 am	Tea / Coffee
11.10 am	**Jitinder Singh Wikhu** (Aston University) 'Using differential scanning calorimetry (DSC) to understand thermal properties of surfactants which are used to formulate bilayer vesicles'
11.25 am	**Maha Nasr** (University of Central Lancashire) 'An alternative route of administration for bisphosphonates: From theory to practice'
11.40 am	**Claire Forbes** (Queen's University Belfast) 'Novel silicone elastomer gels for sustained vaginal delivery of the HIV-1 entry inhibitor maraviroc'
11.55 am	Poster Session 1
12.40 pm	Lunch (Canada Room)
1.40 pm	**Prof Morgan Alexander** (University of Nottingham) 'New polymers for stem cell culture: a high throughput materials discovery adventure'
2.10 pm	**Robert Ahern** (University College Cork) 'Investigating the effect of processing conditions on fenofibrate dissolution rate: A design of experiments approach'
2.25 pm	**Amr ElShaer** (Aston University) 'Could amino acid salts fool fussy bacteria to improve antibiotics uptake?'
2.40 pm	**Wei Chen** (Queen's University Belfast) 'A novel bacterial protease-triggered polymeric antimicrobial release system'
2.55 pm	Tea / Coffee
3.15 pm	Poster Session
3.45 pm	**Marija Bezbradica** (Dublin City University) Ethylcellulose / pectin coated microspheres in controlled drug delivery: Agent based modelling'
4.00 pm	**Sarah McNeil** (Aston University) 'Formulation and in vitro assessment of liposomal DNA vaccines'
4.15 pm	**Martin Garland** (Queen's University Belfast) 'Clinical evaluation of a polymeric microneedle array for transdermal drug delivery applications'
4.30 pm	Poster Prizes / Close of Meeting

INVITED SPEAKERS

VLADIMIR TORCHILIN - NORTHEASTERN UNIVERSITY

Vladimir Torchilin is Distinguished Professor and Director of the Center for Pharmaceutical Biotechnology and Nanomedicine at Northeastern University. He has over 30 years of experience in drug delivery, pharmaceutical nanocarriers, nanomedicine, nanotechnology, and biocompatible polymeric materials. His Center for Translational Cancer Nanomedicine at Northeastern University has made seminal contributions in the area of multifunctional pharmaceutical nanocarriers, mainly liposomes and polymeric micelles, for targeted delivery of imaging agents, drugs, and genes in cancer and cardiovascular diseases.

His current work, which dovetails with Northeastern's focus on use-inspired research that solves global challenges in health, security and sustainability, focuses on developing drugs that target specific organelles inside human cells in order to maximize the therapeutic outcome.

Prof Torchilin is also the world's second-most prolific researcher in pharmacology and toxicology, according to Times Higher Education, a London-based international publication.

MORGAN ALEXANDER - UNIVERSITY OF NOTTINGHAM

'New polymers for stem cell culture: a high throughput materials discovery adventure'

Morgan Alexander is Professor of Biomedical Surfaces at the School of Pharmacy, University of Nottingham. He received his Bachelor of Science in Materials in 1988 and his PhD from the same department at The University of Sheffield in 1992.

His work comprises making and characterising material in order to determine what relationships exist between surface chemistry and biological response. This question is critical in the development of biomaterials and is the theme running through his group's work across a variety of biomedical application areas including bacterial adhesion to polymers and retaining stem cell pluripotency in synthetic culture systems.

He has contributed to books on surface chemical modification and analysis and has authored over 100 papers dealing with surfaces in high quality peer reviewed publications, including research articles in Nature Materials, Advanced Materials, and Biomaterials. This research is highly interdisciplinary, involving collaborators from a wide variety of fields including regenerative medicine, neuroscience, developmental biology, pharmaceutics, materials processing, plasma physics and nanofabrication. This work is funded by The Wellcome Trust, EPSRC, BBSRC, EMDA, MRC, DSTL and industry. A number of his group have gone on to take up lectureships.

ORAL ABSTRACTS

1 MORPHOLOGICAL AND PERMEABILITY CHARACTERISTICS OF CACO-2 AND CALU-3 LAYERS: A COMPARISON

R Fowler, D Vllasaliu, C Alexander, M Garnett and S Stolnik
Division of Drug Delivery and Tissue Engineering, School of Pharmacy, Boots Science Building, University of Nottingham, University Park, Nottingham, NG7 2RD
E: paxrf1@nottingham.ac.uk

This work compares morphological and barrier properties of filter-cultured Calu-3 and Caco-2 cells, which are commonly used as in vitro models of airway and intestinal epithelia in drug discovery/delivery research. Cell morphology was examined using electron and confocal microscopy. The barrier of the resulting polarised cell layers was evaluated by measuring the permeability of varying molecular weight dextrans. Immunostaining for a key tight junction protein (Zonula Occludens-1, ZO-1) revealed expression in both cell lines and tight junctions were visualised by TEM. In Calu-3 cells ZO-1 distribution appeared linear at points of cell-cell contacts, whilst in Caco-2 cells a more convoluted organisation was apparent. Although Caco-2 monolayers exhibited a higher transepithelial electrical resistance (~2000 Ωcm^2 vs 800 Ωcm^2), dextrans traversed these monolayers at a markedly higher rate (up to 4.5-fold) than in Calu-3 layers. Studies at 4°C revealed a molecular weight-dependent effect on permeability, suggesting involvement of different transport pathways. The use of a tight junction-opening absorption enhancer increased the rate of permeability of two dextrans (M_W 4 and 70 kDa) across the layers of both cell lines to a similar extent. Our work demonstrated that Calu-3 and Caco-2 epithelial cell lines differ in their morphology and Calu-3 cell layers present a greater barrier to macromolecular permeability than Caco-2 cells. This could be due to the larger surface area of the tight junctions in Caco-2 cells (shown by microscopy data) and/or the presence of mucus in Calu-3 cells. The molecular size-dependent effect of temperature on dextran permeability revealed mechanistic insight into the nature of macromolecular transport. Opening the tight junctions elevates macromolecular permeability to a similar extent in both cell lines, but the leakier nature of Caco-2 monolayers results in achievement of a markedly higher permeability across this model of the intestinal epithelium with or without the use of absorption enhancers.

2 USING DIFFERENTIAL SCANNING CALORIMETRY (DSC) TO UNDERSTAND THERMAL PROPERTIES OF SURFACTANTS WHICH ARE USED TO FORMULATE BILAYER VESICLES

J Wilkhu (1), D Anderson (2) and Y Perrie (1)
(1) School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, UK.
(2) Variation Biotechnologies INC, 1740 Woodroffe Avenue, Ottawa, Ontario
E: jitinder@gmail.com

Particulate delivery systems using bilayer vesicles are currently recognised for their efficacy as drug delivery systems either by encapsulation or surface adsorption of the active compound to vesicles. For example, niosomes which are vesicles formed from non-ionic surfactants have been investigated as vaccine delivery systems. The manufacture of such vesicles is often carried out by melting of the surfactants hence, it is vital to understand analytically the thermal properties of the surfactants used in addition to characteristics such as vesicle size and charge. The aim of this study was the utilisation of DSC to enhance understanding of the thermal properties of the surfactants used to form vesicles. DSC works on the principle of measuring the difference in heat energy of a sample pan against a reference pan under the same experimental method and atmospheric conditions (Demetzos, 2008). The surfactants used for this study include Monopalmitoyl glycerol (MPG) (Genzyme), Cholesterol (CHO) (Sigma) and Dicetyl Phosphate (DCP) (Genzyme) at ratios of 5:4:1 molar respectively for the mixture. The individual lipids were placed into Aluminum pans ensuring the weight of sample were kept constant to ensure accurate enthalpy data. The method used for DSC had a heating rate of 10°C/min over a temperature range from 0-160°C.

DSC scans of the individual components in the solid state prior to mixing show a wide melting range for each of the surfactants with MPG having the lowest melting point at 70.10±0.20°C, followed by DCP (75.59±0.34°C) and Cholesterol having the highest melting onset point of 148.74±0.07°C. The mixture of surfactants in their ratio of 5:4:1 (MPG:CHO:DCP) has an onset of 69.09±0.18°C. Studies show that multiple component surfactant mixtures can melt at a temperature below that of the highest single component due to inter-digitation and that vesicles can be produced at this lower combined melting point temperature.

This work was funded by VBI technologies and BBSRC.

Demetzos, Costas (2008) Differential Scanning Calorimetry (DSC): A Tool to Study the Thermal Behavior of Lipid Bilayers and Liposomal Stability', Journal of Liposome Research,18:3,159 — 173

3 AN ALTERNATIVE ROUTE OF ADMINISTRATION FOR BISPHOSPHONATES: FROM THEORY TO PRACTICE

M Nasr (1,2), G A S Awad (2), S Mansour (2), I Taha (3), A Alshamy (2) and N Mortada (2)
(1) Institute of Nanotechnology and Bioengineering, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, United Kingdom.
(2) Department of Pharmaceutics, Faculty of Pharmacy, Ain Shams University, Egypt.
(3) Hot lab center, Atomic Energy Authority, Egypt.
E: MNasr@uclan.ac.uk

Bisphosphonates is the most important class of drugs when it comes to treatment of osteoporosis and other resorptive bone disorders. They are only available commercially as oral tablets of low bioavailability (less than 1%) and exhibiting serious gastric and esophageal side effects. In addition, the high hydrophilicity of this group presented a challenge in their formulation in biodegradable hydrophobic systems. Therefore in order to address these problems, we attempted to use the pulmonary route for the delivery of a model bisphoshponate: risedronate sodium (RS) owing to its thin absorption barrier and its capability of enhancing absorption of hydrophilic moieties.

Our project was divided into four phases. First phase was to optimize the encapsulation of RS into biodegradable microspheres prepared by double emulsion method using polylactide-co-glycolic acid (PLGA) as polymer. Factors investigated were the glycolide content, amount of polymer, internal aqueous phase ratio and the amount of drug. Second phase was to apply these optimized conditions in preparing porous PLGA using different porogens (i.e. NaCl, Hydroxypropyl-beta-cyclodextrin and oil). Characterization of the prepared systems was performed through entrapment efficiency, scanning electron microscopy, particle size, in vitro release, particle flow, aerodynamic properties and differential scanning calorimetry. Third phase was to assess the safety of the optimized formulae through MTT assay performed on Calu-3 cells in addition to histopathological study performed on rats. Fourth phase was to examine the in vivo behavior of the selected formula in radiolabelled form through the calculation of RS bone deposition after pulmonary administration the microspheres to rats.

Results of this project showed that RS microspheres were safe to the lungs. RS was successfully deposited in high concentration in the bones via the pulmonary route using this biodegradable system, a finding which opens the opportunity for the large scale application of this route in delivery of this class of drugs.

4 NOVEL SILICONE ELASTOMER GELS FOR SUSTAINED VAGINAL DELIVERY OF THE HIV-1 ENTRY INHIBITOR MARAVIROC

C Forbes (1), D Lowry (1), L Geer (2), R Shattock (3), P J Klasse (4), M Mitchnick (2), L Goldman (2), J Moore (4), Ronald Veazey (5), David Woolfson (1) and Karl Malcolm (1)

(1) School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK

(2) Particle Sciences, USA

(3) St George's Hospital Medical School, Tooting, London, UK

(4) Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA

(5) Tulane National Primate Research Center, Tulane University Health Sciences Center, Covington, LA 70433, USA

E: cforbes06@qub.ac.uk

Aqueous semi-solid gels, such as those based on hydroxyethylcellulose (HEC) and polyacrylic acid (e.g. Carbopol), have long been used for vaginal drug administration, and are currently being developed for delivery of HIV microbicides. Although inexpensive and easy to manufacture, these gels do not provide solubilisation of the growing number of poorly water-soluble microbicide candidates, resulting in suboptimal absorption and activity. Also, aqueous gels are readily diluted by vaginal fluid, resulting in poor vaginal retention. Alternative formulations are required to overcome these obstacles. Here we report the development of a non-aqueous silicone elastomer gel for vaginal administration of the HIV-entry inhibitor compound maraviroc. Flow rheological assessment and mucoadhesive retention studies were performed on placebo silicone elastomer and HEC gels in vitro. Mucosal toxicity of gels containing maraviroc was measured using the slug mucosal irritation test. In vitro release testing was performed on maraviroc-loaded silicone elastomer and HEC gels into both simulated vaginal fluid (SVF) and a solvent/water system. Finally, the pharmacokinetics (blood, vaginal fluid and vaginal tissue) of the maraviroc silicone and HEC gels were compared in rhesus macaques. The viscosity of the silicone elastomer gel can be readily manipulated by co-formulation with cyclomethicone, and is significantly higher than the standard HEC gel. Unlike the HEC gel, the silicone elastomer gel was retained without dilution for 6 hr on an inclined, mucin-coated, glass slide. Maraviroc was released at a greater rate from HEC gels into both release media due to its relatively rapid dissolution. For the more sustained release silicone gel, 27mg maraviroc was released into 1:1 IPA/water at 48hr, 13mg into 1:4 IPA: water and 5mg into SVF. Increased concentrations of maraviroc were observed in the macaque vaginal fluid (7mg/mL at 24 hr) compared to the HEC gel (1.4 mg/mL). The silicone elastomer gel did not cause mucosal irritation in the slug irritancy model, as evidenced by LDH and protein levels comparable to the negative controls and HEC gel. Significantly greater concentrations of maraviroc were measured in blood and vaginal fluid for the silicone gels compared with the HEC gels following vaginal administration in rhesus macaques. The studies demonstrates that silicone elastomer gels are non-irritant and capable of providing sustained release of maraviroc both in vitro and in vivo compared with aqueous-based HEC gels. The results indicate that there is great potential for use of non-aqueous silicone gels for coitally-independent administration of HIV microbicides.

5 INVESTIGATING THE EFFECT OF PROCESSING CONDITIONS ON FENOFIBRATE DISSOLUTION RATE "A DESIGN OF EXPERIMENTS APPROACH"

R Ahern (1, 2), A Crean (1, 2) and Katie Ryan (1, 2)
(1) School of Pharmacy, University College Cork, Ireland
(2) Solid-State Pharmaceutical Cluster (SSPC)
E: robert.ahern@umail.ucc.ie

The objective of this research was to increase the dissolution rate of fenofibrate by loading it onto a high-surface area carrier, mesoporous silica. Fenofibrate and mesoporous silica (SBA-15) powders were physically mixed in a supercritical CO2 environment at various operating pressures (2000, 4000 and 6000 psi) and times (4, 12, and 24 hrs) followed by depressurisation. Processing conditions were investigated using a 32 full factorial design of experiments with 3 true replicates at each set of conditions (N=27 runs).

Different characterisation techniques were used to investigate changes in fenofibrate and mesoporous silica solid state properties after processing. These techniques included scanning electron microscopy to study morphology, powder x-ray diffraction and differential scanning calorimetry to study changes in crystalline form, Fourier transform-infrared (FTIR) spectroscopy to study drug-silica interactions, along with BET surface area and pore volume analysis. In-vitro dissolution studies were also performed to determine fenofibrate dissolution profiles.

All processing conditions studied resulted in amorphorisation of the fenofibrate starting material. There was a reduction in the surface area and pore volume of the fenofibrate-mesoporous silica systems that was attributed to the presence of the drug loaded on the surface of the mesoporous silica. A considerable enhancement of drug dissolution rate was observed for all processed systems and was attributed to (1) the amorphous nature of the drug, (2) the hydrophilic nature of silica and (3) the increased surface area of fenofibrate exposed to the dissolution medium due presence of the silica substrate.

Statistical analysis using analysis of variance (ANOVA) was used to determine the impact of the processing conditions investigated on fenofibrate dissolution rate in the first 5 minutes. No statistically significant main effects or interactions were observed at a significance level of $p = 0.05$.

6 COULD AMINO ACIDS SALTS FOOL FUSSY BACTERIA TO IMPROVE ANTIBIOTICS UPTAKE?

A ElShaer, P Hanson, P Lambert and A R Mohammed.
Aston Pharmacy School, Aston University, Birmingham
E: elshamk1@aston.ac.uk

Introduction: Trimethoprim (TMP) is a dihydrofolate reductase (DHFR) inhibitor which prevents the conversion of dihydrofolic acid into tetrahydrofolic acid, resulting in the depletion of the latter and causing bacterial death. The formulation of TMP is hampered due to its poor aqueous solubility and therefore requires extensive research to ensure sufficient bioavailability. This study aims to prepare novel salts of TMP using anionic amino acids counter ions; aspartic acid and glutamic acid and since amino acids are essential nutrients for bacterial growth and have a full transporter system in the bacteria [1], our study will investigate whether intrinsic resistant bacteria will take up amino acid salts and in turn improve the uptake of TMP.

The two new salts were prepared by lyophilisation and characterised using FT-IR spectroscopy, proton nuclear magnetic resonance (^{1}HNMR), Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TGA). FT-IR data confirmed salt formation by showing a new band at 1664.53 cm^{-1} corresponding to $\nu C=O$ stretching which confirms that trimethoprim cationic nitrogen interacted with the carboxylic group of aspartic acid to form a salt, while, ^{1}HNMR suggests that aspartic acid and glutamic acid form salts with TMP in a 1:1 molecular. Solubility studies have demonstrated that the novel salts improved the solubility of TMP by 250 folds. Antibiotic activity of the prepared salts was studied in Pseudomonas aeruginosa due to the presence of a tough cell wall. The results showed that the new salts were equally effective as the basic drug. Further investigation of the prepared salts to determine synergism in antibiotic activity due to the presence of Na+ dependant transporter system for amino acids across Pseudomonas aeruginosa cell wall showed the amino acids salts failed to lower the minimum inhibitory concentration required for the uptake of TMP suggesting the possibility of ion dissociation due to weak electrostatic forces

[1] Hoshino T and Kose . K., (1990), American Society for Microbiology, 172 (10)

7 A NOVEL BACTERIAL PROTEASE-TRIGGERED POLYMERIC ANTIMICROBIAL RELEASE SYSTEM

W. CHEN, B. WALKER, S.P. GORMAN, B.F. GILMORE
Queen's University Belfast, School of Pharmacy, 97 Lisburn Road, Belfast, UK. BT9 7BL
E: w.chen@qub.ac.uk

There is an urgent necessity for biomaterials which exhibit pathogen-responsive release of antimicrobials to tackle device associated infections, since sub-optimal antimicrobial release from antimicrobial devices may contribute to the emergence of drug-resistance. The aim of this program is to develop novel hydrogel device coatings where antimicrobial release is triggered by bacterial proteases, such as S. aureus V8 protease and to investigate the ability of these materials to prevent microbial adherence (S. aureus NCTC10788).

Prodrug monomers, Acryl-$(PEG)_2$-DVFE-GIGKFLKKAKKFGKAFVKILKK-NH_2 (Acryl-$(PEG)_2$-DVFE-G20K), Acryl-LLE-Trimethoprim (Acryl-LLE-TMP) and Acryl-DVFE-TMP, were synthesized. Each prodrug monomer (1.5 mM) was incubated with V8 protease from S. aureus (Merck) (4U/mL) at 37 °C for 24 h. The supernatant was analyzed by HPLC to determine the sensitivity of monomers against V8 protease. The antibacterial activity of monomers in the presence/absence of S. aureus was assayed by a well diffusion method, wells of 11 mm diameter were punched. Hydrogels, p(60HEMA-co-40MAA), p(60HEMA-co-40MAA-co-1Acryl-$(PEG)_2$-DVFE-G20K) and p(60HEMA-co-40MAA-co-4Acryl-LLE-TMP), were prepared and their resistance to S. aureus adherence at 4-h time point was determined.

Cleavage/liberation of antimicrobial in the presence of V8 protease was followed by HPLC and MS. V8 protease effected release of G20K (1.10 mM) and TMP (32 μM and 39 μM) from Acryl-$(PEG)_2$-DVFE-G20K, Acryl-LLE-TMP and Acryl-DVFE-TMP, respectively. The well diffusion test revealed zones of inhibition of 19 mm and 21 mm in diameter following cleavage of Acryl-LLE-TMP and Acryl-DVFE-TMP by V8 protease, respectively. No inhibition zone was observed with wells in the absence of V8 protease. S. aureus adherence to p(60HEMA-co-40MAA-co-1Acryl-$(PEG)_2$-DVFE-G20K) and p(60HEMA-co-40MAA-co-4Acryl-LLE-TMP) was reduced by 90.49% and 53.81%, respectively, relative to p(60HEMA-co-40MAA). A novel V8 protease responsive, polymer-antibiotic hydrogel system exhibiting reduced adherence of S. aureus was developed which may offer an approach to reduce device associated biofilm formation.

8 ETHYLCELLULOSE/PECTIN COATED MICROSPHERES IN CONTROLLED DRUG DELIVERY: AGENT BASED MODELLING

M Bezbradica, H J Ruskin and M Crane
Centre for Scientific Computing and Complex Systems Modelling, School of Computing
Dublin City University, Ireland
E: mbezbradica@computing.dcu.ie

Novel drug formulations are designed to reduce side effects, such as unnecessary absorption and "dose dumping", as well as to improve dosage administered, through controlled and targeted release. Unlike classical differential-equation models, probabilistic modelling, besides reducing high experimental costs and predicting system-dependent changes, is applicable to a wide range of systems without requiring detailed initial knowledge of dissolution mechanisms. In collaboration with one of the leading biopharmaceuticals in Ireland, (Sigmoid Pharma Ltd.), we present a Monte Carlo model for simulation of the drug dissolution from coated microspheres. Formulations of ethylcellulose/pectin are used to protect cyclosporine, (the active component), in the upper stages of the gastro-intestinal tract and to facilitate targeted delivery of the desired dose in the colon.

Agent-based modelling is used to represent drug particles as intelligent agents, governed by a set of rules, moving through a three-dimensional grid of cells. Each cell state includes information on the type, (i.e. solvent, coating, drug, gelatine and pore) and the corresponding physico-chemical properties. State transitions and drug movement are defined in terms of statistical and physical laws, simulating three important phenomena: diffusion, erosion and swelling. The effect of different design parameters, such as coating thickness, size distribution and polymer/gelatine properties, on release profiles, is considered. Insight on system evolution is also provided by graphical representation of the model, which captures successive stages of the dissolution. The model has been adapted for parallelisation, in order to facilitate simulation speed-up and resolution refinements.

Compared to in vitro data, obtained from Sigmoid Pharma, modelling results show the ability to mimic experimental conditions and outputs for a wider set of parameters. While useful in their own right, these also provide indications of where the model can be further improved and adapted to different experimental needs, such as device design and composition variations.

9 FORMULATION AND IN VITRO ASSESSMENT OF LIPOSOMAL DNA VACCINES.

S. E. McNeil, S. Carter, T. Parekh and Y. Perrie
Aston Pharmacy School, Aston University, Birmingham, UK. B4 7ET
E: s.e.mcneil1@aston.ac.uk

Design of experiment (DoE) is a systematic approach for evaluating the affect of different factors and variables on the outcome of a process. By considering all possible combinations, factorial design allows extensive exploration into the interactions between variables and the overall affect on the final outcome. The program selectively generates a list of experimental parameters, significantly reducing the number of experimental preparations required for evaluation. The aim of this work was to apply a DoE programme to obtain greater precision at estimating the overall main factors which may affect the characteristics of small unilamellar vesicles (SUV) and SUV-DNA complexes, and subsequently influence the cytotoxicity and transfection efficiency of SUV-DNA complexes in vitro. Factorial design was performed by the software MODDE 8.0 (Umetrics, Sweden). SUV-DNA complexes consisting of a cationic lipid, either cholesterol 3b-N-(dimethylaminoethyl)carbamate (DC-Chol) or 1,2-Dioleoyl-3-Trimethylammonium-Propane (DOTAP) and the helper lipid, L-alpha-Dioleoyl Phosphatidyl ethanolamine (DOPE) were prepared at various lipid ratios and concentrations of gWIZ plasmid DNA, selected from the DoE program and systematically tested. The physicochemical characteristics were measured and transfection efficiency and cytotoxicity to COS-7 cell line were assessed.

The most critical parameter influencing the mean size and zeta potential of liposomes-DNA complexes is the concentration of the cationic lipid component for both cationic lipids tested, DC-Chol and DOTAP, whereby particle size decreases with an increase in cationic lipid content. The concentration of plasmid DNA is also shown to be a contributing factor. SUVDNA complexes form spontaneously upon mixing DNA with positively charged liposomes and the complex system formed is dependent on the charge ratio. DCChol formulations exhibited slightly higher levels of cell viability than DOTAP formulations, presumably due to the presence of quaternary amine head groups within DOTAP, which are shown to be more toxic towards cells than tertiary amine head groups within DC-Chol.

10 CLINICAL EVALUATION OF A POLYMERIC MICRONEEDLE ARRAY FOR TRANSDERMAL DRUG DELIVERY APPLICATIONS

M J Garland, T R Raj Singh, A D Woolfson, and R F Donnelly.
School of Pharmacy, Queen's University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast, BT9 7BL, UK.
E: mgarland01@qub.ac.uk

Microneedles (MNs) have been shown to penetrate the skin, across the stratum corneum, and into the viable epidermis, avoiding contact with nerve fibres and blood vessels that reside primarily in the dermal layer. Despite promising results from delivery studies, the future of MN technology would be inauspicious if their application caused pain and/or distress in patients. The aim of this six volunteer clinical study was to obtain an insight into the effect that application of a hydrogel MN, based upon poly(ethylene glycol) crosslinked poly (methyl vinyl ether co maleic acid), had upon volunteer perception of pain, the disruption of skin barrier function, and the degree of skin irritation. Following local ethical committee approval, four patches containing either of no formulation, a non-MN hydrogel, a hydrogel MN of density 121 MNs / 0.5 cm^2, or a hydrogel MN of density of 361 MNs / 0.5 cm^2 were applied to the left ventral forearm of the human volunteers, using a spring activated impact applicator. These patches were then removed at different time periods (i.e. 0, 2, and 24 hours), with pain perception assessed using a visual analogue scale (VAS), barrier disruption assessed via transepidermal water loss (TEWL) measurements, and skin irritation graded through scoring of clinical photographs by an experienced consultant dermatologist. The insertion of MN arrays was found to be barely perceptible, and described as more of a "rubbing" feeling rather than a sharp cut. Interestingly, an increase in MN density led to an increase in the VAS scoring for pain perceived during insertion (0.14 ± 0.08 for 121 MNs, and 0.33 ± 0.10 for 361 MNs). MN insertion led to an increase in the TEWL measurements recorded in comparison to the control patches, indicating that MN insertion successfully disrupted the barrier properties of the skin. However, in all MN cases it was found that TEWL values returned to baseline values within 1 hour following MN removal. Importantly, the degree of skin irritation associated with the application of MN array was graded as being only minimal and transient in nature, with any skin redness that occurred disappearing within 1 hour. In conclusion, the results of this short clinical study indicate that a hydrogel MN array has potential as a minimally invasive, safe device for transdermal use. Future studies are now required to investigate the need for sterilisation of MN devices, and if so, to determine a suitable method for sterilisation of such polymeric systems.

POSTER ABSTRACTS

11 QUALITY BY DESIGN STUDY FOR THE FORMULATION OF LYOPHILISED ORALLY DISINTEGRATING TABLETS

F A Alhusban, Y Perrie and A R Mohammed
Aston University, School of Life and Health Sciences, Birmingham, B4 7ET, UK
E: a.u.r.mohammed@aston.ac.uk

Research from our laboratory has demonstrated the role of gum arabic as a binder in the formulation of lyophilised orally disintegrating tablets (ODTs) resulting in its potential to improve formulation, production process and performance of the tablet and consequently widening of its pharmaceutical applications. In the current study, the feasibility of incorporating therapeutics doses of ibuprofen was investigated using a full factorial design (3^2) study that evaluated the influence of two formulation variables; alanine and active drugs concentrations, on five crucial responses; disintegration time, glass transition temperature (Tg'), hardness, friability and drug content. The application of 3^2 factorial design revealed the influence of varying the selected formulation factors individually and together on the quality of the ODTs, which led to a statistical model and three dimensional plots that described adequately the relationship between dependent and independent variables.

Based on the response surface plots, the software was used to perform hot spot analysis to find the optimum formulation variables (alanine and ibuprofen concentrations) to produce ODTs with optimum characteristics consisting of short disintegration time, high Tg', high hardness and low friability. The optimal formulation was determined as 40% (w/w) alanine and 40 % (w/w) ibuprofen. The characterisation results verified, experimentally, the established statistical models, as only small differences were observed between the actual (observed) and calculated (predicted) values. The dissolution results showed that the prepared lyophilised tablets showed faster dissolution rate with around 90% drug release after 5 minutes, compared to around 50% in case of commercially available compressed ODTs (Nurofen Meltlets).

12 FORMULATION OF SOLUBLE MICRONEEDLE ARRAYS FOR ENHANCED INTRADERMAL DELIVERY OF A MODEL ANTIGEN

S Alzahrani, C Scott and R F Donelly
Queen's University belfast, School of Pharmacy, 97 Lisburn Road. Belfast, UK. BT97BL
E: salzahrani01@qub.ac.uk

Vaccines are usually administrated by hypodermic injection. This route has several drawbacks, including accidental needle-sticks, pain, and needle phobia. New vaccination techniques have been proposed to replace needles. One of the most promising techniques is minimally invasive soluble microneedles loaded with antigen which could have a potential to replace hypodermic needles and produce robust immune responses. Soluble microneedles have several advantages over conventional methods of vaccination as well as other types of microneedles such as solid and coated microneedles. Soluble microneedles can provide safe, painless, self-administration and quickly dissolve in body fluid leaving behind no biohazardous waste. The aim of the present work was to determinate the stability of a model antigen (ovalbumin) incorporated into microneedles, after different storage times.

Microneedles were prepared from aqueous blends of 20% w/v poly (methyl vinyl ether/maleic acid) (PMVE/MA) loaded with the model antigen ovalbumin. Ovalbumin stability after being incorporated into microneedles was determined through probing its primary, secondary structure and content, at different storage times using Western blot, circular dichroism and BCA kit.

The results showed that, PMVE/MA has a negligible effect on ovalbumin integrity. This was confirmed by the three different stability assays. Furthermore, Western blot analysis showed no ovalbumin degradation. Ovalbumin, secondary structure remained in its native state since no difference was seen in ovalbumin spectrum after being incorporated into microneedles. Ninety six per cent of the theoretical ovalbumin loading was recovered from dried microneedles.

Microneedles prepared from aqueous blends of 20% w/v PMVE/MA incorporated with antigen may be useful in intradermal vaccination due to targeting immune cells in the skin more effectively than conventional hypodermic injections.

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13 THE IMPACT OF AGEING ON ORAL DRUG ABSORPTION AND BIOAVAILABILITY: A SYSTEMS-BASED PHARMACOKINETIC APPROACH

R K Singh Badhan
Aston University, School of Life and Health Sciences, Birmingham, B4 7ET, UK.
E: r.k.s.badhan@aston.ac.uk

Important pharmacokinetic and pharmacodynamic changes occur with ageing. The small-intestine is a major site of drug absorption following oral drug administration and ageing-associated changes in small-intestine physiology (geometry, pH, and permeability) and enterocyte physiology (metabolising enzyme and drug transporter enzyme abundance and ab-oral distribution) may impact on the bioavailability (F) of orally delivered drugs. To assess the impact of ageing on oral drug absorption, a previously described physiologically-based pharmacokinetic (PBPK) model of the human small-intestine was adapted to simulate solid-dosage form dissolution and oral drug absorption ab-orally and across intestinal epithelial cells. The adapted model described incorporates important geometric and physiological variations along the small-intestine in addition to descriptions of the abundance and distribution of major intestinal metabolising enzymes (cytochrome P450 3A4 [CYP3A4]), drug uptake transporters (organic anion transporting polypeptides [OATP]; oligopeptide transporters [PEPT]) and drug efflux transporters (P-glycoprotein [Pgp]).

Simulations were performed for three stages of life: paediatric, adult and geriatric, using preclinical in-vitro data for model drugs, to establish the impact of changes in small-intestine physiology, Pgp, CYP3A4, OATP and PEPT abundance and distribution and intestinal permeability on oral drug absorption throughout ageing. Model-based physiological and enzyme/protein expression model parameters were adjusted over typical ranges reported in the literature for each age group. The impact of ageing on oral drug absorption was assessed by characterisation of the fraction of drug absorbed across the lumen (fa), intestinal enterocyte drug kinetics, fraction of drug escaping the intestinal enterocytes intact (fg) and F for model drugs.

R.K. Badhan, J.Penny, A. Galetin and J. Brian Houston. (2009) Journal of pharmaceutical sciences, 98, 2180-97.

14 USING IN-VITRO DISSOLUTION SCREENING TO ASSESS THE ROBUSTNESS OF HPMC ORAL CONTROLLED RELEASE MATRIX TABLET FORMULATIONS

M Beauchamp (1), R Elkes (2) and C Neri (1)
(1) Analytical Sciences, MSD Ltd, Hoddesdon, UK.
(2) Formulation Sciences, MSD Ltd, Hoddesdon, UK
E: martyn_beauchamp@merck.com

The ruggedness of an HPMC oral CR matrix dosage form is dependent upon several factors, such as the amount of HPMC polymer % w/w, the HPMC polymer grade, the surface area to volume ratio, levels of disintegrants and other excipients and the physical properties of the API. Among these factors, functional polymer type and loading play a key role. To support the formulation development an in vitro dissolution screening was developed to assess potential robustness liabilities for the three different release rates formulations developed.

To assess the robustness of the dosage forms the formulations were subjected to a battery of dissolution testing utilising USP apparatus II and III. The effects of the dissolution medium used, ionic strength of the medium, pH and agitation were all investigated. Two HPMC polymer grades, K4M and K100LV, were assessed independently and as a combination of the two, to identify their relative robustness. The 'break points', where the dosage form was no longer exhibiting a controlled release rate mechanism, of the formulations was determined with respect to HPMC loading.

This work demonstrated that the three formulations developed to support commercial manufacture and to explore the potential for establishing an IVIVC were robust and suitable for large scale manufacture.

15 ALTERATION OF THE SOLID STATE NATURE OF SULFATHIAZOLE AND SULFATHIAZOLE SODIUM ON SPRAY DRYING

S Bianco, V Caron, L Tajber, O I Corrigan and A M Healy
School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2.
E: sbianco@tcd.ie

Solid state characterisation of a polymorphic drug following pharmaceutical processing and upon storage is a fundamental aspect in the development of drug formulations. Sulfathiazole (ST) and its corresponding sodium salt form (STNa) were spray dried using a laboratory scale spray drier. The aim of the study was to investigate the effects of using different solvents, feed concentrations and spray drier configuration on the solid state nature of the processed materials. The storage stability of the spray dried materials was also determined. The physicochemical properties of the spray dried powders were compared to the unprocessed materials. Characterisation techniques included thermal analysis, X-ray diffraction and dynamic vapour sorption (DVS). Spray drying of ST from either acetonic or ethanolic solutions with the spray drier operating in a closed cycle mode yielded crystalline powders. In contrast, the powders obtained from ethanolic solutions with the spray drier operating in an open cycle mode were amorphous. Amorphous ST powders were physically unstable and tended to recrystallise rapidly. Interestingly, the final polymorphic composition was dependent on the storage conditions. Recrystallisation to pure form I was observed when the amorphous ST powders were stored at 25 and 40°C and ≤ 35% RH. At higher RH values amorphous ST recrystallised into a mixture of polymorphs. In contrast, STNa converted to an amorphous phase upon processing, regardless of the solvent and of the spray drier configuration employed. RH was found to have a strong plasticising effect on the amorphous salt, inducing its phase transformation into a sesquihydrate when exposed to step changes of RH in a DVS apparatus. Control of spray drying adjustable parameters is essential to ensure consistent solid state characteristics of the spray dried product.

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16 SEDIMENTATION CHARACTERISTICS OF LIPOSOME FORMULATIONS FOR USE AS REFERENCE STANDARDS IN THE ELISPOT ASSAY

S Bibi (1), E Lattman (1), B Walker (2), D Bryan (2) and Y Perrie (1)
(1) Aston University, Aston Triangle, Birmingham, B4 7ET, United Kingdom.
(2) NIBSC Immunology and Cellular Immunity Section, Potters Bar. EN6 3QG
E: s.bibi8@aston.ac.uk

Whilst normally it would be a disadvantage for liposome vesicles to sediment quickly, for the purposes of producing reference standards for an ELIspot (Enzyme Linked Immunosorbent spot) assay this would be a required characteristic. The aim of this work was to establish the settling characteristics of liposomes. Quantitative and qualitative assessment was made of an SUV and MLV formulation over an 18 hour time period. In order to increase the density of the liposomes, brominated cholesterol was synthesised and incorporated into the liposome formulations. The sedimentation of various percentages of brominated cholesterol formulations were assessed alongside the previous data. Physical characterisation including vesicle size and zeta potential was carried out of all liposome formulations.

Basic multilamellar vesicle (MLV) formulations of 2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and Cholesterol (Chol) encapsulating 5 μg/ml Bovine Serum Albumin conjugated with Fluoroscein Isothiocyanate in PBS, did not exhibit the desired rate of sedimentation for use within the ELISpot assay. Dibromocholesterol was then synthesized and techniques such as Thin Layer Chromatography, Melting point determination, Infra Red Spectroscopy and Carbon NMR were carried out to confirm the end product dibromocholesterol. It was then incorporated within the formulations at different ratios to modify sedimentation characteristics.

Results indicated that whilst inclusion of brominated cholesterol resulted in liposomes becoming more anionic they exhibited increased efficiency in sedimentation due to the change in density. The size of the vesicles of the brominated formulations when compared to the DPPC:Chol MLV formulation, showed no significant difference between formulations. Microscopy analysis showed intact vesicle formation with no negative impact on vesicle morphology of adding increasing amounts of brominated cholesterol. However, there does appear to be less aggregation with higher amounts of brominated Cholesterol between the vesicles which maybe a result of the anionic zeta potential.

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17 EFFECT OF MICRONEEDLE GEOMETRY ON THE PERFORMANCE OF POLYMERIC DISSOLVING MICRONEEDLES FOR TRANSDERMAL DRUG DELIVERY

E C Salvador, M J Garland, A D Woolfson and R F Donnelly.
School of Pharmacy, Queens University Belfast, Belfast, UK.
E: ecaffarelsalvador01@qub.ac.uk

Microneedle arrays are minimally invasive devices that can be used to by-pass the stratum corneum barrier and thus achieve enhanced transdermal drug delivery. [1] Microneedles (MN) have the potential to penetrate the dermis avoiding stimulation of dermal nerves and overcoming the problems associated with needle-sticks, pain and needle phobia. The aim of this study was to determine the effect of MN geometry (MN height, MN density) upon MN mechanical strength, in-skin dissolution and release of a model hydrophilic small molecule (methylene blue).

Firstly, a range of MN geometries, prepared with aqueous gels of 20% w/w poly (methyl vinyl ether co- maleic acid) and 1% w/w methylene blue, was engineered into silicone micromoulds. A TA-XT Plus Texture Analyser was used to assess mechanical strength following the application of an axial force. Dissolution of MN was assessed within full thickness neonatal porcine skin in vitro by removing MN at defined time intervals and measuring the height of MN remaining. Drug release of methylene blue loaded MN was appraised using a Franz cell diffusion set up across dermatomed (350µm thick) neonatal porcine skin, with methylene blue levels determined using UV spectroscopy at 664nm.

MN geometry did not affect mechanical strength or MN dissolution; with 50% of the array dissolving within the first 30 minutes, and complete dissolution achieved within 2 hours. However, the release of methylene blue achieved varied with the design of the MN used. In particular, an increase in MN height and MN density lead to increase the rate of drug release at 6 hours. For example, MN with a height of 600µm released 63.38 ± 1.53%, whereas 900µm MN released 71.21± 1.97%; when the density was of 121 MNs/0.5cm^2 the release was measured at 63.38 ± 1.53% whereas for 361 MNs/0.5cm^2 the measured release was 79.65 ± 2.07%.

In this study, it has been shown that extended of drug delivery can be adjusted through simple alteration of the design of MN array. Further studies could be focussed on the investigation of the effect of geometry in the release of larger molecules which could be useful for vaccination.

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18 DESIGN AND EVALUATION OF TIME AND pH DEPENDENT DRUG DELIVERY SYSTEM OF DOXOFYLLINE: A CHRONOTHERAPEUTIC APPROACH FOR TREATMENT OF NOCTURNAL ASTHMA

C Dharmarajsinh, S Shrenik, P Kunal and P Bhagirath
Sat Kaival College of Pharmacy, Sarsa-388365. Gujarat. India.
E: dharmraj_chauhan@yahoo.com

In the present study, an oral colon specific pulsatile device was developed to achieve time and site specific release of doxofylline, which was based on chronotherapeutic drug delivery. The system was design as the hard gelatin capsule body was treated with formaldehyde solution, filled with microspheres, which were plugged using different hydrogel polymers. Microspheres were prepared using combination of Eudragit L-100 and S-100 with different core: coat ratios by solvent evaporation technique. Different plugging materials like gaur gum, sodium alginate and HPMC were used in the preparation of pulsatile device. The insoluble body was cap sealed by 5% ethanolic solution of ethyl cellulose and then entire capsule was enteric coated with HPMCP to make pulsatile device insoluble in gastric pH. The Microspheres were evaluated by two methods: estimation of drug content and in-vitro dissolution study and the pulsatile drug delivery system was evaluated by test for formaldehyde treated empty capsule bodies, qualitative chemical test for free formaldehyde and in-vitro dissolution study. The shape of the microspheres was found to be spherical and covered completely with coat material as indicated by SEM studies. Encapsulation efficiency was in the range of 84 to 94% and proportionate with the concentration of coat material. Dissolution studies of pulsatile drug delivery system revealed that the absence of the drug release in the first three hours and negligible release in the fourth hour in all formulations and thus lag time of 3-4 hrs was achieved. FT-IR and DSC characterization revealed the absence of drug polymer interaction. The stability studies showed the absence of any significant changes in the microspheres with respect to drug content and release profiles. Programmable pulsatile, colon-specific release has been achieved from a capsule device over a 2-24 h period, consistent with the demands of chronotherapeutic drug delivery.

19 THE INFLUENCE OF DISSOLUTION METHOD ON IN VITRO DRUG RELEASE FROM POLYETHYLENE OXIDE EXTENDED RELEASE MATRIX TABLETS

D Palmer (1), M Levina (1), A. Nokhodcni (2), and A R. Rajabi-Siahboomi (3)
(1) Colorcon Ltd., Dartford, Flagship House, Victory Way, Dartford, Kent, England
(2) Medway School of Pharmacy, Universities of Greenwich and Kent, Chatham, Kent, England
(3) Colorcon Inc., Global Headquarters, 275 Ruth Road, Harleysville, PA 19438 USA

To investigate the influence of dissolution method (apparatus, agitation speed and dissolution media) on release of drugs with various aqueous solubility (ibuprofen, <1mg/mL; theophylline, 8mg/mL and propranolol HCl, 360mg/mL) from polyethylene oxide (PEO) extended release (ER) matrices. Formulations containing 49.75%w/w drug, 49.75%w/w PEO (POLYOX™ 1105 or Coagulant) and 0.5%w/w magnesium stearate were investigated. Round 10mm flat-faced tablets with a target weight of 320mg were produced using hand-press (Specac) at 20kN. Dissolution tests were conducted in a dissolution bath (Sotax) using Apparatus I (baskets) or Apparatus II (paddles) with 15x31mm sinkers; in 900mL of various media (water, buffers with pH 1.2, 6.8 and 7.2) at 50, 100 and 150 rpm. Absorbance readings were obtained using UV/Vis spectrophotometer (PerkinElmer) at 222, 272 and 319nm for ibuprofen, theophylline and propranolol HCl, respectively.

Mechanically strong (>10kp) tablets were produced for all studied formulations. For all matrices, USP II produced slightly faster release than USP I possibly because tightly woven mesh of the basket can potentially interfere with the erosion process of the matrix gel layer. That difference was more pronounced with a very slightly-soluble ibuprofen (f_2=52) compared to theophylline (f_2=68) and propranolol HCl (f_2=71). For all tested formulations, the release obtained at 50rpm was slower compared to 100 and 150rpm. The difference was particularly obvious for ibuprofen (f_2=47,56). Dissolution medium had no significant effect on the release of the neutral drug, theophylline (f_2=84, 93) and ionic drug propranolol HCl (f_2=62,64), which has pH-dependant solubility. For ionic drug ibuprofen, sink conditions were only achieved in pH 7.2 buffer.

Robust POLYOX™ compacts were produced for all studied formulations. It was found that for all matrices, Apparatus II produced slightly faster drug release than Apparatus I and the release obtained at 50rpm was slower compared to 100 and 150 rpm.

20 THE INFLUENCE OF HYDRO-ALCOHOLIC MEDIA ON DRUG RELEASE FROM POLYETHYLENE OXIDE EXTENDED RELEASE MATRIX TABLETS

D Palmer (1), M Levina (1), T Farrell (2) and A R Rajabi-Siahboomi (2)
(1) Colorcon Ltd., Dartford, Flagship House, Victory Way, Dartford, Kent, England
(2) Colorcon Inc., Global Headquarters, 275 Ruth Road, Harleysville, PA 19438 USA

To investigate the influence of hydro-alcoholic media on drug release from polyethylene oxide (PEO) extended release (ER) matrices. Two formulations containing practically water-insoluble drug, gliclazide or freely water-soluble drug, metformin HCl, PEO (POLYOX™1105 or 301), microcrystalline cellulose (Avicel®PH102), fumed silica (Aerosil®200) and magnesium stearate were investigated. Metformin HCl (7x18mm convex, 1000mg) and gliclazide (7 mm double-radius, 200 mg) tablets were produced using Piccola (Riva) press at 20kN. Dissolution tests were conducted using USP II (paddles) apparatus at 100 rpm and quadrangular baskets in 1000 mL water, 5% or 40%w/v ethanol-water solutions. Tablets were subjected to the hydro-alcoholic media for duration of 24 hours or 1 hour followed by 23-hour dissolution in water. Absorbance readings were obtained using UV/Vis spectrophotometer (PerkinElmer) at 228 nm and 233 nm for gliclazide and metformin HCl, respectively.

Mechanically strong (>13kp) tablets were produced for both formulations with reproducible drug release profiles in all tested media. Gliclazide release from PEO matrices was not significantly affected by a 24-hour exposure to 5% or 40%w/v ethanol solutions (f_2=91, 59) or by a 1-hour exposure to 5% or 40%w/v ethanol-water solutions followed by 23hours in water (f_2=82, 74). Metformin HCl release in hydro-alcoholic media was similar to the dissolution results in water (f_2>50) with the exception of the 24-hour exposure to 40%w/v ethanol (f_2=42) where drug release was slower due to a reduction in drug solubility in alcohol.

Robust POLYOX™ ER matrices were produced for both studied drugs. The extended release dissolution performance of both formulations was not adversely influenced by their exposure to the 5%w/v hydro-alcoholic media. Although gliclazide release was not affected by 40%w/v hydro-alcoholic media, metformin HCl release was slower as compared to dissolution in water. No matrix failure was observed with gliclazide and metformin HCl formulations in any of the dissolution media.

21 EFFECT OF SYSTEMATIC CHANGE IN AGITATION ON DRUG RELEASE FROM HPMC MATRICES IN DIFFERENT PH MEDIA (FASTED AND FED CONDITIONS)

K Asare-Addo (1), M Levina (2), A R Rajabi-Siahboomi (2), A Nokhodchi (1)
(1) Medway School of Pharmacy, Universities of Kent and Greenwich, Kent, UK
(2) Colorcon Ltd., Dartford, Flagship House, Victory Way, Dartford, Kent, UK

To investigate the effect of systematic change in agitation during dissolution testing in different pH media on drug release from HPMC extended release (ER) matrices.

Three viscosity grades of HPMC, METHOCEL™ K100LV, K4M and K100M, were used as a hydrophilic matrix former. Tablets with a target weight of 250 mg were prepared by mixing theophylline with HPMC in the ratio of 4:1 and compressed at 6 kN (22 MPa). An automated USP type III Bio-Dis was used for dissolution testing. The dip rates ranged from 5 to 30 dpm. Vessels contained 250 mL of the appropriate media (pH 1.2-7.5) at 37.0±0.5°C. Theophylline release was measured using a UV/ Visible spectrophotometer at 271 nm.

Robust matrix tablets with breaking force values of 61-70 N were produced for all three formulations used in the study. It was found that performance of the matrices made with the lower molecular weight polymer, K100LV, was more affected by agitation intensity. Stronger gels produced by K4M and K100M provided a slower drug release at higher agitation.
The type and composition of a meal is important to consider when evaluating a potential effect of food on tablet behaviour and this can be mimicked by using a variety of different agitation rates.

Ascending and descending agitations resulted in significant differences in theophylline release for all three tested formulations. The resilient nature of the K4M and K15M tablets suggest that these polymers might be the best candidates to be used as matrix formers that can facilitate a zero-order drug release. When formulating hydrophilic matrix tablets, polymer viscosity grade and its concentration in a formulation should be carefully considered. Use of a systematic change in agitation during dissolution testing may help to identify potential fed and fasted effects on drug release from hydrophilic ER matrices.

22 THE INFLUENCE OF HYDROPHILIC PORE FORMERS ON METOPROLOL SUCCINATE RELEASE FROM MINI-TABS COATED WITH AQUEOUS ETHYLCELLULOSE DISPERSION

H Vuong (1), M Levina (1), T Farrell (2) and A R Rajabi-Siahboomi (2)
(1) Medway School of Pharmacy, Universities of Kent and Greenwich, Kent, UK
(2) Colorcon Ltd., Dartford, Flagship House, Victory Way, Dartford, Kent, UK

To investigate the influence of incorporating a water-soluble pore former based on polyvinyl alcohol (PVA) into aqueous ethylcellulose (EC) film coating dispersion (Surelease®) on in vitro release of a model drug metoprolol succinate, from mini-tabs.

Mini-tabs containing freely water-soluble metoprolol succinate, lactose (FastFlo®), fumed silica (Aerosil® 200), stearic acid and magnesium stearate. Mini-tabs (2 mm double radius 16-tip tooling, 8 mg) were produced using Piccola (Riva) press at 12 kN. Mini-tabs were seal-coated (PVA-based Opadry® II, Colorcon), followed by EC dispersion (Surelease, Colorcon) with pore former (Opadry II Clear) at two ratios 85:15 and 80:20 in a fluid bed coater (Glatt). Dissolution tests were conducted using USP II (paddles) apparatus at 50 rpm in 500 mL of pH 6.8 phosphate buffer at 37 ± 0.5°C. Absorbance measurements were obtained using UV/Vis spectrophotometer (PerkinElmer) at 274 nm.

Mechanical strength of mini-tabs improved significantly with a seal-coat. Breaking force increased from 2.1 kp (uncoated) to 3.0 kp (seal-coated) and friability was reduced from 0.46% to less than 0.01% respectively. Immediate release of the drug was recorded for low coating weight gains (WG) of 2%-4% (85:15) and 2%-6% (80:20). Metoprolol succinate release decreased significantly with an increase in the coating level and a decrease in the pore former concentration. For example, at 10% WG only 62% of the drug was released from 85:15 coating compared to 86% metoprolol succinate dissolved from 80:20 system, after 24 hour dissolution testing. This can be explained by the increased permeability of the film when more pore former was used.

Robust mini-tabs were manufactured with improved mechanical strength upon seal coat application. Metoprolol succinate release rate from ethylcellulose coated mini-tabs was modulated by varying the amount of hydrophilic pore former and/or the level of film coating applied.

23 CONTROLLED PROTEIN RELEASE FROM PLGA MICROSPHERES BY MODIFICATION WITH PLGA-PEG-PLGA TRIBLOCK CO-POLYMER

H C Cox, L J White, G T S Kirby, R Qodratnama, O Qutachi, F R A J Rose and K M. Shakesheff
School of Pharmacy, University of Nottingham, University Park, Nottingham, UK.
E: helen.c.cox@nottingham.ac.uk

We have developed procedures to manufacture protein loaded polymeric microspheres and aim to improve the well documented tri-phasic in-vitro release profile by the incorporation of a hydrophilic component. By using a model protein we plan to manipulate release profiles in-vitro to mimic growth factor requirements for bone regeneration in-vivo.

Spherical microparticles were fabricated from poly(lactic-co-glycolic) acid (PLGA with a lactide: glycolyde ratio 50:50 or 85:15) formulated with PLGA-PEG-PLGA triblock co-polymer in a tightly controlled double emulsion solvent evaporation process. The model protein lysozyme was delivered in conjunction with human serum albumin (HSA) as a bulk carrier. Microspheres were sized using laser diffraction and protein release was monitored by suspending loaded microspheres in phosphate buffered saline, incubating at 37°C on a rocker shaker and regularly sampling the release media. The supernatants were assayed for protein content using a bicinchoninic acid assay and for lysozyme activity using a Micrococcus lysodeikticus bioassay. Cumulative release profiles were constructed over time for each formulation.

Microspheres were loaded with protein (1% (w/w) HSA: lysozyme ratio 9:1) and were sized at 50-100 micron in diameter. Entrapment efficiencies were 65-95% across the batches. The addition of triblock had a distinct effect on release profiles. Without modification, PLGA 50:50 demonstrated an initial burst followed by a lag phase for 11 days before further release as a result of polymer degradation. The lag time was longer for PLGA 85:15. The addition of triblock resulted in sustained release of protein over this period and the rate of release could be correlated to triblock concentration. Released lysozyme remained active throughout. The ability to tailor protein release rates will potentially enable the simultaneous administration of different growth factors by delivering them in microspheres specially formulated to release at different rates, giving the temporal control required for osteogenesis.

24 EFFICIENT LIGHT-TRIGGERED ANTI-INFECTIVE OCULAR BIOMATERIALS

R A Craig, S M M^{c}Glinchey, C P M^{c}Coy, S P Gorman and D S Jones
School of Pharmacy, Queen's University Belfast, Northern Ireland
E: rcraig07@qub.ac.uk

Bacterial adherence to implanted intraocular lenses (IOLs) has been identified as a contributing factor to the development of postoperative endophthalmitis. Recently, we described a series of novel porphyrin-incorporated hydrogels for anti-infective ocular applications using tetrakis(4-N-methylpyridyl)porphyrin (TMPyP)[1,2]. Porphyrin photoactivation results in generation of highly reactive singlet oxygen ($^1O_2$), which can indiscriminately initiate further oxidative reactions with bacterial cell components, thus reducing bacterial adherence to the material surface. TMPyP penetration of 180μm was achieved[1], however as the effective distance of $^1O_2$ is short, improved porphyrin surface localisation is required to maximise efficiency. Modification of polymer composition was examined to achieve such localisation, whilst maintaining high antimicrobial activity and optical transparency. Two series of random copolymer films were prepared, altering either the methyl methacrylate (MMA) or methacrylic acid (MAA) content at the expense of hydroxyethylmethacrylate (HEMA), to produce varying ratios of MMA:MAA:HEMA. Polymer impregnation was performed by immersion in buffered solutions of TMPyP (1μg/ml) for two minutes. Physiochemical properties were characterised and materials were challenged with Staphylococcus aureus and Pseudomonas aeruginosa. A greater uptake of TMPyP was observed in the MMA series, but without detriment to the degree of surface localisation, with 89.87±1.21% decreased penetration into the bulk polymer observed. This is in contrast to the MAA series where a comparatively lower loading and degree of surface localisation was seen. Significant reductions of bacterial load relative to control were observed. Overall, the MMA series of materials exhibited more favourable porphyrin loading, surface localisation, mechanical properties, and reduction in bacterial adherence on light exposure. This therefore demonstrates a simple method of obtaining a high, localised concentration of photosensitiser at the surface of polymeric materials.

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25 FACTORS TO CONSIDER DURING REFORMULATION IN THE CONTEXT OF RAMIPRIL

C A Russell (1), M Hussain(2), Y Perrie (1) and A R Mohammed (1).
(1) Medicines Research Unit, School of Life & Health Sciences, Aston University, Birmingham, B4 7ET.
(2) Pharmaspec Ltd, Birmingham.
E: russelca@aston.ac.uk

There is a growing interest in the delivery of poorly soluble and bitter-tasting drugs in formulations intended for children. Since 2007 the European Medicines Agency has produced a priority list for studies into off-patent paediatric medicinal products. The list is periodically updated and names a number of drugs for which studies are required. Of the wide range of drugs listed, angiotensin converting enzyme inhibitors (ACE) have been classified for reformulation. The current work focuses on the formulation of oral liquid preparation of ramipril (ACE inhibitor) and systematically investigates formulation protocol.

Reformulation of ramipril is influenced by a range of pharmaceutical profiling characteristics such as; poor drug solubility, pH sensitivity, susceptibility to Oxidation, and sensitivity to light. To address the limitations, co solvent and cyclodextrin complexes were investigated. The effect of temperature and pH on drug-cyclodextrin complexation was investigated as well as the effect of drug-cyclodextrin complexation on drug stability. The next stage involved excipient selection according to the conditions needed for the drug was carried out e.g. inclusion of antioxidants and preservatives, followed by Long term and Accelerated stability testing. Co-solvency and Cyclodextrins were both suitable methods for the solubilisation of ramipril. The inclusion of cyclodextrins resulted in significant improvement in solubility. Preliminary investigations were carried out in the range of 15 – 75C to determine the influence of temperature on the complexation behaviour cyclodextrin and ramipril. The results show that the complexation of the drug promoted with an increase in temperature suggesting the increase in entropy promoting electrostatic association between the drug and the carrier. Investigation of pH showed that pH range 3-5 was ideal in retaining drug solubility. Data from these studies provided the required platform for the choice of additional formulation excipients. Further analysis of the final formulations stored under accelerated and long term testing conditions showed that the formulations retained the chemical stability of the drug candidate after one month.
Recently, we described a series of novel porphyrin-impregnated hydrogels capable of producing biocidal singlet oxygen ($^1O_2$) on photoactivation[1]. Indirect assessment using microbiological techniques has been detailed[1], but due to the

26 EXPLOITATION OF PHOTOBLEACHING TO PROBE FOR BIOCIDAL SINGLET OXYGEN IN PHOTOREACTIVE BIOMATERIALS

R A Craig, C P McCoy and S P Gorman
School of Pharmacy, Queen's University Belfast, Northern Ireland
E: rcraig07@qub.ac.uk

known associated problems with direct physical methods, a direct measurement of the $^1O_2$ produced by each hydrogel has not yet been performed on such materials. Anthracene-9,10-dipropionic acid (ADPA) is known to degrade to an endoperoxide on reaction with $^1O_2$, resulting in photobleaching of its UV absorbance maximum[2]. This reaction was utilised to provide a quantitative measure of $^1O_2$ generation at the surface of hydrogels, and give an indication of their potential to act as infection-resistant biomaterials. ADPA was dissolved in a methanol/water solution. Porphyrin-impregnated and untreated polymer samples[1] in this solution were subjected either to a white light source (4000 lux) at a fixed distance of 1cm, or to dark conditions, and UV analysis performed. $^1O_2$ production was quantified by the rate of photobleaching of ADPA. On irradiation of porphyrin-impregnated materials, ADPA absorbance maxima were observed to decrease, and the first order plot of ADPA absorbance for porphyrin-incorporated materials illustrated significantly greater reductions in ADPA absorbance in light when compared to dark conditions. This confirmed the requirement of light for $^1O_2$ production. A small ingress of ADPA into the untreated materials was observed, but not with porphyrin-incorporated materials. This may be explained by the formation of a porphyrin layer at the material surface, and neutralization of surface anionic charges, thus facilitating a lower energy chain conformation, decreasing the material porosity, and preventing ADPA ingress. ADPA uptake was accounted for when quantifying $^1O_2$ generation by each material. Exploitation of ADPA photobleaching therefore provides a method for determining $^1O_2$ production at the surface of porphyrin-impregnated anti-infective biomaterials.

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27 INHIBITION OF PLATELET AGGREGATION BY PLGA NANOPARTICLES LOADED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

J Crean, S Endter, O I Corrigan, M W Radomski and L Tajber.
School of Pharmacy and Pharmaceutical Sciences, Trinity College, University of Dublin, Dublin 2, Dublin.
E: creanj@tcd.ie

Poly–lactide-co-glycolide (PLGA) nanoparticles (NPs) have been previously shown to be platelet-compatible. We have now loaded PLGA NPs with hydrophobic, non-steroidal anti-inflammatory drugs – indomethacin and ketoprofen, known to inhibit platelet aggregation, and investigated whether the new formulation affected platelet function. PLGA NPs were prepared using the emulsion-solvent diffusion method. Briefly, PLGA and the drug were dissolved in ethyl acetate and emulsified in Pluronic F-68 solution before addition to more surfactant solution for solvent diffusion. Ketoprofen and indometacin were loaded into the PLGA NPs at concentrations of 0.2 or 0.1 mg/mg of PLGA. The size, zeta potential drug loading and release profiles of loaded NPs were determined. The ability of these NPs to inhibit collagen (2 µg/ml) induced platelet aggregation was investigated using light aggregometry.

The average size of PLGA loaded NPs with indometacin (indo-NPs) and ketoprofen (keto-NPs) at 0.2 mg/mg was 323±8 and 316±3 nm and the zeta potential was -35±1 and -33±1 mV, respectively. Encapsulation efficiency was high for all NPs, being > 90% for indo-NPs and 60-75% for keto-NPs. Release profiles showed and initial burst release and then slow liberation of the drug over the next 14 days. At nanoparticle concentration equivalent to drug concentration of 3 µg/ml inhibition of collagen induced platelet aggregation was significantly higher with indo-NPs (52.3±8.3%, 0.2 mg/mg drug) compared to keto-NPs (32.5±5.4%, 0.2 mg/mg drug). After 10 minutes of preincubation with platelets the indo-NPs, but not keto-NPs, induced greater inhibition of aggregation when compared to similar concentrations of free drug. For ketoprofen 0.2 mg/mg NPs and free drug it was 71.4±12.3% and 96.41±6.0% inhibition, respectively, at 1 µg/ml drug concentration and for the equivalent indometacin systems it was 87.4±3.0% (3 µg/ml) and 55.9±29.1% (2 µg/ml), respectively. In conclusion, indometacin and ketoprofen PLGA NPs can effectively inhibit collagen induced platelet aggregation.

28 THE IMPACT OF CO-MILLING SULFADIMIDINE WITH LOW GLASS TRANSITION TEMPERATURE EXCIPIENTS AS A STRATEGY FOR PREVENTING PROCESS INDUCED AMORPHISATION

V Curtin, V Caron, L Tajber, O I Corrigan, A M Healy
School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Ireland.
E: curtinv@tcd.ie

Since co-processing of active pharmaceutical ingredient (API) with high glass transition temperature (Tg) excipients can be used as a strategy to stabilise the amorphous form of the API, it was hypothesised that co-processing with low Tg excipients might instead prevent or reduce amorphisation. This work investigates the impact of low Tg excipients on the solid state nature of sulfadimidine following co-milling.

Sulfadimidine was co-milled with adipic acid (AA) and glutaric acid (GA) in a Retsch PM100 Planetary Mill for 10 hours. Physical mixtures were also prepared for comparison purposes. Characterisation was performed by powder X-ray diffraction (PXRD), thermal analysis and Fourier transform infrared spectroscopy.
Co-milling with both dicarboxylic acids resulted in an improvement in Bragg peak intensity and resolution for the API in the PXRD, relative to the API milled alone. This, coupled with the absence of a Tg or recrystallisation exotherms in the DSC thermograms, with 50% w/w AA and 30% w/w GA, and the presence thereof in the corresponding physical mixtures, confirmed that the presence of these excipients in the milling process reduced amorphisation of the API. The difference in the calculated Hildebrand solubility parameter (δ) and logP values between the API and the acids was small (glutaric acid: $\Delta\delta = 0.1$, ΔlogP = 1.84 and adipic acid: $\Delta\delta = 0.8$, ΔlogP = 1.60). These small differences suggest ease of mixing and indicate that these excipients could preferentially concentrate at the surface of the API, act as catalytic seeds, destabilise the amorphous phase and promote recrystallisation.

The strategic selection of crystalline excipients with favourable structural, kinetic and thermodynamic properties can improve the crystalline form of a milled drug.

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29 APPLICATION OF NEWLY DEVELOPED GRADE OF LOW-SUBSTITUTED HYDROXYPROPYLCELLULOSE TO THE ORALLY DISINTEGRATING TABLETS

M Fukasawa, Y Hirama, N Maruyama, and Sakae Obara
Shin-Etsu Chemical Co., Ltd., Specialty Chemicals Research Center, Niigata, Japan.
E: miyuki-fukasawa@shinetsu.jp

Aim: to develop orally disintegrating tablets (ODTs) using newly developed grade of low-substituted hydroxypropylcellulose (L-HPC) as binder and disintegrant.

The powder properties of various disintegrants such as the current grade of L-HPC (LH-21), newly developed grade of L-HPC (NBD-022), Crospovidone (cl-PVP), Croscarmellose sodium (cl-CMC-Na), Sodium starch glycolate (CMS-Na) and Microcrystalline cellulose (MCC) were evaluated. Specific surface area was measured by BET method, swelling speed was analyzed by texture analyzer and water absorption speed was tested with water-dropping method. ODTs were prepared through 2 methods, wet-granulation and direct compression with disintegrants. The wet-granulation process was done with a fluid-bed granulator (Powrex Multiplex MP-01)by spraying aqueous dispersion of disintegrant on to D-mannitol, followed by compression using a rotary tableting machine (Kikusui VIRGO). The direct compression was done with the same rotary tableting machine and lactose was used as filler. The tablets were tested to evaluate hardness and disintegration time.

NBD-022, which had larger specific surface area resulted in higher tablet hardness for ODTs. The water absorption and swelling speed of NBD-022 was faster than the current L-HPC, not inferior to other disintegrants which are known as super disintegrants. Due to these features, the ODTs prepared with NBD-022 showed shorter disintegration time (< 20 sec) even if they had sufficient tablet hardness (> 50 N) . Also in the sensory test, the tablets were disintegrated within 20 seconds. This improvement was obtained not only from wet-granulation process but also from direct compression process, and ODTs prepared from direct compression process had shorter disintegration time. Newly developed grade of L-HPC (NBD-022) had different physical features from the current L-HPC even though they have the same chemical characteristics, NBD-022 had larger specific surface area and quicker swelling performance. Therefore ODTs that were prepared with NBD-022 showed higher tablet hardness and shorter disintegration time.

Aim: To develop a timed-release coating method that can release API after lag

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A TASTE MASKING COATING METHOD

M Fukasawa, Y Nishiyama, and S Obara
Shin-Etsu Chemical Co., Ltd., Specialty Chemicals Research Center, Niigata, Japan.
E: miyuki-fukasawa@shinetsu.jp

time for 5-10 min after administration for taste masking effect.

The combination of a water soluble cellulose ether (Hypromellose,HPMC, Pharmacoat®, Shin-Etsu Chemical) and an enteric coating material (Hypromellose Acetate Succinate, HPMCAS, Shin-Etsu AQOAT®, Shin-Etsu Chemical) was evaluated for tablet coating. The tablet was prepared with riboflavin (VB2) and coated by a side-vented pan coater (Freund, SE coater). The coating fluids were prepared with various ratios of polymers and solvent composition (water or mixed with water and ethanol). For comparison, an aqueous dispersion of HPMCAS and a copolymer dispersion of methacrylic acid and ethyl acrylate (Eudragit® L30D55, Evonik) were tested. The coated polymer amount were varied from 3 to 10%. The dissolution tests were carried out according to USP 30 dissolution procedure (paddle method, 50 rpm, 37°C, and 900 mL of purified water). Riboflavin dissolved in the test fluid was assayed by measuring absorbance at 444 nm with a UV-VIS spectrophotometer (UV-160, Shimadzu). Stability test was also implemented for comparison to sugar coating which also had timed-release behavior.

The tablets coated with HPMC/HPMCAS by solution showed a lag time. The lag time depended on ratio of polymers and coated amount. 6% coating which consisted of 90% of HPMC and 10% of HPMCAS had immediate release of API after lag time of 10 minutes, which was similar dissolution profile to sugar coating. From the stability test, the dissolution of the HPMC/HPMCAS coating was maintained although that of sugar coating was delayed. Aqueous dispersion coating with HPMCAS itself and Eudragit didn't show lag time.

The method of timed-release coating was developed with combination of HPMC and HPMCAS, which was effective for taste masking. Coated tablets had similar dissolution profile to sugar coated tablets but had better stability.

31 MICROEMULSION FORMULATIONS FOR THE TRANSDERMAL DELIVERY OF OLMESARTAN MEDOXOMIL

R M Hathout (1) and A H AlShafeey (2)
(1) Department of Pharmaceutics, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.
(2) Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt
E: r_hathout@yahoo.com

The development and characterisation of a microemulsion system for the transdermal delivery of olmesartan medoxomil. Microemulsion formulations were prepared using oleic acid as the oil phase, Labrasol® as a surfactant, Transcutol® as a co-surfactant, and water. The microemulsions were characterized visually, with the polarizing microscope, and by photon correlation spectroscopy. In addition, the pH and conductivity (σ) of the formulations were measured. The type of microemulsions formed were determined using conductivity measurements analysis, Freezing Differential Scanning Calorimetry (FDSC) and Diffusion Ordered Spectroscopy (DOSY). Alterations in the molecular conformations of porcine skin caused by the investigated microemulsions were determined using Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR). Finally, olmesartan medoxomil delivery from a selected formulation was assessed across porcine skin ex vivo using Franz diffusion cells; the drug was analyzed by liquid chromatography mass spectroscopy (LC/MS/MS). Conductivity measurements revealed, as function of the weight fraction of the aqueous phase, the point at which the microemulsion made the transition from water-in-oil to bicontinuous. FDSC and DOSY confirmed these results. ATR-FTIR demonstrated that SC hydration increased in proportion to the water content of the microemulsion as revealed by amide I / amide II bands. Each of the microemulsion components penetrated into the SC, but to different extents. Oleic acid decreased the conformational order of the SC lipids, and induced some phase separation, as revealed by the frequency shifts and peak areas of CH_2 symmetric and asymmetric stretching vibrations absorbances. Olmesartan medoxomil was delivered successfully across the skin with the flux achieving (3.15 µg cm^{-2} hr^{-1}) from a formulation containing 0.5 % w/v of the examined drug and the composition (w/w) of 16% oleic acid, 32% Labrasol®, 32% Transcutol® and 20% water. The microemulsion system considered offer potentially a useful vehicle for the transdermal delivery of lipophilic drugs like olmesartan medoxomil.

32 PRONIOSOME FORMULATIONS FOR FUTURE APPLICATIONS IN PULMONARY DRUG DELIVERY

K Hidayat (1), W Ahmed (2) and A Elhissi (1)
(1) Institute of Nanotechnology and Bioengineering and School of Pharmacy and Biomedical Sciences, University of Central Lancashire.
(2) Institute of Nanotechnology and Bioengineering, School of Computing, Engineering and Physical Sciences, University of Central Lancashire.
E: AElhissi@uclan.ac.uk

In recent years there has been more interest in noisomes for various drug delivery applications including pulmonary. Previous studies have shown that pulmonary delivery of liposome-entrapped drugs can extend drug residence in the respiratory tract which may reduce systemic side effects. Unfortunately, liposomes in aqueous preparations are very unstable, since phospholipids included may hydrolyse and oxidise during storage. Therefore the utilization of niosomes can be advantageous because of their enhanced stability in comparison to liposomes.

In this study all noisome formulations were made using Span 60 and cholesterol (1:1). Conventional niosomes were prepared using hand shaking method (thin film Hydration) followed by bath sonication and probe sonication. A novel proniosome formulation was designed using sucrose as carrier particles and beclomethasone dipropionate(BDP) as a model drug, followed by sonication. Different Characterisation methods have been applied, including size and surface charge analysis and electronic microscopy. Size Measurements were performed using photon correlation spectroscopy and surface charge (zeta potential) was analysed using laser Doppler velocimetry. Transmission electron microscopy (TEM) was performed to study the morphology of niosomes.

Size of niosomes generated by conventional and proniosome methods were in micron-size range. After using bath-sonication niosomes decreased in size to less than 200nm. Moreover the size of niosomes generated from proniosomes was lager that that of niosomes. All vesicles had negative zeta-potential values, and inclusion of the steroid did not affect the size or surface charge of the vesicles.

This study has demonstrated that proniosomes can generate niosomes having the potential for pulmonary drug delivery. Further studies in aerosol generation of these formulations are currently ongoing in our laboratory.

33 THE USE OF CATIONIC LIPOSOMES FOR THE DELIVERY OF A NOVEL SUB-UNIT TUBERCULOSIS VACCINE

M J Hussain (1), V Bramwell (1), Dennis Christensen (2) and Yvonne Perrie (1)
(1) Aston Pharmacy School, Aston University, Birmingham, B4 7ET, UK
(2) Statens Serum Institut, Department of Infectious Disease Immunology, Copenhagen, Denmark
E: hussaimj@aston.ac.uk

Cationic liposomal adjuvants of dimethyldioctadecylammonium bromide (DDA) and α,α′-trehalose 6,6′- dibehenate (TDB) administered with vaccine antigen can stimulate cell-mediated immunity, an essential response for protection against Tuberculosis (TB). The introduction of further stabilising lipids to DDA-TDB liposomes was assessed for its ability to initiate immunity in response to a novel sub-unit TB vaccine. The effect of incorporating 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) to DDA-TDB was evaluated upon replacement of the cationic DDA content with the aim of enhancing stability and possibly reducing associated toxicity. Liposomes were characterised for particle size, zeta potential, morphological features, main melting points and toxicity upon macrophages. An immunisation study was conducted providing immunological analysis of splenocyte cells cultured upon immunisation of mice in response to the TB antigen administered with the proposed DDA-TDB based liposomes. Female C57BL/6 mice were used with all experimentation strictly adhering to the 1986 Scientific Procedures Act (UK). The particle size and zeta potential of DDA-TDB and replacement of DDA with DSPC in DDA-TDB were 500-700 nm and 50 mV respectively. Complete cationic replacement (DSPC-TDB) resulted in a system of two micrometers and -10mV (confirmed for size via Transmission electron microscopy) with all systems generating man phase transitions beyond physiological temperature. DDA-TDB had a cell viability of 50-60% and as DDA was increasingly replaced with DSPC, cell viability increased by 20-30%, reducing toxicity. The necessity of an adjuvant carrier system was displayed upon determination of splenocyte proliferation with all cationic systems stimulating significantly higher levels compared to administration of H56 antigen alone. DDA-TDB and partial DDA replacement with DSPC induced higher proliferation levels and IgG2b antibodies indicative of cell mediated immunity when compared to DSPC-TDB. Replacement of cationic content could provide an alternative to the DDA-TDB liposomal adjuvant, showing great potential in inducing Th1 type immune responses essential for protective efficacy in TB patients.

34 REVERSED-PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR THE ANALYSIS OF FLUCLOXACILLIN IN ALGINATE MICROSPHERES

P M Ikamati (1), D J Kirby (1), Y Perrie (1), J Marriott (1) and R B Walker (2)
(1)Aston University, Birmingham, B4 7ET, UK;
(2) Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa, 6140
E: ikamatpm@aston.ac.uk

Many pharmaceutical products have an unpleasant taste and/or odour. This may limit patient acceptability and adherence when using oral formulations. This is a particular problem with patients who may require liquid dosage forms (e.g. children and the elderly) as they are often easier to swallow and can offer fractional doses. Flucloxacillin, a β-lactam antibiotic, has both an extremely bitter taste and odour. To improve patient adherence, there is a need for the development of a suitably taste masked liquid dosage system. The intended formulation is novel and there is a need to develop a RP-HPLC method that is simple, accurate and precise. The influence of organic modifier concentration, pH and buffer molarity was studied. The chromatographic conditions were: a C18 column (Phenomenex®, 250 mm x 4.6 mm, 5μm); phosphate buffer and acetonitrile in varying proportions; flow rate of 1.0 mL/min; detection wavelength of 225 nm; injection volume of 20 μl and a column temperature of 25 0C.

The method was validated according to ICH guidelines. The retention time of flucloxacillin decreased with increasing acetonitrile concentration and mobile phase pH due to reduced stationary phase hydrophobicity and increased degree of flucloxacillin ionization, respectively. A pH of 6.5 resulted in a very high degree of retention time specificity. The optimized mobile phase was 20 mM phosphate buffer: acetonitrile 60:40 %v/v, final pH 6.5. The method was linear over the concentration range 2.5 μg/ml and 25 μg/ml while the LOQ and LOD were 0.126 μg/ml and 0.04 μg/ml, respectively. The high sensitivity is useful in release studies. A stability study shows that PBS pH 7.4 is effective in preserving flucloxacillin in released studies conducted in Simulated Gastric Fluids. Preliminary results of alginate microsphere processing by external gelation using a w/o emulsion technique lead to a yield that was > 100% implying high residual oil. The isocratic RP-HPLC method developed is selective, accurate, precise and highly sensitive. It is stability indicating and thus is useful not only for the initial quantitation of the payload and drug release studies but also for stability studies of optimised formulations.

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35 BRAIN TARGETING OF OLANZAPINE BY INTRANASAL APPLICATION OF TRANSFERSOMES

M A Hady (1), A A. Mahmoud (1), **A O Kamel Hassan** (2), G A S Awad[(2)] and H A Salama (1)
(1) Department of Pharmaceutical Technology, National Research Center, Dokki, Cairo, Egypt.
(2) Department of Pharmaceutics, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.
E: amany.kamel@yahoo.com

One of the main drug delivery system that is able to overcome the blood-brain barrier is the intranasal drug delivery system. The objective of this study was to prepare intranasal olanzapine-loaded phospholipid based vesicles and to explore the possibility of improving brain targeting by increasing their elasticity using different surfactants in their formulations. Transfersomes were developed using soybean phosphatidylcholine as the lipid matrix and sodium deoxycholate, span 60, chremophor EL, Brij 58 or Brij 72 as surfactant. Liposomes were also prepared for comparison. The influence of process variables, including the type of surfactant and phosphatidylcholine:surfactant ratio on vesicles morphology, particle size, drug encapsulation, elasticity and in vitro drug release was studied. The best performing vesicles were evaluated for their potential in brain targeting on albino rats. The prepared vesicles demonstrated mainly a spherical morphology and an average particle size from 310 to 925 nm. The prepared transfersomes improved olanzapine encapsulation efficiency compared to that of liposomes. The release profile of the vesicles followed a Higuchi release kinetic. Transfersomes consisting of phosphatidylcholine and sodium deoxycholate or span 60 were flexible nanocarriers showing about 490 and 380 nm in size and had a 1.5 and 1.8-fold greater deformability index than that of conventional liposomes, respectively and thus were chosen for in-vivo study. The AUC in brain tissues and cerebrospinal fluid obtained after nasal administration of olanzapine-loaded transfersomes in rats were 1.7 and 2.7-fold greater than that obtained after liposomal administration using sodium deoxycholate or span 60 as surfactant, respectively.

These results suggest that the elastic vesicles transfersomes serve as a promising carrier for enhancing the nasal absorption of olanzapine than the use of liposomes.

36 TREATMENT OF GLIOMA USING LIPOSOMES GENERATED FROM ALCOHOL-BASED PROLIPOSOMES

S R Jaiswal (1, 2), G Manoharan(1, 2), W Ahmed (1, 3) and A Elhissi (1, 2)
(1) Institute of Nanotechnology and Bioengineering,
(2) School of Pharmacy and Biomedical Sciences
(3) School of Computing, Engineering and Physical Sciences,
University of Central Lancashire, Preston PR1 2HE, UK.
E: AElhissi@uclan.ac.uk.

Every year approximately 2% of cancer patients in the UK are diagnosed with glioma (Garside et al., 2005). All the treatments available pose risks such as surgical procedures which are dreadful and very painful, radiation therapy damages normal cells and in chemotherapy some of the drugs cannot get into the brain because of the blood brain barrier. Unfortunately, glioma can regenerate even after the treatment.

Liposome has the interesting properties of entrapping hydrophilic and hydrophobic drugs and targeting tumours cells. Liposomes are vesicles made of phospholipid molecules which are similar to biological membranes and hence biocompatible and biodegradable. The major drawback of conventionally prepared liposomes is that, they are chemically and physically unstable and they are difficult to manufacture on a large scale. Stability problems can be avoided by formulation of liposomes using the solvent based proliposome. The resultant liposomes provide high entrapment of hydrophilic agents and can also be prepared on a large scale.

The aim of our project is to use herbal extracts such as Taxol, Crude M. Charantia and Alpha-beta momorcharin binded to the phosphatidylcholine to manufacture solvent-based proliposome which can be used to generate liposomes when the aqueous phase is added. The resultant size of the vesicles was compared with the conventional method of producing liposome and also with the increasing concentration of the model anticancer drug. The efficacy of the anticancer-liposome formulations was investigated for the viability of normal glial cells (SVGP12) and glioma cell lines (1321N1, Gos-3 and U87-MG) using the proliposome method. On measurement of ATP release by SVGP12, 1321N1, Gos-3 and U87-MG after treatment with anticancer liposomes generated from proliposomes showed more significant growth inhibition of glioma cell line without effecting the growth of the glial cells. Further experiments are required to determine the mechanism action of anticancer liposome in inhibiting glioma.

37 PREPARATION OF NANOSTRUCTURED CHITOSAN DERIVED MICELLES FOR ENCAPSULATION OF A HIGH MOLECULAR WEIGHT DRUG

G M Mekhail, **A O Kamel Hassan**, G A S Awad and N D Mortada
Faculty of Pharmacy, Department of Pharmaceutics, Ain Shams University, Cairo, Egypt
E: amany.kamel@yahoo.com

Polymeric micelles are colloidal delivery systems formed by self-assembly in an aqueous environment. They possess a core-shell structure which acts as a micro-reservoir for the encapsulation of hydrophobic drugs. To develop various chitosan-based micelle systems by introducing hydrophobic and/or hydrophilic groups to its backbone and to encapsulate a relatively high molecular weight drug of more than 500 Da in these micelles.

Various concentrations of stearic anhydride were used for the production of 4 acyl chitosan. These stearyl chitosan were further sulphated. The obtained derivatives were characterized by FTIR, ^{1}H-NMR, X- ray diffraction, degree of acylation and elemental analysis for determination of degree of sulphation. The encapsulation efficiency EE% of a relatively high molecular weight drug>500Da were also determined.

The degree of acylation of the synthesized polymers was in the range of 1.7% to 18.8%. The degree of sulphation was in the range of 1,9% to 3.1%. X-ray diffraction showed that acylation of the polymer decreased its degree of crystallinity, hence enhancing its water solubility. In all chitosan derivatives, increasing the degree of acylation decreased the CAC. The CAC of sulphated acyl chitosans were higher than that of acyl chitosan because of their higher water solubility and due to the presence of the repulsive sulphate groups. The nanomicelles were spherical with particle size range of 113-139 nm for acylated chitosan derivatives and 118-161 for sulphated acyl chitosan ones. The EE% increased by increasing the degree of acylation in acylated chitosan derivatives due to the increase in hydrophobic interaction between the drug and the polymer. However, in case of the sulphated group the degree of sulphation had no influence on the EE%.

These results suggest that the stearyl chitosan serve as a promising carrier for encapsulating high molecular weight drugs.

38 SYSTEM BIOLOGY EVALUATION OF DRUG FORMULATION: A TALE OF DRUG TRANSPORTERS

A ElShaer, S Khan, A S Rahman, P Hanson, Y Perrie and A R Mohammed.
Aston Pharmacy School, Aston University, Birmingham
E: elshamk1@aston.ac.uk

Pharmaceutical excipients have been used extensively as bulking agents, disintegrants, solubility and permeability enhancers. Recent studies [1,2] have demonstrated that some excipients could affect the level of gene expression across the cells. Jonson et al have demonstrated that polyethylene glycol 400 and pluronic P85 have an inhibitory effect on P-glycoprotein (P-gp) transporter genes [1]. The aim of the current study was to prepare a solid dispersion of indomethacin and paracetamol using PEG-8000 and compare the effect of the free drug and its solid dispersion on the expression of different genes across Caco-2 cells with a focus on ABC and SLC transporters. Melt fusion method was used to prepare the solid dispersions and the formulation was characterised using infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Caco-2 monolayers coupled with DNA microarrays were used to investigate the effect of paracetamol and indomethacin formulations on its absorption and the level of different transporter gene expression. Characterisation studies suggest that both indomethacin and paracetamol converted from crystalline into the amorphous form upon dispersing within PEG. While, permeability studies demonstrated that higher amount of indomethacin and paracetamol were absorbed from the solid dispersion formulation when compared to drug alone. Interestingly, the gene expression analysis revealed that none of the transporter carriers or efflux proteins were involved in the absorption of paracetamol formulation. Yet, the expression of some hepatic biomarkers (ABCC13 & ABCB4) and glutathione transporter increased upon exposure to paracetamol alone formulation and no significant effect was observed when solid dispersion formulation was used. These results suggest that paracetamol was metabolised within Caco-2 cells and the glutathionyl metabolite was transported by glutathione transporters. Incorporating PEG within paracetamol was found to lower the metabolic effect and reduce the toxicity of paracetamol as reflected by ABC gene expression data. Such inhibitory effect could be due to down regulation of SLC25 transporter gene expression resulting in depletion of ATP. On the other hand, efflux transporter genes such as P-glycoprptein were over-expressed upon exposure to indomethacin which suggests the involvement of these genes in drug efflux. Interestingly, using indomethacin solid dispersion formulations resulted in decreasing the expression of this gene and in turn the overall uptake of indomethacin increased as suggested by the permeability studies. The studies concluded that gene expression data provides vital information and can be used as a screening tool to determine in vitro formulation performance.

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39 FABRICATION OF NANO-SIZED POLYMER-PROTEIN POLYELECTROLYTE COMPLEXES FOR ORAL PROTEIN DELIVERY

A Khan, M Traynor and W P Cheng
School of Pharmacy, University of Hertfordshire, College Lane, Hatfield AL10 9AB
Email: A.2.khan@herts.ac.uk

Today the advancement of biotechnology has led to the discovery of a plethora of therapeutic proteins. Although oral route is the preferred choice of patients, however this route of delivery is not feasible for proteins due to enzymatic susceptibility, instability and poor mucosal permeability. Many formulation technologies have been employed to improve oral delivery of protein and one of the promising delivery systems is nano-sized polyelectrolyte complexes (PEC). Polyelectrolytes are polymers containing ionisable groups which can form polyelectrolyte complexes (PECs) spontaneously with oppositely charged polymers/proteins through intermolecular interaction. The aim of the present study was to fabricate polycationic-polyanionic PECs containing a model protein, insulin for oral delivery. Polycationic polymer, polyallylamine (PAA) and its amphiphilic counterparts namely palmitoyl grafted-PAA (Pa-PAA), dimethylamino-1-naphthalenesulfonyl (dansyl-PAA) and quaternized palmitoyl-PAA (QPa-PAA) were synthesized and characterized. The polycationic polymers were mixed at 4.8:1, 7.2:1 polymer to insulin weight ratios in pH7.4 Tris buffer at room temperature. Polyanionic polymers dextran sulphate (DEX) or polyacrylic acid (PoA) was subsequently added to form PEC in the presence or absence of 100μM $ZnSO_4$. Measurement of particle size, zeta potential (ZP), kilo count per sec (kcps) and polydispersity index (PDI) were performed by dynamic light scattering. Morphology of the PECs was determined by transmission electron microscope (TEM). Stability of PECs was investigated at varying gastrointestinal pH (1.2-7.4), temperature (25˚C, 37˚C and 45˚C) and ionic strength (NaCl 68mM, 103M and 136mM) conditions. Results showed that $ZnSO_4$ plays an essential role in the fabrication and stabilization of PECs. Overall amphiphilic PAA PECs encountered less fluctuation in the size and zeta potential at acidic pH and high ionic strength conditions while unmodified PAA PECs were not stable in these conditions. This indicates that the presence of hydrophobic pendant groups on PAA is essential to maintain the stability of these PECs. Future work will investigate the complexation efficiency with insulin, in vitro insulin release profile and cytotoxicity of these formulations.

40 PLGA-BASED MICROPARTICLES FOR THE SUSTAINED RELEASE OF BMP-2

G T S Kirby (1), L J White (1), C V Rahman (1), H C Cox (1), O Qutachi (1), F R A J Rose (1), D W Hutmacher (2), K M Shakesheff (1) and M A Woodruff (3)
(1) School of Pharmacy, University of Nottingham, University Park, Nottingham, UK
(2)Regenerative Medicine Group. Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Queensland, Australia
(3) Biomaterials and Tissue Morphology Group. Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, Queensland, Australia
E: paxgk@nottingham.ac.uk

We aim to deliver therapeutic doses of growth factors with temporal kinetics desired in analogous repair environments. This research outlines the development of a polymeric bone morphogenetic protein-2 (BMP-2) delivery system with validation of the controlled release profile and efficacy in vitro.

Polymer microparticles were formed using a double emulsion solvent evaporation pro- cess. The BMP-2 was combined with human serum albumin as a bulk carrier. A formu- lation consisting of poly(lactic-co-glycolic acid) (PLGA) 85:15 (lactide:glycolide) and a more hydrophilic plasticiser was selected because of favourable release kinetics. Par- ticles were sized using laser diffraction. Protein release was measured by suspending particles in phosphate buffered saline, incubating at 37○C on a rocker shaker and reg- ularly sampling the release media. This release media was assayed for protein content and activity. BMP-2 containing microparticles and appropriate controls were cultured with the MC3T3-E1 cell line and assayed at three time points (10, 17 and 24 days). At these time points bone-like calcium deposition was qualitatively determined using Alizarin red and the early osteogenic differentiation marker alkaline phosphatase was quantitatively measured.

Particle size was tightly controlled within defined limits by optimizing the emulsion process. Mean particle diameters of 110-120μm were obtained. The release profile demonstrated sustained zero order release kinetics with minimal burst release. These particles induced MC3T3-E1 bone-like mineral deposition in a dose dependent man- ner. The expression of alkaline phosphatase was also detected at significantly higher concentrations in the BMP-2 group showing that differentiation was taking place.

This delivery system for BMP-2 may have clinical potential as therapeutic doses can be maintained over a sustained duration.

41 MELT EXTRUSION OF SOLID DISPERSIONS: AN EVALUATION OF PROCESS AND FORMULATION FACTORS

S Li (1), C Johnston (1), E Meehan (2), J Booth (2), D S Jones (1) and G P Andrews (1)
(1) Queen's University Belfast, School of Pharmacy, Belfast, UK.
(2) AstraZeneca Pharmaceutical Development, Charterway, Macclesfield, Cheshire. SK10 2NA. UK
E: sli03@qub.ac.uk

The dissolution behaviour and storage stability of extruded solid dispersions are closely related to drug/polymer interactions, drug particle size and drug content distribution within the extrudate. Thus the rationale for selection of extrusion process parameters as well as functional excipients is crucial in the development and application of this technique to overcome solubility issues. The aim of this research was to address the influence of both formulation and process factors on the dissolution and stability of melt extruded solid dispersions. The effects of extrusion screw speed, (20 & 120 rpm), drug load (10 & 50% w/w), drug particle size ([90-180μm], and [355-500μm]), and polymer molecular weight (200K and 1M PEO) on the physicochemical properties of extrudates were characterized using standard solid-state methods. Physical mixed and extruded samples (~10mg) were subjected to DSC from 0 - 200°C at a rate of 20°C/min in order to define melting of API. PXRD (range 3–40°, sample width 0.03°, step rate 2°/min.) was used to characterize the crystalline properties of the extrudates, following manufacture and after defined periods of storage (40°C/75% RH). Dissolution studies were conducted in pH 6.8 media using the USP paddle method (75 rpm, 37°C) during a 5-hour period. Cross sections of extrudates were analysed using Raman microscopy (20x). All extrudates showed an enhanced dissolution profile relative to pure drug (felodipine was used as a model) and physical mixtures. X-ray diffraction patterns and Raman mapping confirmed the presence of crystalline felodipine in dispersions containing 50% drug, immediately after manufacture. Conversely all 10% extrudates yielded amorphous dispersions. As expected, high drug loads and high polymer (PEO 1M) M_w showed decreased dissolution rates. Interestingly, increasing the screw speed (20 to 120 rpm) at a high drug load increased the release rate and enhanced drug solubility (PEO 200K). Formulations with different drug contents and extruded at different screw speeds recrystallised over a range of storage times. Felodipine and PEO binary solid dispersions were successfully manufactured using twin screw hot melt extrusion. Screw speed, drug loading, and polymer molecular weight all showed a significant effect on dissolution and stability performance.

42 NANOPARTICLE TRANSPORT ACROSS SUPPORTING CELL CULTURE FILTERS

J Lord (1) F Falcone (2) and S Stolnik (1)
(1) Drug Delivery and Tissue Engineering Division.
(2) Division of Molecular and Cellular Science, School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD
E: paxjl6@nottingham.ac.uk

In vitro studies on drug absorption via mucosal surfaces are typically conducted using epithelial cells cultured on supporting semi-permeable filters; such a system offering the opportunity to investigate absorption aspects of potential drug candidates in a reproducible and relatively inexpensive manner (for instance using Caco-2 cell monolayers). Whilst cells cultured on filters have been extensively characterised, studies investigating the barrier that the supporting filter poses to drug and particularly nanoparticle transport are sparse. Present study investigates supporting filters composed of polycarbonate (Transwell®, PC) and polyethylene terephthalate (Transwell®, PET) and the effect that these two materials and their nominal pore sizes have on the movement of fluorescently-labelled nanoparticles of 50 nm and 100 nm diameter.

Study shows that PET inserts with 0.4 μm pore size significantly hinder transport of nanoparticles; in a three-hour experiment, achieved diffusion of 50 nm and 100 nm nanoparticles is time dependent and final concentration at the basolateral (acceptor) side is only a portion of a theoretical equilibrium. This is particularly pronounced for 100 nm nanoparticles. For a larger 3.0 μm pore size PET filter, the diffusion of both 50 and 100 nm nanoparticles was significantly improved reaching concentrations at the acceptor side similar the theoretical equilibrium. However, the 3.0 μm 'unmodified' PET filters proved unsuitable for culturing Caco-2 cells; the formed cell layer lacked properties observed when culturing on 0.4 μm pore size filters. Both 3.0 μm PC and PET filters were therefore coated with varying densities of collagen (Type I from rat tail). Diffusion profiles for 100 nm nanoparticles suggest that nanoparticulate movement was not compromised after collagen coating with densities between 5 and 20μg/cm^2 while these densities allowed for Caco-2 cell culture to be established. The study hence demonstrates the importance of selecting an adequate supporting filter when culturing epithelial cells for nanoparticle transport studies. The 0.4 μm pore size filters significantly hinder nanoparticle transport, while collagen coating of 3.0 μm PC or PET inserts provides conditions with improved nanoparticle transport and allows for appropriate cell cultures to be established.

43 A MULTI-COMPONENT, HIGH THROUGHPUT SCREENING METHOD FOR THE EVALUATION OF DRUG DELIVERY SYSTEMS

K Lovrics (1), S Stolnik (1), M C Davies (1), M Alexander (1) and K Hill (2)
[1]School of Pharmacy, University of Nottingham, Nottingham, UK.
[2]Pharmaceutical Development, AstraZeneca, Alderley Park, UK.
E: paxkl3@nottingham.ac.uk

Extensive research in drug discovery has generated a wide variety of lead compounds which created a demand for drug delivery formulations. The success of a drug delivery system depends both on the active compound and the effectiveness of the formulation. High throughput screening (HTS) is an automated process suitable for analysing large numbers of compounds in a short time. The utilisation of HTS in formulating and assessing drug delivery systems to date is very limited.

The small amount of research in high throughput formulation preparation and screening follow a similar pattern. Drug formulation is carried out in an automated way and a selected feature of the formulation is assessed in an automated manner. Most formulations also require additional manual (low-throughput) measurements to provide adequate information.

In the present work a more advanced, fully HT method was developed for preparing and analysing a model drug delivery system. An automation-compatible equilibrium dialysis unit (a multiwell plate with each plate divided into two parts by a vertical dialysis membrane) was selected to be the main experimental device. A hyaluronic acid – insulin polyelectrolyte complex was utilised as a model drug delivery system. Samples were prepared and handled by a liquid handling robot. Complex formation, formulation analysis and drug release analysis were carried out in one continuous experiment with no significant manual intervention in a high throughput process. Different hyaluronate and insulin ratio complexes were prepared and assessed in the dialysis unit. The preparation and drug release evaluation processes were both monitored by multiple analytical indicators such as pH, ionic strength, insulin amount etc.

The polyelectrolyte model system was successfully formulated and analysed over time showing drug retention. The use of automation also provided previously unexpected results regarding favourable formulation ratios. Future work includes employing the same set-up for other type of drug delivery systems.

44 SOLUBLE POLYMERIC MICRONEEDLE-MEDIATED TRANSDERMAL DELIVERY OF CAFFEINE AND LIDOCAINE FOR PAEDIATRIC APPLICATION: COMPARISON OF THREE IN VITRO MODELS

T M T Mahmood, J McElnay and R F Donnelly
School of Pharmacy, Queen's University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast, BT9 7BL, United Kingdom
E: ttuanmahmood01@qub.ac.uk

Microneedles are one strategy employed to overcome the stratum corneum barrier. In this study, we determined the percutaneous release profiles of soluble polymeric microneedles containing the hydrophilic drugs caffeine and lidocaine hydrochloride across three different in vitro models. These models were dermatomed (300-350 µm) and full thickness (700-750µm) neonatal porcine skin and a synthetic lipophilic membrane, Silescol®. Soluble polymeric microneedles were fabricated from Gantrez® AN-139 by micromoulding. The in vitro release of caffeine and lidocaine from soluble polymeric microneedles was evaluated using Franz diffusion cell studies over 24-hours. We found that dermatomed neonatal porcine skin was the superior in vitro model for microneedle release studies. The possible reasons were the presence of water molecules within porcine skin that was lacking in Silescol® membranes, allowing higher dissolution of soluble microneedles arrays upon application. Also, due to the very thin nature of dermatomed skin, the drug release profile was driven by the concentration of the drug loaded in microneedles. In contrast, the skin thickness become the rate-limiting step and governed the release of drug across full thickness skin. The cumulative percentage of caffeine and lidocaine released across dermatomed porcine skin studies followed first order kinetic and the amounts of drug released were 58.45% ± 8.60 and 39.33% ± 8.92 respectively. Meanwhile, a percentage of 49.55% ±3.90 of caffeine and 26.13% ± 2.15 of lidocaine were released across the full thickness porcine skin over 24-hours and the release profile followed zero order kinetics. The least release of caffeine and lidocaine were observed across Silescol® synthetic membranes, with cumulative release of 7.87% ± 3.20 and 3.28% ± 0.64, respectively over 24-hours. This was also explained by the possibility of the membranes to rapidly close the pores created by microneedles after microneedle dissolution, as observed by microscopy and TEWL studies.

45 LANGMUIR STUDY ON LIPID MONOLAYERS OF CATIONIC LIPOSOMES

B Moghaddam, Q Zheng and Y Perrie
The School of Life and Health Sciences, Aston University, Birmingham, UK.
E: moghadb1@aston.ac.uk

Liposomes are well recognised for delivering drugs and nucleic acids. Lipid monolayers can be considered as building blocks for bilayer vesicles, therefore, using a Langmuir-Blodgett trough to study monolayers at the air/water interface in combination with the lipid attributes can give an insight into areas such as the bilayer lipid packaging configuration, drug-lipid interaction and liposome stability, hence these parameters can be considered prior to design a liposome formulation.

Monolayers of helper lipids of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) and (1,2-distearoyl-sn-glycero-3-phosphoethanolamine) (DSPE) together with cationic lipids of 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and 1,2-stearoyl-3-trimethylammonium-propane (DSTAP) were prepared separately. Pressure on the monolayers on the air/water interface was calculated via Wilhelmly method. When the mixture of monolayer lipids contained both saturated (DSPE:DSTAP) or both unsaturated (DOPE:DOTAP) lipids, the deviation from the ideal molecular area was negative compared to DOPE:DSTAP and DSPE:DOTAP. These monolayers with a high condensed effect make a packed monolayer structure and more likely the bilayer structure would have the same packing trend; therefore may prohibit the incorporation of drugs within the bilayer vesicle causing a decrease in drug loading, however such bilayers can promote drug retention of water soluble drugs within the vesicles. In contrast, unsaturated lipids are more bulky and their condensing effect is less than saturated lipids. This will cause a higher release profile and better stability for them. Substitution of dH_2O with PBS in the subphase resulted in notable reduction in A^2/Molecule and an increase in collapse pressure just for DOTAP.

The choice of buffer is known to influence the characteristics of liposomes including stability. It has also illustrated that the lipid chain length and its structure has a remarkable effect on packing configuration of the monolayer and consequently can affect the liposome characteristics. The above monolayer studies allow the molecular mechanics of lipid monolayers to be translated into liposomal systems.

46 ENHANCEMENT OF THE AQUEOUS SOLUBILITY OF RIBOFLAVIN USING HYDROTROPIC EXCIPIENTS

P W J Morrison, C J Connon and V V Khutoryanskiy
School of Pharmacy, University of Reading, Whiteknights, PO Box 224, Reading, RG6 6AD, United Kingdom.
E: p.w.j.morrison@pgr.reading.ac.uk

Many potential pharmaceutically active compounds are presently unsuitable as therapeutic resources due to their poor aqueous solubility, hence having poor bioavailability. Riboflavin (vitamin B_2), an important compound essential for many metabolic processes, is a molecule with a complex multi-aromatic ring structure of moderate molecular weight and is relatively non-polar. Riboflavin is only slightly soluble in water, reported in the literature to be less than 0.1 mg ml^{-1} at 25°C. These attributes make it an appropriate representative material of slightly water soluble aromatic compounds. Riboflavin has more recently been used as a photosensitive cross-linking agent in the treatment of Keratoconus; an ocular disorder whereby the cornea becomes weakened and deteriorates leading to sight problems. For some patients the condition progresses to the stage where penetrating keratoplasty (corneal transplant) becomes necessary. Historically, symptoms of the condition could be managed, for example, by specially made contact lenses, but this cannot stop the progression of the disease. Many sufferers are further compromised because they are unable to tolerate contact lenses.

A series of experiments were designed to investigate enhancement of the aqueous solubility of riboflavin, using it as a model drug of poor solubility compounds. A number hydrotropic solutions where prepared; α-, β-, γ- and HP-β-cyclodextrin, nicotinamide and urea, in varying concentrations, under temperature controlled conditions, their effect on the solubility of riboflavin was analysed using UV-Vis spectrophotometry.

The study found that cyclodextrin solutions achieved riboflavin solubility enhancement between 0.6% and 56%, urea solutions achieved enhancement up to 40%, whilst nicotinamide achieved up to a 94 fold enhancement. Further studies are planned to examine the permeability of riboflavin enhanced solutions across corneal membranes.

The study has demonstrated significant enhancement to riboflavin solubility using hydrotropic agents, it could be appropriate to extend the study for other compounds of poor aqueous solubility in future work.

47 DEVELOPMENT OF A DARUNAVIR-RELEASING SILICONE ELASTOMER INTRAVAGINAL RING

D Murphy, A D Woolfson and R K Malcolm
School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK
E: d.j.murphy@qub.ac.uk

Intravaginal rings (IVRs) are currently being developed for the controlled delivery of microbicide compounds to reduce the heterosexual transmission of HIV. To date, the focus has been on rings releasing small molecule reverse transcriptase inhibitors (RTIs) and fusion/entry inhibitors. Protease inhibitors (PIs), which act later in the HIV replication cycle, are now also being considered, particularly in combination with RTIs, due to their high genetic barrier to the evolution of resistance. Here we report on the preliminary development of a darunavir-releasing, matrix-type, silicone elastomer vaginal ring. Silicone elastomer vaginal rings were manufactured by reaction injection molding on a laboratory scale device. In vitro release testing was performed on 10, 20 and 30% darunavir-loaded IVRs into both simulated vaginal fluid (SVF) and an isopropanol:water system. Darunavir solubility in the silicone elastomer was evaluated and residual content was analysed following extraction.

Based on upper limits for the volumes of cervicovaginal fluid (8 mL) and semen (8 mL), and assuming that the in vivo release rate of darunavir from a vaginal ring is similar to the release rate observed in vitro; release of darunavir from the 20% IVR yielded predicted concentrations at least 1200 times greater than its in vitro EC_{90}. The release kinetics suggested predominantly diffusion controlled release. As expected, release was significantly better into isopropanol:water than into SVF, in line with the hydrophobic nature of the drug. Surprisingly a greater release rate was observed with 20% compared to 30% darunavir loaded rings. 20% rings released over double the amount of darunavir into isopropanol:water compared to 30% rings over 28 days. In SVF, the release from both drug loadings was approximately similar, suggesting a solubility limiting effect. Darunavir was not soluble above 0.73% w/w at its melting temperature in the silicone elastomer. Results from residual drug content analysis matched the release profiles in all cases. A 20% darunavir loaded IVR releases drug at levels greater than 1200 times the in vitro EC_{90}. The curing temperature of the IVR appears to have a role in determining the amount of drug initially dissolved in the elastomer with subsequent effects on release.

48 PULMONARY DELIVERY OF AMPHOTERICIN B USING TWO COMMERCIALLY AVAILABLE NANOEMULSIONS FOR TREATMENT OF ASPERGILLOSIS

M Nasr (1, 2), S Nawaz (1), A Elhissi (1), Waqar Ahmed (1,3) , A D'Emanuele (1)
(1) Institute of Nanotechnology and Bioengineering, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, United Kingdom.
(2) Faculty of Pharmacy, Ain Shams University, Egypt.
(3) School of Computing, Engineering and Physical Sciences, University of Central Lancashire
E: MNasr@uclan.ac.uk

Potentiation of therapeutic effects of drugs while minimizing their side effects is the target being pursued by most pharmaceutical researchers. Topical delivery of antifungal formulations to the lung via nebulization has attracted a lot of attention. This local delivery is expected to decrease the systemic side effects of the drugs whilst increasing their local effectiveness, through the provision of high pulmonary level, which is particularly advantageous for immunocompromised hosts with invasive diseases. Among the widely known fungal species causing severe implications are Aspergillus species, which are inevitably inhaled into the airways. Inhalation of Aspergillus conidia or mycelium fragments could result in colonization of the airways of susceptible hosts. This colonization would subsequently cause severe disease. Invasive Aspergillosis causes serious damage to lung tissue due to invasive hyphal growth. Dissemination of aspergillosis may also occur to other organ systems, correlating with a poorer diagnosis and high mortality rates. Aerosolized treatment of pulmonary aspergillosis has been suggested as an adjunctive local therapy for invasive fungal disease. Amphotericin B, being the drug of choice for treatment of aspergillosis was chosen for the current study. The hydrophobic nature of Amphotericin B presented a challenge for proper formulation in an inhalable form. In this context, the potential of two commercially available isotonic lipid nanoemulsions: Intralipid® and Clinoleic® to solubilize amphotericin B was investigated in this study. Their possible nebulization and respiratory tract deposition were also studied, to assess their ability to target the alveolar macrophages within which the fungus resides. Amphotericin B loaded nanoemulsions were characterized for their entrapment efficiency, particle size, zeta potential and nebuliziation potential. Results showed that both nanoemulsions were of comparable nebulization behavior, with Intralipid® being superior in solubilizing amphotericin B than Clinoleic®, suggesting that both nanoemulsions can be used successfully for pulmonary delivery of amphotericin B.

49 PULMONARY DELIVERY OF BECLOMETHASONE DIPROPIONATE USING PAMAM DENDRIMERS AS NANOCARRIERS

M Nasr (1, 2), A Elhissi (1) and A D'Emanuele (1)
(1)Institute of Nanotechnology and Bioengineering, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, United Kingdom.
(2) Faculty of Pharmacy, Ain Shams University, Egypt.
E: MNasr@uclan.ac.uk

Dendrimers have recently attracted increasing attention for their applications in many pharmaceutical fields, especially in drug delivery. The suitability of dendrimers as drug delivery nanocarriers is attributed to the fact that they are hyperbranched, monodisperse, biocompatible, three dimensional molecules with a defined molecular weight. Dendrimers are also known for their host-guest entrapment properties. Testing the hypothesis that dendrimers, specifically PAMAM dendrimers would encapsulate hydrophobic guest molecules such as beclomethasone dipropionate (BDP) in their macromoleculer interior and that they would be successfully used for pulmonary delivery was the subject of our present study.

Two full generation amine terminated dendrimers (G3) and (G4) were utilized in our study. Solubility experiments were performed and determination of BDP encapsulated within dendrimers was carried out using HPLC. Construction of phase solubility curves was performed to study the effect of increasing concentration of dendrimer on solubility of BDP, with the calculation of the stability constant for the complexes between BDP and PAMAM dendrimers. Dendrimers were further characterized for their nebulization behavior using different nebulizers.
Phase solubility profiles showed that the molar solubility of BDP increased in an approximately linear manner with the increase in the dendrimer concentration. In addition, this increase in solubility was found to be generation-dependant, with G4 dendrimers being more superior than G3 dendrimers in solubilizing BDP. Soluble complexes between BDP and the dendrimers appeared to have 1:1 stochiometries. Nebulization studies showed that PAMAM dendrimers were promising carriers for pulmonary delivery of BDP.

50 THE ROD INSERT VAGINAL RING: A STABILITY EVALUATION USING A MODEL PROTEIN

A Pattani, R M Curran,V L Kett, G P Andrews and R K Malcolm
School of Pharmacy, Queen's University of Belfast, Northern Ireland.
E: apattani01@qub.ac.uk

Conventional permeation-controlled vaginal ring devices are ineffectual for the delivery of macromolecules such as proteins and DNA. Rod-insert rings (RiR) for the release of macromolecular and/or hydrophilic actives have recently been reported comprising dissolvable or swellable dosage units inserted into a silicone elastomer ring body.1 In this study we manufactured vaginal rings devices containing bovine serum albumin (BSA)-loaded, freeze-dried, low MW hydropropylmethylcellulose (HPMC) rod inserts. Both the insert rings (3 inserts per ring) and the gels that were freeze-dried to prepare the inserts were subsequently evalauted for BSA stability under the premise that the freeze-dried systems would offer greater stability. The rings and gels were stored either at 4°C and 40°C/75%RH for 12 weeks, with sampling timepoints at weeks 0, 3, 6 and 12. The rings were evaluated for their mechanical properties (using the cyclic compression test), BSA content using RP-HPLC (fluorescence and U.V detection) and native gel electrophoresis for evaluating the formation of soluble aggregates. At the end of the study, the microbial load on the inserts and the gel were also measured. The inserts and gels stored at 40°C / 75% RH showed a brownish discoloration (mild for insert/strong for the gel) over the weeks of the study, while the inserts and gels stored at the 4oC did not exhibit this discoloration. The degradation of BSA was accelerated at 40°C/75%RH as compared to 4°C. A systematic analysis consisting of SDS PAGE, tubidimetry, microbial analysis and precipitate solubility study seems to suggest that the major mechanism of degradation of BSA in these systems at 40°C/75%RH is the formation of insoluble aggregates.

1. RJ Morrow, AD Woolfson, L Donnelly, R Curran, G Andrews, D Katinger and RK Malcolm, Sustained release of proteins from a modified vaginal ring device, Eur J Pharm Biopharm, 77: 3-10, 2011

51 INVESTIGATION OF MILLING ON THE FORMULATION CHARACTERISTICS OF GELATIN-BASED LYOPHILISED ORALLY DISINTEGRATING TABLETS (ODT'S)

R J. Jones (1), M Levina (1), A R Siahboomi (2), Y Perrie (1), A R Mohammed (1).
(1) Drug Delivery Research Group, School of Life & Health Sciences, Aston University, Birmingham, B4 7ET
(2) Colorcon Ltd., Flagship House, Victoria Way, Crossways, Dartford, Kent, DA2 6QD
E: jonesrj1@aston.ac.uk

A disadvantage of gelatin as a binder in lyophilised ODT's is that a heating step is required during the manufacturing process, to dissolve gelatin. This study investigated the affect of milling the excipients, on the characteristics of the excipients and the formulated tablets, with the aim of eliminating the need for the heating step during manufacturing the tablets. This study was performed in order to investigate if milling the excipients, would result in an improvement or deterioration in the characteristics of the excipients and tablets. The characteristics of the excipients which were investigated, included; wettability, dissolution, glass transition and porosity. The characteristics of the tablets which were investigated included; glass transition, mechanical properties, porosity, morphological examination of the tablet matrix structure, disintegration time, and dissolution, in which ibuprofen was used as a model drug. Statistical design of experiments software was used to determine the milling conditions for the eleven formulations. In terms of wettability, two of the eleven formulations exhibited significant improvement, relative to the control (non-milled) formulation. Six of the eleven formulations (in raw excipient form) exhibited increased onset glass transition temperature. Milling showed not to influence the dissolution behaviour of the excipients. All eleven formulations exhibited significant differences in powder porosity, relative to the control formulation. In terms of glass transition temperature, five of the eleven formulations (in frozen form) exhibited significantly different onset glass transition temperatures, relative to the control formulation. In terms of the characteristics of the tablets, milling did not have a significant effect on tablet; mechanical properties, porosity (also analysed with morphological examination of the tablet matrix structure), disintegration time or dissolution. Milling has shown to be more influential on the characteristics of the excipients in their powdered form (prior to formulating into tablets), rather than the characteristics of the formulated tablets.

52 DRY-MILLED POLYMER FOR USE IN NANOPARTICULATE ENCAPSULATION OF LANSOPRAZOLE

A Shabir, Y Perrie and A Mohammed
Aston Pharmacy School, Aston University, Birmingham, UK B47ET
E: shabira3@aston.ac.uk

Currently there is great interest in nanoparticulate drug delivery, which can be used to reformulate licensed drug products into liquid oral formulations for use in the treatment of paediatric and geriatric patients. The objective of the current work was to study the suitability of poly-(DL-lactide-co-glycolide) (PLGA) in nanosphere systems for the reformulation of a proton pump inhibitor, lansoprazole, into a liquid formulation. Lansoprazole is a hydrophobic drug that is currently only formulated in a tablet form. The objective of the study was "to determine the impact of polymer ratio on drug loading, and whether dry-milling of the polymer prior to nanoparticle preparation would enhance the drug-loading of lansoprazole within the nanoparticle matrix".

Utilising non-milled PLGA for the preparation of nanospheres, the particle size of the nanoparticles increased from 259+17nm to 292+21nm with increasing PLGA concentrations. The particle charge was observed to increase from -25.89+3mV to -37.64+4mV. Lanzoprazole has a water solubility profile of 0.97mg/L, by using a nanoparticlulate suspension the solubility of lansoprazole was increased to 800mg/L, however the ratio of polymer within the system had no impact on the drug loading. By dry-milling the polymer prior to nanoparticle formulation, the nanoparticle was observed to decrease in size by 20 nm, with a further decrease in particle charge. The entrapment efficiency however increased to 92+1, 96+0 and 95+3 % with increasing polymer concentration, thereby increasing the solubility profile to 950+2mg/L.

These results show that PLGA-based nanoparticulate delivery systems can provide a practical alternative for the reformulation of lansoprazole as an oral liquid-based medicine, thereby overcoming the hydrophobicity nature of lansoprazole. This study has further shown that by milling PLGA prior to nanoparticle formulation, the solubility of lansoprazole has been enhanced by being formulated as a nanoparticulate liquid oral delivery system.

53 UNDERSTANDING RECRYSTALLISATION WITHIN AMORPHOUS SOLID DISPERSIONS: THE ROLE OF POLYMERIC CARRIERS

Y W Tian (1), E Meehan (2), J Booth (2), D S Jones (1) and G P Andrews (1)
(1)Queen's University Belfast, School of Pharmacy, 97 Lisburn Road, Belfast. BT9 7BL. UK.
(2)AstraZeneca, Pharmaceutical Development, Macclesfield, Cheshire. SK10 2NA.
E: ytian02@qub.ac.uk

The potential of amorphous drug forms to enhance the dissolution performance of BCS class II compounds has not been widely recognised due to the inherent poor physical stability during storage and/or dissolution. Therefore, one of the most important/significant challenges facing the pharmaceutical industry is to produce a sufficiently stable formulation for practical use. This study investigates the different crystallisation behavior of amorphous felodipine embedded within solid dispersions containing HPMC AS-LF, MF, HF and Soluplus.

40% drug loaded amorphous felodipine/polymer mixtures were prepared by solvent evaporation. Felodipine and polymer were dissolved in solvent (state solvent), poured into petri-dishes and cast in a vacuum oven at room temperature, 10-2 mbar for at least 24 hours. Samples were then stored under 40°C, 75%RH for defined periods and studied using polarised light microscopy (PLM BX50, Olympus, UK), Raman spectroscopy (Perkin Elmer Microscopy300, Perkin Elmer, UK) and HyperDSC (DSC8000, Perkin Elmer, UK). FT-IR and Raman were used to indicate the existence of interactions between felodipine and polymer carriers immediately following preparation. The complex viscosity of each system was also determined using Dynamical Mechanical Thermal Analysis (DMTA Q800, TA instruments, UK) across a temperature and frequency range from 10 to 50 °C and 0.3 to 30 Hz, respectively.

IR spectra indicated the existence of interactions between felodipine and polymer HPMC AS-LF, MF, HF and Soluplus. Strong red shifts for felodipine/Soluplus solid dispersion (92 cm-1) were observed compared to sample felodipine/HPMCAS (21 cm-1), indicating that a stronger interaction was formed between felodipine and Soluplus. However, after three-months storage, the particle size of crystalline felodipine was much larger in felodipine/Soluplus solid dispersion than that of felodipine/HPMCAS solid dispersion. This phenomenon may be attributed to the contribution of viscosity and water uptake. Moisture uptake during storage may weaken the intermolecular interaction between polymer and drug and/or increase the mobility, thereby, accelerating the recrystallisation process. DMTA results confirmed the viscosity difference between polymer carriers.

This study demonstrates that the interaction between drug and polymer is not the only factor in stabilisation of an amorphous drug within solid dispersion.

54 AN INVESTIGATION INTO THE DISSOLUTION ENHANCEMENT OF A POORLY WATER-SOLUBLE MODEL DRUG USING HOT MELT EXTRUDATES COMPRISING ENTERIC POLYMERS

S Tipping (1), D S Jones (1), K Nollenberger (2) G W Smith (2) and G P Andrews (1)
(1) Queen's University Belfast, School of Pharmacy, 97 Lisburn Road, Belfast. BT9 7BL. UK.
(2) Evonik Röhm GmbH, Kirschenallee, 64293 Darmstadt, Germany
E: t1539603@qub.ac.uk

The aim of this study was to compare the effectiveness of EUDRAGIT L100-55 and HPMCAS-LF as matrix formers in enhancing the solubility of felodipine using hot melt extrusion technology. The effect of felodipine/polymer ratio on the drug solubility within the matrix, and upon the in vitro drug release properties was determined. The storage stability of the formulations was also investigated. Felodipine was extruded in combination with either EUDRAGIT L100-55 or HPMCAS-LF at a temperature of 140°C using a Haake MiniLab micro-compounder. TEC was used as a plasticizer at a loading of 15% w/w. Drug loadings at 10% and 50% w/w were investigated. The physicochemical properties of the extrudates were characterised using DSC, MTDSC and PXRD. Furthermore, in vitro drug release studies were preformed in blank FaSSIF pH6.5 and pH change dissolution media (pH 1.2, pH 6.8, pH 7.4). DSC and PXRD confirmed the formation of molecular dispersions of the drug within the polymer at 10% w/w loading. In vitro drug release studies showed a significant enhancement of solubility at the higher polymer loadings. The pH change dissolution experiments showed the effectiveness of the polymers in maintaining their integrity in highly acidic conditions. Using a heat-hold-heat method during DSC, an indication of the miscibility of drug and polymer was elucidated.

55 THE USE AND CHARACTERISATION OF A NOVEL ANIONIC LIPOSOME SYSTEM FOR USE IN VACCINE DELIVERY AND FORMULATION

A Wilkinson, M Henriksen-Lacey, A R. Mohammed and Y Perrie
School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, B4 7ET, England
E: wilkina1@aston.ac.uk

The need for effective vaccine delivery systems which are capable of eliciting a strong specific immune response is becoming an increasingly important area in the field of vaccine formulation. In our laboratory, the cationic adjuvant liposome formulation DDA:TDB has been used in research studies. These liposomes are formulated from the cationic surfactant, dimethyldioctadecylammonium (DDA) bromide in combination with the immunomodulating glycolipid, trehalose 6, 6'-dibehanate (TDB). The adjuvanticity of DDA:TDB has been ascribed to its cationic surface charge. The specific capacity of these liposomes to adsorb anionic antigens leads to increased presentation to APCs together with the ability to promote an antigen depot at the site of injection (SOI).

To investigate the potential role of liposome charge in the development of adjuvants, a novel anionic liposome formulation comprising the anionic lipid surfactant, 1,2 -distearoyl-sn-glycero-3-phospho-L-serine (DSPS) in combination with TDB has been developed using the lipid film hydration method.

The main findings from initial studies are that both liposome systems are of relatively similar size (~ 500-600 nm), with DDA:TDB displaying a high positive zeta potential (~ 63 mV) and high adsorption of OVA antigen (~ 88 % of 1 mg/ml OVA), whilst DSPS:TDB liposomes display a highly negative zeta potential (~ -60 mV), and thus high adsorption of the cationic protein lysozyme (~ 87 % of 1 mg/ml lysozyme). Investigating the biodistribution of the various systems show that the delivery of lysozyme with DDA:TDB results in a rapid antigen clearance from the SOI due to the lack of electrostatic interaction between liposome and antigen. Whereas, an antigen depot of lysozyme at the SOI can be promoted when lysozyme is delivered with DSPS:TDB. The retention of DSPS:TDB at the SOI, and the ability of lysozyme to electrostatically bind to DSPS:TDB leads to lysozyme remaining at the SOI with this delivery system.

56 PHYSIOCHEMICAL CHARACTERIZASTION OF HOT-MELT EXTRUDATES CONTAINING EUDRAGIT L-100 AND EUDRAGIT 4155F

M A Williams (1), D S Jones (1), K Nollenberger (2) G W Smith (2) and G.P. Andrews (1)
(1) Queen's University Belfast, School of Pharmacy, 97 Lisburn Road, Belfast. BT9 7BL. UK.
(2) Evonik Röhm GmbH, Kirschenallee, 64293 Darmstadt, Germany
E: mwilliams16@qub.ac.uk

To compare the dissolution and stability profile of felodipine solid dispersions containing Eudragit polymers, L-100 and 4155F with that of Polyvinylpyrrolidone K30, a widely used polymer for dissolution enhancement.

Felodipine (10%) solid dispersions were prepared via a hot-melt extrusion process comprising either PVP K30 (with 10% TEC), Eudragit L-100 (with 20% TEC), or Eudragit 4155F. The thermal properties of the extrudates were characterized using DSC. PXRD was used to characterize the crystalline properties of the extrudates, immediately after manufacture and after defined periods of storage at 40°C/75% RH. Dissolution studies were conducted in changing pH media (pH 1.2, 6.8, 7.4) using a USP paddle method at 75 rpm and 37°C over a twelve hour period. Samples were analyzed with the aid of a UV-VIZ spectrophotometer. All measurements were conducted in triplicate and statistically analysed using a repeated measures ANOVA.

DSC and PXRD studies confirmed the formation of amorphous one phase systems for all formulations. The maximum drug concentration occurred during dissolution in pH 1.2, 6.8 and 7.4 media for PVP K30, Eudragit L-100 and 4155F respectively. This is expected as the solubility of PVP is pH independent, while L-100 dissolves at pH above 6 and 4155F above pH 7. Maximum drug concentration values were highest for 4155F (45mg/L ± 11 mg/L), followed by L-100 (16mg/L ± 5mg/L) and PVP (10 mg/ L ± 1.8mg/L). Interestingly, rapid recrystallization of felodipine following supersaturation, as evidenced by the sharp decline in drug concentration, was observed in the case of PVP and L-100, but not with 4155F. Stability studies of the Eudragit polymers revealed amorphous stability for up to 4 months. The PVP K30 extrudate, however, absorbed moisture (19%) and became rubbery.

This study clearly demonstrates the significant potential for using Eudragit L-100 and 4155F polymeric platforms for manufacturing solid dispersions.

57 HOT MELT EXTRUDED BINARY SOLID DISPERSIONS CONTAINING EUDRAGIT L-100 AND PLURONIC

M A Williams (1), D S Jones (1), K Nollenberger (2) G W Smith (2) and G.P. Andrews (1)
(1) Queen's University Belfast, School of Pharmacy, 97 Lisburn Road, Belfast. BT9 7BL. UK.
(2) Evonik Röhm GmbH, Kirschenallee, 64293 Darmstadt, Germany
E: mwilliams16@qub.ac.uk

To investigate the use of binary polymeric systems containing Eudragit L100 and Pluronic F127 (10, 20 & 50% w/w) in manufacturing solid dispersions containing a model poorly soluble drug (10% w/w Felodipine, FD). L-100 and F127 combinations were manufactured via hot melt extrusion (185°C/300RPM). The thermal properties of the extrudates were characterized using DSC. Samples (~7mg) were subjected to heat cool heat cycles from 20 - 200°C at a rate of 20oC/min. PXRD (range 5–40o, step rate 0.1°/sec.) was used to characterize the crystalline properties of the extrudates, following manufacture and after defined periods of storage (40oC/75% RH). Dissolution studies were conducted in changing pH media using the USP paddle method (75 rpm, 37°C) during a 12-hour period. All measurements were conducted in triplicate and statistically analysed using repeated measures ANOVA. Surfactants have the potential to reduce surface tension and hence improve the dissolution rate of poorly soluble drugs. We have undertaken this study to characterize binary polymeric systems containing a model surfactant. It was not possible to extrude Pluronic F127 or 50% L-100/50% F127 due to their low viscosity. At a loading of 10 and 20% F127, DSC and PXRD studies confirmed the formation of amorphous one-phase systems, characterised by a single Tg and an amorphous halo. There was no observed drug release during the first two hours of the study (media pH 1.2). An increased F127 concentration, (20% compared to 10% w/w) significantly increased the drug concentration achieved at pH 6.8 (39±4mg/L versus 27±1mg/L). These values were significantly higher ($p < 0.05$) than that obtained from the single L100 polymer system (16± 5mg/L). Interestingly, rapid recrystallization of felodipine occurred in binary and single polymer systems, following supersaturation. However, the equilibrium solubility after 12 hours was significantly higher (7mg/L) for the binary systems compared to the single polymer system (3mg/L). PXRD studies indicated that the amorphous character of the extrudates was maintained after storage at 40oC/75% RH for > 4 months. This study demonstrates the potential of binary polymeric platforms for manufacturing solid dispersions. In this study, we had identified the advantage of using a surface-active agent in combination with a hydrophilic extrudable polymer.

58 DRUG ELUTING PH-TRIGGERED SELF-CLEANSING BIOMATERIALS

H Zhai, O Altarawneh, D S Jones, B F Gilmore, S P Gorman, and G.P. Andrews
Queen's University Belfast, School of Pharmacy, The Biomaterials Group, 97 Lisburn Road, Belfast. BT9 7BL. UK
E: oaltarawneh01@qub.ac.uk

Healthcare-acquired infections (HCAI) are a major public health concern resulting in patient morbidity and mortality. Biofilms play a pivotal role in HCAIs, especially those related to the implant of urinary catheters. Consequently, over the last two decades numerous strategies have been developed to prevent device-related infections. The aim of this research is to design and develop pH-triggered self-cleansing biomaterials to prevent / delay bacterial adherence and encrustation. Hydroxypropylmethylcellulose acetate succinate (HPMCAS, AQOAT® HF) was used as a potential responsive layer. Salicylic Acid (SA) was used as a model drug, Triethyl Citrate (TEC), Dibutyl Sebacate (DBS) and Polyethylene Glycol (PEG 8000) were evaluated as plasticizers. Thermal properties of initial materials were analysed using TGA and DMA. Films with different drug content, plasticizer type and plasticizer content were produced using hot melt extrusion (HME). Surface properties of the films were investigated using optical microscopy and contact angle analysis. Mechanical properties of the films were determined using a Texture Analyser. The self-cleansing and drug release properties of the films were tested in PBS pH 6.0 and pH 7.0, respectively to represent normal and infected urine. Initial materials had acceptable thermal stability below 120 °C. The glass transition temperature (Tg) of HPMCAS was affected by the concentration of drug, plasticizer and type of plasticizer used. Improved surface smoothness was observed in formulations containing higher plasticiser concentration and lower drug loadings. All films had hydrophobic surfaces and flexible properties. PH-dependent self-cleansing and controlled drug release mechanisms were found in all the formulations. Self-cleansing and drug release rate was affect by drug loading, plasticizer concentration and plasticizer type. Drug eluting pH-triggered self-cleansing HPMCAS-HF films were successfully manufactured using a rapid, continuous processing technique (hot melt extrusion). The films showed satisfactory tensile, surface, and self-cleansing properties. Drug content, plasticiser content and plasticiser type had a range of effects on the drug release properties and self-cleansing rates of the films.

LATE ABSTRACTS

Not included in printed booklet

59 LIPOSOMES AS CARRIER SYSTEMS FOR SYSTEMIC DELIVERY OF SALMON CALCITONIN BY INHALATION

Swaminathan J and Ehrhardt C
School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Ireland.
Email: swaminaj@tcd.ie

Delivery to the lungs has evolved as one of the most widely investigated methods for systemic or local delivery of biopharmaceuticals over the past two decades. In addition to fast-acting medications, the design of drug delivery systems for sustained release across the respiratory barrier is of interest, to allow exploitation of all possible advantages the pulmonary route offers. In the present work, liposomal formulations for aerosol delivery of salmon calcitonin (sCT) were developed and characterised.

Liposomes were prepared by the dry film hydration method. Unilamellar vesicles were obtained by extrusion using an extruder (Lipex), non-encapsulated sCT was separated by gel filtration through polyacrylamide gel columns. Size and ζ-potential were measured with a Zetasizer Nano (Malvern). sCT concentration was determined using RP-HPLC and phospholipid concentration by Stewart's assay. The influence of the loading buffer's pH value (3.5 - 10) and that of the liposomal membrane charge (using PG/DPPG and SA) as well as fluidity (DPPC:Chol vs. PC:Chol), on sCT encapsulation were studied. Moreover, Liposomes (0, 10 and 20% SA) with and without 5% DSPE-PEG2000 were aerosolised using an Aeroneb Pro vibrating mesh nebuliser (Aerogen).

Our data suggest that DPPC liposomes with positive surface charge, hydrated at pH 3.5 were the optimal formulation, obtaining encapsulation efficiencies of 35±4%, particle size of 140 nm (PDI of 0.06). The ζ- potential (in buffer pH 7.4) was 24±1 mV. All liposomes investigated proved to be stable during nebulisation.

Liposomal systems for sCT delivery to the lungs were successfully optimised. Ongoing PK studies will determine if these results can be translated into an in vivo setting.

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