**Project Title:** Nanoparticulate formulations of insulin and their analysis

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**Project Area:** (one or more of the following)  
Drug Delivery

**Project Description:**

**Background**  
Subcutaneous or intradermal injection of insulin remains the central treatment of Type 1 diabetes. Non-invasive protein delivery is actively sought but has met with intractable problems, such as the experience with Exubera™ (Pfizer), an inhalable formulation of insulin. Given orally, insulin is enzymatically digested and undergoes first pass metabolism. Oral insulin formulations based on microemulsions show some promise, [1], as do liposomal [2] and solid-particulate formulations [3]. However, the stability of insulin during encapsulation into these systems and controlled release remains problematic and will be addressed in this project proposal.

**Aims**  
To develop insulin-entrapped nanoparticles that will maintain the native peptide backbone conformation and facilitate controlled release *in vitro*. To compare the *in vitro* performance of these nanoparticles with microemulsion-type formulations of insulin.

**Objectives**  
1. Formulate insulin-entrapped nanoparticles and microemulsions for oral delivery.  
2. Characterise the conformation and aggregation of insulin during formulation.  
3. Determine the release profile and stability of insulin in the formulations *in vitro*.

**Techniques to be used (cf. objectives)**  
1. Emulsion-solvent extraction formulation techniques, lyophilisation, size distribution analysis and zeta potential measurement.  
2. Steady state and real-time fluorescence techniques, liquid-state circular dichroism (microemulsions) and solid-state circular dichroism (nanoparticulates).  
3. HPLC assay development.

**References:**


**BMS 15  Project Title: Melanin-biopolymer interactions: influence of pH and electrolytes**

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**Project Area:** (one or more of the following)  
Drug Delivery

**Project Description:**

**Background**  
Melanin is a ubiquitous pigment in the animal kingdom, existing as a reddish-brown coloured biopolymer *pheomelanin* and the black pigment *eumelanin*. The role of melanin appears to be (i) as protective agent reducing the effect of uv light, (ii) as an antioxidant shortening the life times of highly active radicals and finally (iii) as an absorber of metal cations. Melanin binding of drugs has been shown to significantly alter the pharmacokinetics of applied ocular dosage forms [1]. All basic, hydrophobic materials are bound to some extent and drugs used to treat ocular hypotension such as timolol, pilocarpine and epinephrine are known to have an affinity for melanin binding and have been shown to be less effective in highly pigmented eyes as opposed to those which are less pigmented. The strong binding is affected by pH and electrolytes [2] which prompted the thought that interaction with biodegradable polymers might form the basis of a sustained release mechanism for suitable drugs [3]. In order to characterise the interaction more fully, the influence of biodegradation products on melanin binding will be investigated.

**Aims**

To quantify the pH and electrolyte effects on synthetic and natural melanin with regard to the binding of a suitable drug.  
To investigate models of competitive binding between plasma and melanin as a function of drug concentration, and nature of melanin.

**Objectives**

1. Examine the characteristics of synthetic and natural melanin binding of brimonidine tartrate as a function of pH and anion concentration.  
2. Measure the interaction of melanin and plasma with regard to competitive binding.  
3. Quantify the release of brimonidine tartrate in a combined melanin- polylactide combination.

**Techniques to be used (cf. objectives)**

1. Development of HPLC assays for brimonidine tartrate to quantify binding characteristics.  
2. Development of micro pH assays to measure interior pH of gel constructs.  
3. Fabrication of biopolymer/synthetic polymer constructs

**References:**

**BMS 16  Project Title: Nasal formulations of poorly soluble compounds**

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**Project Area:**  
Drug delivery

**Project Description:**

The nasal route is increasingly being considered as an alternative to parenteral injection for drugs that for various reasons cannot be administered orally. Interest in nasal drug delivery stems from its patient acceptability, direct systemic absorption, and the potential to overcome problems associated with oral instability, low bioavailability, and unacceptable side effect profiles\(^1\). A major drawback of the nasal route however, is the rapid mucociliary clearance that exists as a part of the natural defence mechanism of the body. Lyophilised mucoadhesive insert formulations designed to overcome difficulties of administering viscous gels nasally have been shown to increase nasal residence time\(^2\) and achieve prolonged therapeutic plasma levels\(^3\).

A further challenge increasingly encountered in pharmaceutical research is drugs with poor solubility profiles. This project proposes to investigate formulation strategies for the incorporation of poorly soluble compounds into the nasal insert dosage form. Characterisation of the process of hydration will be linked to the solubilisation and release of drugs, and in conjunction with physical characterisation will be used to optimise the performance of the system.

**Techniques to be used:** Lyophilisation, dynamic vapour sorption, texture analysis, dissolution analysis

**References:**

**Project Title:** Oral delivery of cyclosporine-A using mesoporous silica nanoparticles

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**Project Area:** (one or more of the following) Drug Delivery

**Project Description:** In drug delivery, the need to improve the aqueous solubility of drugs is particularly urgent. The low solubility of some drugs in aqueous media is problematic with regard to their administration via the oral route, and limits bioavailability. In addition, newly discovered drug molecules are generally lipophilic but typical strategies for drug solubilization: cosolvents, low molecular weight surfactant micelles, emulsions and cyclodextrins, are not always effective.

A promising new technique is the use of mesoporous silicas to increase the solubility of poorly bioavailable drugs [1]. Silica materials are non-toxic and are known for their excellent biocompatibility. With the advent of ordered mesoporous silica materials, new tools to construct drug delivery carriers became available, originally focussing on controlled drug delivery. However, it was soon realised that ordered mesoporous materials having monodimensional pores with sufficiently wide pore diameter could accelerate the release of the poorly soluble drugs.

Simple techniques can be used to make the mesopores more hydrophobic so that hydrophobic peptides can be loaded into the silica particles for oral delivery [2]. The project here will used that technique to load cyclosporine A into mesoporous silica particles. Cyclosporine A is a cyclic undecapeptide, lipophilic immunosuppressant drug used to treat transplant and autoimmune disease patients, is currently administered orally as a microemulsion formulation (Neoral). Cyclosporine A has a molecular weight of 1202 Da, a very low intrinsic water solubility (19.9 µg/mL at 25 °C) and a log P (octanol/water) of 4.3 at room temperature. There is currently a strong research focus to develop improved orally available preparations in this manner through control of drug dissolution and release [3].

**Techniques to be used:**
1. Formulation and synthesis of mesoporous matrices
2. Imaging techniques including confocal laser scanning microscopy
3. Drug release studies and dissolution apparatus
4. Protein analysis including circular dichroism and fluorescence
5. Porosimetry techniques (BET isotherms)

**References:**
BMS 13 Project Title: Optimising nasal drug delivery formulations

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Project Area: (one or more of the following)
Drug delivery

Project Description:

The nasal route is an attractive option for drug delivery of compounds which for some reason are not suitable for oral administration. A major drawback of nasal drug delivery can be the rapid mucociliary clearance rate, reducing the length of time the formulation is in contact with the mucosal surface. The half life of clearance of a substance administered nasally is approximately 15-20 minutes. Lyophilised bioadhesive nasal insert formulations that enable convenient single unit dosing, but re-hydrate in-situ to form mucoadhesive gels, have been used in attempts to overcome this difficulty. In-vivo confirmation of increased nasal residence times mean that such formulations have the potential to enhance drug delivery for a variety of therapeutic applications – e.g. extended release, anti-emetics, analgesics, peptides etc.

As the lyophilised formulations must hydrate to exert their mucoadhesive effect, the process of water uptake and interaction with mucous will be key to the performance of the system. The project will investigate the use of the nasal insert formulation to achieve optimised topical delivery of compounds of interest. The factors controlling the effective delivery of the active agent from polymer carriers will be characterised. This initial information can then be used to re-design the formulation to provide greater efficacy.

Techniques to be used: Lyophilisation, dynamic vapour sorption, texture analysis, dissolution analysis, microscopy

References:
BMS 14 Project Title: Optimising nasal drug delivery formulations

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Project Area: (one or more of the following)
Drug delivery

Project Description:

The nasal route is an attractive option for drug delivery of compounds which for some reason are not suitable for oral administration\(^1\). A major drawback of nasal drug delivery can be the rapid mucociliary clearance rate, reducing the length of time the formulation is in contact with the mucosal surface. The half life of clearance of a substance administered nasally is approximately 15-20 minutes. Lyophilised bioadhesive nasal insert formulations that enable convenient single unit dosing, but re-hydrate in-situ to form mucoadhesive gels, have been used in attempts to overcome this difficulty\(^2\). In-vivo confirmation of increased nasal residence times mean that such formulations have the potential to enhance drug delivery for a variety of therapeutic applications – e.g. extended release, anti-emetics, analgesics, peptides etc.

As the lyophilised formulations must hydrate to exert their mucoadhesive effect, the process of water uptake and interaction with mucus will be key to the performance of the system\(^3\). The project will investigate the use of the nasal insert formulation to achieve optimised topical delivery of compounds of interest. The factors controlling the effective delivery of the active agent from polymer carriers will be characterised. This initial information can then be used to re-design the formulation to provide greater efficacy.

Techniques to be used: Lyophilisation, dynamic vapour sorption, texture analysis, dissolution analysis, microscopy

References:
**BMS 19 Project Title:** The physicochemical stability of medicines when mixed with soft foods and beverages

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**Project Area:** (one or more of the following)  
Biomedical Analysis/Food Science

**Project Description:**
Many medicines commonly used in paediatric treatment are unsuitable for direct administration to children as the dosage forms were originally designed and licensed for adult usage. For example, large tablets and capsules are difficult for a child to swallow and sour or bitter tasting liquid medicines can be unpalatable. Sometimes there may be clinical reasons why a child cannot take their medication as a tablet or capsule e.g. difficulty in swallowing. In these situations, the tablets may be crushed or the contents of the capsule emptied and mixed with various soft foodstuffs such as yoghurts or drinks to aid administration. However, by altering the dosage form and admixing with food or beverages, some of the drug’s physical or chemical properties may be altered. This may affect the rate or extent of drug absorption into the body and compromise the intended clinical effect of the medicine. The proposed study intends to evaluate how medicines commonly used in treating mental health disorders in children are affected by addition to foods or beverages and will allow doctors, nurses and pharmacists to optimise their clinical usage and provide safer and better outcomes for the patient.

**Techniques to be used:** HPLC, drug dissolution, particle sizing (laser diffraction, sieve analysis), extraction techniques (solid phase, liquid-liquid), rheology, texture analysis.

**References:**


# BMS 25 Project Title: Development of a amphotericin B formulation for the treatment of leishmaniasis

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**Project Area:** (one or more of the following)  
Microbiology/Parasitology/Pharmacology

**Project Description:**  
Leishmaniasis is a major problem in many parts of the World. It is endemic in 88 countries in the World and there are 2 million new cases/year and approximately 12 million people are infected worldwide. There are a limited number of drugs available to treat the infection and development of drug resistance in the parasite population has limited the clinical utility of some of the drugs available. Amphotericin B is now used as a first line therapy in some parts of the World, but its use is associated with adverse side effects and it has to be given by the intravenous route. Lipid formulations of amphotericin B are available for the treatment of leishmaniasis, which are less toxic but their high cost makes their use prohibitive in endemic regions, and they are also given by the intravenous route. In this project novel formulations of amphotericin with be developed for deliver by non-nvasive routes and their effect on the growth of *Leishmania donovani* determined *in vitro* and *in vivo*.

**Techniques to be used:** This project will allow the project student to study drug formulation, determination of *in vivo* and *in vivo* parasite burdens, determination of tissue drug levels by HPLC, maintenance of parasite lines and cell culture,

**References:**