Nanostructured materials are of interest for a variety of applications. This talk describes the synthesis and properties of nanostructured materials that are made up of crystallites or particles of ~10 nm. They may be generated by various physical and chemical approaches with ultrahigh surface reactivity. Through controlled synthesis in reverse microemulsions, my laboratory has achieved polymeric nanoparticles for the glucose-sensitive delivery of insulin. These stimuli-responsive materials allow for the appropriate insulin delivery to diabetic patients only when their blood sugar levels are high, without the need for external blood sugar monitoring. We have also developed apatite-polymer nanocomposite particles for the sustained, zero-order delivery of protein therapeutics. By adsorbing valuable bone morphogenetic proteins on carbonated apatite nanocrystals that were then encapsulated within biodegradable polymeric microparticles, we are able to achieve controlled release of this growth factor for the bone healing process over an extended period of time.

Lastly, we have generated fluorescent semiconductor quantum dots for bioimaging and biolabeling applications. These nanoparticles were surface modified to provide for high colloidal stability, efficient fluorescence, low cytotoxicity and excellent water solubility. They were biocompatible and biofunctionalized for target-specific recognition, and could be used for biosensing and targeted drug delivery applications.

Nanoparticles as Detection Labels for Bioaffinity Assays in Point of Care Testing
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Nano-particles are commonly used in Point-of-Care Testing (POCT) as detection labels. These small low cost clinical analyzers use particles as detection labels. Optical signals generated by latex agglutination, colored latex particles, and colloidal gold commonly provide little interference and picomolar detection limits (10^{-12} mol/L). Miniaturization to nL specimen volumes and lower analyte concentrations resulting from proteomics discoveries are challenging these limits. Flourimetric, luminescence and enzyme-linked particles offer more sensitivity at the expense of complexity. Simple nano-particle electrochemical methods have recently shown sensitivity to single molecule limits.

Nano-particles also impact recognition and separation steps in POCT. Immunological recognition of antigens with antibodies greatly enabled POCT. Particles attached to antibodies are separated when antibodies reacts to antigens captured on solid phases. Particle variations impact the ability of recognition components to separate after binding the target substance. The CLINITEK Status analyzer demonstrates the impact of particles on chromatography separations using incubation, capture and separation zones. Immunoassay of a new maker for inflammation demonstrates the complexity of recognition components. Another fluidic approach is shown in the HbA1c immunoassay on the DCA 2000+ analyzer, while examples of micro-fluidic chips show the impact of future miniaturized on bio-affinity separations in POCT.
7-03

**Cellular Probes Using Amplified Light Scattering**
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Silver/gold nanoparticle-aminodextran (Amdex)-coated polystyrene (PS) beads offer their use either as elastic or inelastic light scattering probes for diagnostic biological assays. Amplified Mie scattering from CD4/CD8 antibody conjugates of these beads has allowed their use in enumerating the targeted white blood cells in whole blood by flow cytometry. Recent observations of SERS (surface-enhanced Raman scattering) from the same beads hold the promise of using Raman in similar diagnostic tests. Citrate/Amdex SERS bands were detected from beads either as singlets or small clusters. However, citrate on individual silver nanoparticles or on gold nanoparticle-Amdex-PS beads were not detected with 633nm excitation. SERS of dyes such as rhodamine 6G were readily observed on individual silver particles or on gold beads.

Three distinct modes of citrate/aminodextran binding to the silver nanoparticle-Amdex-PS beads were characterized: (1) exchangeable citrate bound through one or more carboxylate group(s)---citrate could be washed away with H2O or D2O; displaced by successively greater concentrations of R6G; or squeezed out mechanically by applying the pressure of a second coverslip on top of a droplet of bead suspension; (2) non-exchangeable citrate/Amdex bound via an alkoxide of a deprotonated alcohol of citrate/Amdex; (3) non-exchangeable citrate/Amdex bound via carboxylate group(s) but with H/D exchangeable alcohol hydrogen atom. The 3 modes of binding provide flexibility in selecting intrinsic, fixed SERS probes as well as the opportunity to add selected, variable probes to the beads for multiple diagnostic targets. Such probes could be used in micro-Raman imaging and, potentially, in a Raman-activated flow cytometer.

7-04

**Determination of Dissolution Rates of Colloidal Dispersion Prepared From Poorly Water Soluble Drugs Using a Light Scattering Technique**
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Classic theory predicts that the diffusion limited rate of dissolution of fine particles increases as the particle size becomes smaller. This has been demonstrated in numerous pharmaceutical formulations incorporating NanoCrystal technology. The threshold where the rate limiting transport step changes from dissolution limited to permeation limited oral absorption defines a size below which no further kinetic benefits to absorption are theoretically observed. Pharmacokinetic results suggest a smaller particle size threshold than classic theory (Noyes-Whitney).

A light scattering method was used to determine the in-vitro rate of dissolution for drug dispersions in the absence of solubilizing agents. The experimental results were compared with two different theories, a classic Noyes-Whitney and a modified Noyes-Whitney type equation constrained by a surface mass transfer rate. The new theory treats the surface mass transfer step and diffusion step as two consecutive reactions. The overall dependence on particle size is 1/r for very small particles and 1/r² for larger particles (both limits assuming a time dependent boundary layer h = r).
results revealed dissolution rates much smaller than ones predicted from classic theory. The corresponding surface mass transfer coefficient could be extracted from such experiments.

7-05

**PFG-NMR Investigation of Liposome Systems Containing Hydrotrope**

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Particle size is crucially important in determining the usefulness of a liposome system. This is particularly true for drug delivery applications. Until now, the particle size of a liposome is typically determined using a light scattering method. Although the NMR pulsed field gradient (PFG) experiments are known to yield self-diffusion coefficient for micelles and other particulate matters, the application of this technique to vesicle systems has been limited due to the rigid nature of the lipid bilayer which usually does not give well-defined NMR signals for PFG experiments. This study shows that the polyethylene oxide chains on a pegylated lipid could serve as an excellent tracer to measure the self-diffusion coefficient via PFG method. In addition, liposomes containing a hydrotrope also give adequate signal from the lipid for PFG experiments due to the increased flexibility of the lipid molecules. In addition to particle size, PFG-NMR is also used to determine the extent of association of a hydrotrope with the liposome bilayer.

7-06

**Fabrication of Supraparticles, Janus Microparticles and Microlens Arrays by a Gel Trapping Technique**

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Particles with asymmetric shapes that can be used to make crystals with novel optical properties have attracted much attention in recent years. We have shown that the Gel Trapping Technique (GTT) can be used to asymmetrically coat colloidal monolayers creating so-called 'Janus' particles, after the two-faced Roman god of doors. Partially embedded monolayers of monodisperse polystyrene microparticles in polydimethylsiloxane (PDMS) were used to coat the exposed particle surface with gold, resulting in particles with two 'faces'. The technique is relatively simple and could easily be used to make a variety of Janus particles. Monodisperse polystyrene microparticles are spread at a water-oil interface and super long range repulsion between particles adsorbed at the interface leads to a near perfect hexagonal lattice. The water contains the gelling polysaccharide gellan which, on cooling, forms a gel that traps the monolayer and the oil layer may then be removed without disturbing the particles. Pouring liquid PDMS over the gel followed by curing leads to the formation of a partially embedded monolayer trapped within the PDMS resin which can be peeled away from the gel. To make the Janus particles the trapped polystyrene particles were 'half-coated' with gold. Use of particles of different contact angles allows the creation of monolayers with varying degrees of entrapment of the polystyrene particles within the gel and thus to different degrees of coverage on their surface. At certain conditions we have successfully molded the particle monolayer together with its gelled meniscus around the particles which produced 'flying saucer particles' where the polystyrene particles are surrounded by a ring of gellan.
Stretching the PDMS releases the trapped particles and the PDMS films produced, with an ordered array of microholes, could have interesting potential applications as filters or antireflective coatings. By further replicating the microhole array with a photopolymer we produced hexagonally ordered microlens arrays where the lattice constant is fixed by the amount of particles spread at the initial liquid surface.

We also used the same Gel Trapping Technique as a novel method for determining the contact angle of particles adsorbed at air-water and oil-water interfaces. The trapped particles have been imaged on the surface of the PDMS replica with SEM. The particles position with respect to the air-water interface or the oil-water interface has been determined from the SEM images of the PDMS replica which gives information for the particle contact angle at the liquid interface. Particle samples of different size and surface chemistry have been examined. We present results for the particles contact angles at air-water and decane-water interface obtained for sulfate latex particles, hydrophobized silica particles, gold particles and polymer microrods.

7-07

**Bone Tissue Engineering: Towards a Better Understanding of Interfacial Biology**

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Approximately 1 million bone grafts are performed annually in the USA. Current methods of grafting, such as autograft and allograft, are subject to significant limitations. These limitations are driving the development of a range of “off the shelf” materials that can expedite osseous healing. Our strategy has been to develop a three phase macroporous co-polymer of polylactide-co-glycolide and calcium phosphate that can function as a temporary trellis to take advantage of the appositional nature of bone formation. Using data garnered from in-vitro and in-vivo experiments, the iterative development of this scaffold, in response to both material and biological design criteria, will be discussed. In addition to developing a scaffold material suitable for bone tissue engineering, the notion of exogenous delivery of mesenchymal progenitor cells to the repair site to accelerate bony repair is attractive. Our recent characterization of an exciting and uncontroversial source of these cells, the human umbilical cord perivascular tissue, will be described, as will the challenges remaining to clinical realization of cell based therapy for bone tissue engineering.

7-08

**Surface Modification of Mineral Fillers for Dental Composites and Acrylic Bone Cement**

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The surface modification of mineral fillers for acrylic composites is very promising in bone cement and dental applications. Using surface modified mineral fillers, such as silica and zirconia, in polymer composite materials allowed us to improve substantially the filler–matrix adhesion and the mechanical properties of the composite. In the present work the surface of the mineral filler was
modified by adsorption of peroxide copolymer (5-methyl-5-tert-butylperoxy-2-hexen-3-in and maleic anhydride) as well as by the covalent immobilization of methacryloxy- and styryl groups due to interaction with styrylethyl-trimethoxysilane and methacryloxypropyl trimethoxysilane. The peroxide groups were used to initiate the graft polymerization of acrylic monomers. Methacryloxy- and styryl groups interacted with (macro)radicals and formed the covalently attached polymer layers. The efficiency of the grafting was studied on the model smooth SiO\textsubscript{2} substrate. The amount of the grafted polymer layers was measured by ellipsometry. We found that the most efficient grafting was approached for the poly(methyl methacrylate) on the surface modified by the

7-09

**Amphiphilic Core-Shell Nanoparticles with Poly(ethylenimine) Shells as Potential Gene Delivery Carriers**

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Spherical, well-defined core-shell nanoparticles that consist of poly(methyl methacrylate) (PMMA) cores and branched poly(ethylenimine) shells (PEI) were synthesized in the absence of surfactant in aqueous. The PMMA-PEI core-shell nanoparticles were between 130 to 170 nm in diameters, and displayed zeta-potentials near +40 mV. Plasmid DNA (pDNA) was able to complex onto the nanoparticles, and average diameter of the complexed particles was approximately 120 nm and highly monodispersed. The complexing ability of the nanoparticles was strongly dependent on the molecular weight of the PEI and the thickness of the PEI shells. The stability of the complexes was influenced by the loading ratio of the pDNA and the nanoparticles. The condensed pDNA in the complexes was significantly protected from enzymatic degradation by DNase I. Cytotoxicity studies suggested that the PMMA-PEI (25 kDa) core-shell nanoparticles were three times less toxic than the branched PEI (25 kDa). Their transfection efficiencies were also significantly higher. Investigation of the intracellular behavior of the FITC-labeled DNA/nanoparticles indicated that the PMMA-PEI nanoparticles were effective carriers to deliver the DNA into cells by endocytosis and release it into the cytosol. Thus, the PEI-based core-shell nanoparticles show considerable potential as carriers for gene delivery.

7-10

**Microencapsulation of Pharmaceuticals into Biodegradable Colloids Using Supercritical Carbon Dioxide**

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The microencapsulation of pharmaceuticals into biodegradable polymer colloids can be utilized for controlled, extended, and targeted drug delivery. We have developed a solvent-free alternative microencapsulation process that utilizes liquid or supercritical carbon dioxide in place of organic solvents. Here we demonstrate that compressed carbon dioxide may be used to facilitate the transport of pharmaceuticals into aqueous biodegradable polymer colloids. The “nano-precipitation” method was used to form stable aqueous colloids of several types of biodegradable polymers
including poly(lactic acid), poly(lactide-co-glycolide), and poly(lactic acid)-block-poly(ethylene glycol). In all cases, particle formation conditions yield particles less than 200 nm in diameter. Liquid or supercritical carbon dioxide was emulsified into the aqueous biodegradable latex in the presence of a lipophillic drug such as indomethacin and progesterone. The carbon dioxide plasticizes the polymers and greatly enhances the transport of drug into the particles. The carbon dioxide process has also been coupled with traditional microencapsulation approaches to minimize solvent usage and to extract residual solvent from polymers.

7-11
Development of A Three-Dimensional Magnetic Navigation and Magnetically Targeted Drug Delivery System
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One of the key problems associated with drug administration is the difficulty to target specific areas or sites in the body, like cancerous tumors. Typically in these cases, exceedingly large doses of a drug are needed to ensure that some of the drug reaches a specific site, which unavoidably impose substantial toxic side effects at non-targeted organs. In the present study, development of a three dimensional magnetic navigation and magnetically targeted drug delivery system was tried in order to deliver the drug to target specific areas in the body by utilizing magnetic particles and strong magnet. Earnshaw’s theorem states that there is no stable and static configuration of levitating ferromagnetic particle by a combination of a fixed magnetic field and gravitational force. However, the magnetic particle could be levitated in a limited area using by the feedback system. In this paper, designing of the electromagnet was tried to control the movement of particles through the experimental and the computer simulation. The surface modification of the magnetic particles was also discussed in order to control the interaction between the particles and wall of the blood cell.

7-12
Reversible Assembly/Disassembly between Two Different Micelle Morphologies Comprised of Cyclodextrin and Ferrocene/Ferrocenium Derivatized Surfactants
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We report the reversible switching between two different micelle morphologies via the disassembly and re-assembly of redox-active surfactants by electrochemical means. The redox-active surfactant is comprised of an aliphatic chain tethered to a ferrocene group covalently caged in the annular void of beta-cyclodextrin (bCD). While beta-cyclodextrin by itself has a water solubility too low for consideration as a hydrophilic head group, our covalent modification renders this molecule amphiphilic, and thus surface active. Using bCD as the hydrophilic head group, this surfactant is bio-friendly in that protein denaturation is minimal or non-existent. Employing a wide range of characterization techniques such as 2-dimensional NMR spectroscopy, circular dichroism and electrochemistry, we demonstrated that accompanying the oxidation of ferrocene to ferrocenium, the surfactant undergoes a large conformational change that results in the disassembly of the micelle formed and re-assembly of a new micelle morphology. We will discuss/present its potential applications in sequestering membrane proteins and controlled drug release.
Smart Polymer Core-Shell Nanoparticles for Targeted Drug Delivery
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Drug delivery is as important as the development of new drug entities. The main goal of drug delivery is to transport drugs to diseased sites using a therapeutic dosage. A number of nanocarriers have been proposed based on natural and synthetic materials to achieve such a goal. However, the method of delivering drugs to specific cells and cell compartments remains a challenge. The aim of our study is to develop polymer core-shell nanoparticles for transporting drugs/genes to specific tissues, thereby alleviating or eliminating the side effects associated with the use of conventional delivery systems and improving the efficacy of drug or gene therapy. In this talk, pH-triggered temperature-sensitive core-shell nanoparticles will be introduced. The structure of these nanoparticles is stable in the normal physiological environment (pH 7.4), but deforms and releases the enclosed drug molecules in an acidic environment. A signal that recognizes tumor cells is conjugated to the shell of the nanoparticles, making them capable of targeting a drug to tumor cells and then releasing it intracellularly for more efficient and safer cancer therapy. Cellular uptake of the nanoparticles loaded with doxorubicin is higher than free doxorubicin because folate-receptor mediated cell uptake is more specific. Therefore, the nanoparticles loaded with doxorubicin kill cancer cells and suppress cancer growth more efficiently as compared to free doxorubicin.

Synergy of Drug and Gene Delivery Using Cationic Polymer Core-Shell Nanoparticles
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In cancer therapy, two or three agents are often combined to achieve a synergic effect for better killing of cancer cells. For example, p53-encoded gene can be combined with cisplatin to achieve more promising therapeutic results. Co-delivery of cyclosporin A and paclitaxel can improve gene transfection efficiency. To achieve the synergy of drug and gene therapies, we believe that it is necessary to deliver the drug and gene to the same cells. However, up to date, no single nanosized carrier has been reported to deliver a drug and gene simultaneously. In this study, unique polymer core-shell nanoparticles are developed, which can carry a drug and gene simultaneously. For examples, expression levels of luciferase and eGFP genes in 4T1 mouse breast cancer cells are increased by 10 times using the paclitaxel-loaded nanoparticles as compared to the blank nanoparticles. The in vivo studies are conducted in mice bearing subcutaneous 4T1 tumors. Luciferase activity in the tumors, which is transfected by the paclitaxel-loaded nanoparticles/luciferase-encoded plasmid complexes, is 10 times higher when compared to the blank nanoparticles/luciferase-encoded plasmid complexes. Moreover, cyclosporin A has also proved to enhance luciferase gene expression in MB-31-MA cells (a drug resistant cell line). In conclusion, these unique cationic core-shell nanoparticles would provide a promising carrier for co-delivery of drugs and genes.

Controlled Release of Plasmid DNA from Gold Nanorods Modified with Phosphatidylcholine Induced by Pulsed Near-Infrared Light
Gold nanorods (NRs) are rod-like nanoparticles that have unique optical properties depending on their shape. In order to use NRs for biochemical applications, we have first partially modified them with phosphatidylcholine (PC). Partial modification of NRs with PC has been successful by extraction with chloroform containing PC. The resultant PC-modified NRs (PC-NRs) could form complexes with plasmid DNA by electrostatic interactions, denoted as PC-NR/DNA. Pulsed laser irradiation of NRs induces shape changes into spherical nanoparticles. Irradiation of pulsed 1064-nm laser light (250 mJ/pulse, 2 min) to PC-NR/DNA complexes induced shape changes of PC-NRs and at the same time plasmid DNA were released from the complexes as confirmed from gel electrophoresis. Thus, it is clear that the shape changes of PC-NRs trigger the release of DNA from the complexes. It was also found that the plasmid DNA was released without any damage by laser irradiation. Thus, the near-IR laser irradiation onto the PC-NR/DNA complexes has realized the selective release of the plasmid DNA without appreciable structural changes.

7-17
Towards the Development of HFA-based pMDIs for the Delivery of Hydrophilic Drugs: Combined Chemical Force Microscopy, In-Situ High-Pressure Tensiometry and Atomistic Computer Simulations.
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Aerosol inhalation therapy is an alternative to oral and parenteral approaches for the delivery of systemically active drugs. Pressurized metered dose inhalers (pMDIs) are the least expensive aerosol therapy devices available, and have been suggested as potential candidates for the delivery of pharmaceutically relevant biomolecules. However, there have been several challenges in the design of pMDIs as CFCs are being replaced with more environmentally friendly alternatives, such as hydrofluoroalkanes (HFAs). In spite of the fact that the operation of pMDIs with HFAs is similar to those with CFCs, previous formulations are not compatible due to the significantly different properties between these two classes of fluids. Lack of fundamental knowledge on the interfacial properties of volatile propellant mixtures is preventing us from extending the applicability of reliable and simple formulations such as pMDIs for the delivery of polar drugs. Thermodynamic and microstructural properties of the neat and surfactant-modified HFA|Water interface were obtained using a combined experimental and computational approach, including chemical force microscopy, in-situ high-pressure tensiometry and atomistic computer simulations. These studies are relevant not only for the development of aqueous reverse microemulsion-based pMDI formulations, but all HFA-related pMDIs where amphiphilic excipients are generally required.

7-18
Hydrogen-bonded Self-assembled Films and Capsules of Thermoresponsive Polymers
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Temperature responsive polymers, poly(vinyl methyl ether) (PVME) and poly(N-vinyl caprolactam) (PVCL), were assembled in alternation with polymethacrylic acid (PMAA) at acidic pH via hydrogen bonding using a layer-by-layer technique. The construction of PVME/PMAA and PVC/PMAA films and capsules was confirmed by ellipsometry, in situ ATR-FTIR, and Fluorescence Optical Microscopy. The film thickness and pH-stability were shown to be highly dependent on hydrogen bond strength and the critical ionization of PMAA within the films. The permeability of Thymol Blue dye through films deposited onto alumina supporting membranes was investigated at acidic pH as a function of temperature and revealed striking differences between the two polymer systems. While PVCL/PMAA films did not show any significant effect of temperature on dye permeability in the range of temperatures from 20 to 40°C, permeation through PVME/PMAA films showed drastic increase at temperatures higher than 32°C. We explain the observed difference by stronger hydrogen bonding between PVCL and PMAA components of the film, which resulted in suppression of film temperature response. However, weakly bound PVME/PMAA systems allowed dehydration of PVME chains at temperatures above its LCST which caused an increase in dye permeability.

7-19

Development of Redox-Active Surfaces and Micelles for Biocompatible Systems: Caging Ferrocene in Cyclic Oligosaccharides

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We report the development of a redox-active surface that is stable under biological conditions. Our system is based on self-assembled monolayers (SAMs) that present a molecularly caged ferrocene. The oxidized form of ferrocene – ferrocenium ion – is not stable in the present of small anions as simple as chloride. Caging the ferrocenium ion in a cyclic oligosaccharide – -cyclodextrin (CD) renders it stable in biological buffers such as cell culture medium, which contain large concentration of chlorides. We also present a novel micelle system based on the same strategy that covalently cages ferrocene in the annular void of CD. Using OL98f"Symbol"s12CD as the hydrophilic head group, this surfactant is bio-friendly in that protein denaturation is minimal or non-existent. Employing a wide range of characterization techniques such as 2-dimensional NMR spectroscopy, circular dichroism and electrochemistry, we demonstrate that accompanying the oxidation of ferrocene to ferrocenium, the surfactant undergoes a large conformational change that results in the disassembly of the micelle formed and re-assembly of a new micelle morphology. We will present its potential application in sequestering membrane proteins and controlled drug release.

7-20

Self-Assembly of Nanoporous Silica Shapes: Synthesis, Morphogenesis, and Applications

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We study the process of self-assembly of nano(meso)porous silica particles via surfactant templating. Process of formation of the mesoporous silica includes growth of the liquid crystalline template and solidification of this template via polymerization of silica precursor. Material obtained as a result of such synthesis (MCM-41) features highly uniform porosity, a large variety of shapes
and their sizes. To control the assembly of the desired shapes, we study their morphogenesis. New conditions of self-assembly are found to form monoshaped nanoporous fibers. Recently suggested Origami-type mechanism for synthesizing a rich family of nanoporous silica shapes (cones, tubes, and hollow helixes) is examined. Shape details and their evolution are analyzed by means of XRD, SEM, TEM, AFM, and optical microscopy techniques.

The shapes can possibly serve as templates for various electronic and optical applications. Nanoporous shapes are the prospective hosts for lasing dyes (sealing laser dye molecules inside the silica pores saves them from oxidation and prevents their dimerization). Diffusion from the nanoporous shapes can be used for a control drug release. Another application of mesoporous silica is the coating of optical fibers by uniform low refractive index film with a good adhesion – a possible host for laser dyes or quantum dots.

**7-21**

**Particle Engineering Technologies for Enhancing Dissolution and Bioavailability**

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Reports indicate that more than 40% of newly discovered drugs have little or no water solubility. As a result, the development of many exciting new molecular entities is stopped before their potential is realized or confirmed because conducting rigorous preclinical and clinical studies on a molecule that would not have a reasonable pharmacokinetic profile due to poor water solubility is not economical. Further reports indicate that approximately 16% of marketed drugs have less-than-optimal performance specifically because of poor solubility and low bioavailability. Pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs; however, those with aqueous solubility of less than 0.1 mg/mL present some unique challenges. These drugs are particularly good candidates for advanced particle engineering technologies. Unique nanostructured particles, with enhanced performance attributes, can be obtained through the control of particle size, particle surface area and particle morphology. Enhanced dissolution rates (>80% dissolved in 2 min.), improved bioavailability (>2x) and scale-up (to multi-kilo quantities) has been demonstrated with a portfolio of technologies including controlled precipitation, emulsions and cryogenic approaches. Particle engineering technologies produce stabilized particles with enhanced performance characteristics.

**7-22**

**Molecular Configuration of ATP in the Interlayer of Hydrotalcite**

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Hydrotalcite (HT), a layered double hydroxide of magnesium and aluminum, exchanges its interlayer anions with those in external solutions, and has been considered to be a potential vector for anionic medical substances in drug delivery systems. The preparation of well crystallized pure hydrotalcite with nitrate ions in the interlayer (HT-NO$_3$) and the intercalation of adenosine triphosphate (ATP) were studied as a model system. It was found that interlayer nitrate ions were completely exchanged with ATP anions and the average electric charge of the intercalated ATP was evaluated to be -3.6 from the electric neutrality of the intercalate. The intercalation of ATP resulted
in a doubling of the interlayer distance and the ATP molecules in the interlayer support a free distance of about 1nm. This distance could be explained by calculations of the molecular configuration of ATP. The triphosphate group is attached to the layer of positive charges and the organic molecule group bends owing to its bond angles and projects to the interlayer with a height of 0.903 nm. The attraction between the organic molecule groups of ATP stretching between the two opposing layer surfaces is considered to sustain the layer structure.

7-23
Modulation of the Binding Dynamics of Guests with Bile Salt Aggregates with the Addition of Co-solvents
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Bile salts such as sodium cholate (NaCH) and sodium deoxycholate (NaDC) form aggregates in aqueous solutions with two different binding sites. Primary aggregates, formed at low bile salt concentrations and have a binding site that is hydrophobic. The association and dissociation processes for binding of guests to the primary sites are slow. As the concentration of bile salt is increased the primary aggregates agglomerate into secondary aggregates, where the binding dynamics is fast.

Guest molecules, which are known to bind exclusive to each site, were used to study the effect on the binding dynamics by changing the solvent polarity with the addition of acetonitrile or by changing the viscosity with the addition of ethylene glycol. Addition of ethylene glycol did not significantly affect the binding dynamics to either binding site. The residence time of guests in the primary site could be enhanced with the addition of acetonitrile, or decreased by changing the bile salt from NaCH to the more hydrophobic NaDC. The modulation of the residence time of guests in each binding site will be employed to explore intra-aggregate reactivity with these systems.

7-24
Single Surfactant Non-ionic Microemulsions
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A series of microemulsions, both W/O and O/W were prepared using the point method and investigated for insight into formation. Two essential characteristics of the interfacial surfactant film were identified: equal solubility in the oil and water phases (“borderline solubility”), and positive interfacial tension at the W/O interface. Measurement of surfactant(s) transmittance in the two phases demonstrates that microemulsification occurs when the surfactant interfacial film is equally soluble in the oil and water phases. Interfacial and surface tension measurements show that zero interfacial tension is not necessary for microemulsion formation; further, at the equilibrium, the interfacial tension must be positive in order to cause the curling of the interface that enables droplet formation. Calculations of the surfactant molar composition at the interface allowed us to formulate microemulsions with one single surfactant. This finding allows us to formulate Lemon oil in water microemulsion with one single emulsifier. Our results suggest that the structure of the interface is crucial for microemulsion formation and stability.
The Use of Pluronic Microemulsions for Drug Detoxification: Investigation of the Interaction Mechanism by NMR Spectroscopy
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Various Microemulsions (MEs) have been developed to address the problem of the lethal effects of overdosed drugs. Pluronic MEs efficiently abate the induced cardiotoxicity in living animals. However, the exact mechanism and important physico-chemical phenomena by which the drug binds to the ME are not clearly understood and need to be investigated on the molecular level to improve ME design and further enhance the efficacy of the ME. Pulse NMR spectroscopy is an expedient technique for elucidating the structural and dynamic interactions between drug and ME. Investigations were carried out using ¹H chemical shift, ¹³C NMR relaxation and self-diffusion measurements to determine the ME-drug interaction mechanism. Results indicate that at low concentrations molecules of the antidepressant, amitriptyline, initially bind with the hydrophobic portion of the Pluronic but bind to sodium caprylate, with increasing concentration. A steep increase in the slope of sodium caprylate chemical shift on increasing amitriptyline concentration compared to the slope of Pluronic indicates that, in addition to the Pluronic molecules, sodium caprylate molecules in ME617 enhance the amitriptyline binding significantly. Additionally, self-diffusion studies indicate that amitriptyline binding stabilize the self-assembly structure of ME617 and show that amitriptyline preferentially binds to the Pluronic and sodium caprylate molecules than to the ethyl butyrate in the microemulsion.

Evaluation of AFM for Determining Complexation Forces Between Toxins and Antidote Molecules
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Atomic Force Microscopy (AFM) has become a popular instrument over the years for analyzing the topography of a surface as well as measuring forces between molecules. The sensitivity of the instrument allows researchers to determine forces between a tip that can be modified as well as a substrate. This project involves the use and modification of colloid probes to analyze forces between toxins and antidote molecules. Hydrophobic and - complexation forces between molecules were measured in both polar and non-polar solvents. Modification of the colloid probe and substrate will be presented as well as the AFM results.

Covalent Attachment of Biotin to TiO₂ Nanoparticles
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Biotinylated TiO$_2$ nanoparticles (50~150nm) were obtained by treating TiO$_2$ nanoparticles with 3-aminopropyltriethoxysilane (APTES) in an anhydrous DMSO followed by reaction with N-hydroxysuccinimido-biotin. The biotinylated TiO$_2$ was characterized with $^{13}$C and $^{29}$Si CP-MAS NMR and FT-IR. The amount of biotinyltriethoxysilane on TiO$_2$ particles was measured by TGA. The dispersion properties and the mean size of TiO$_2$ particles in different solvents were studied by transmission electron microscopy (TEM) and dynamic light scattering (DLS), respectively. The specific surface area (SSA) of TiO$_2$ particles was measured by nitrogen adsorption before and after the two-step modification. The results demonstrated that the biotinyltriethoxysilane was covalently bonded to the TiO$_2$ particle surfaces and the mass percent of biotinyltriethoxysilane is about 1~2.5%. However, the colloidal stability of TiO$_2$ particles was deteriorated. Anhydrous DMSO was superior to anhydrous toluene in the silanization because TiO$_2$ colloidal stability was superior in DMSO.

7-28

**Characterization of the Complexes between Polyvinylamine and Carboxymethyl Cellulose**

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The complexation of poly (vinylamine) (PVAm) and sodium carboxymethyl cellulose (CMC) was studied by dynamic light scattering, electrophoretic light scattering, isothermal titration calorimetry, circular dichroism, and FT-IR spectroscopy. The phase diagram for the complexes as function of polymer concentration showed that either soluble complexes, colloidal complexes or precipitated complexes formed depending upon the ratio of the polymers. Dynamic light scattering indicated that the complexes exhibit a maximum size at 1 mol/L NaCl, suggesting a strongest interaction at this ionic strength. Moreover, complex molecular weight and density are dependent on pH and polymer ratio. Electrophoretic light scattering revealed that the colloidal particles have excess component absorbing on the surface, thus possessing high stability due to electrostatic repulsion. Isothermal titration calorimetry measurements showed that the complexation is endothermic at pH > 7 and exothermic at pH 4 whether in addition of PVAm into CMC or addition of CMC into PVAm. We propose that the complexation of PVAm and CMC is dominated by electrostatic and hydrogen bonding interactions which vary with pH. Finally, circular dichroism was used to demonstrate the conformational change of polymer during complexation.

7-29

**Development of Supported Lipid Bilayer Cell Membrane Mimics**

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The role of the extracellular matrix (ECM) as a diffusive barrier for proteins approaching the cell surface is not well understood. Our goal is to quantify this effect using supported lipid bilayer cell membrane mimics that include ECM mimics. Lipid vesicle adsorption was used to construct supported lipid bilayers on silica surfaces. Vesicles were formed by an extrusion method and consisted of egg phosphatidylcholine (egg PC), dinitrophenyl tagged phosphatidylethanolamine (dNP-PE), and biotinylated lipids. Adsorption to a silica surface was monitored using quartz crystal microgravimetry with dissipation (QCM-D), and a bilayer conformation was confirmed. There was
negligible nonspecific adsorption of immunoglobulin G (IgG) but significant specific adsorption of anti-dNP IgG to this bilayer. Thus, an intact lipid bilayer was constructed, and some dNP is accessible for antibody binding. Hydrophobically-modified hydroxyethyl cellulose (hm-HEC) or biotinylated hyaluronic acid were anchored to the bilayer and evaluated as ECM mimics. The effect of ionic strength on the swelling and transport properties of these mimics will be presented.

7-30
Properties of Monolayers of the Parkinson’s Disease-Related Protein Alpha-Synuclein at the Air-Water Interface
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The histological hallmark of Parkinson’s disease is the presence of intracellular inclusions called Lewy bodies in neurons of the substantia nigra, a region of the brain that controls voluntary movement. The principle component of Lewy bodies is fibrillar aggregates of the 140-residue protein alpha-synuclein. Alpha-synuclein is disordered in solution; however, it is highly amphiphilic, and is known to bind to lipid membranes. Upon membrane binding, it acquires an ordered, helix-rich structure. Both the natural function of alpha-synuclein and its relationship to disease are likely to be linked to its amphiphilicity. We have therefore examined the properties of monolayers of alpha-synuclein at the air-water interface, an environment that is often used to mimic membranes. We have found that alpha-synuclein self-assembles at the air-water interface, forming monolayers that appear striated when deposited onto mica substrates and examined by atomic force microscopy. The factors governing this self-assembly process will be discussed.

7-31
Arraying of Intact Liposomes on Patterned Island Surfaces formed by Micro-contact Printing of Self Assembled Monolayers
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We are developing protocols to array individual, intact small unilamellar vesicles (liposomes) onto surfaces with potential application as biosensor probes. In the ongoing research, the surfaces prepared by Micro-contact Printing (MCP) of islands of microscale and sub-microscale dimensions using silanes with ‘amine’ (positively charged) terminal groups onto smooth Silica substrates. Typically the silane used in this step is 3-Aminopropyltrimethoxysilane (APS). These amine islands are biotinylated using NHS-PEO4-Biotin. The background phase is then put down using sequential adsorption of Polyethylene glycol (PEG) terminated silanes from solution using a proper solvent. PEG terminated SAMs are resistant to protein/liposome adsorption. Next step is to attach Streptavidin to the Biotin islands to form patterned Streptavidin arrays capable of binding more Biotin. Low Tg Lipid formulations containing 5% Biotinylated lipids are used to prepare liposomes of 1 micron diameter using extrusion technique. The patterned Streptavidin grid is then exposed to the Liposome solution, which results in attachment of intact liposomes onto islands by ‘Biotin-Streptavidin’ interaction specifically onto the Streptavidin grid. The size of liposomes is matched
with the island size so that only one liposome gets attached to each island. Various steps involved in the protocol are confirmed using Fluorescence microscopy, Confocal microscopy and Atomic Force Microscopy.

7-32
The Effect of Humidity on the Adsorption Kinetics of Lung Surfactant at Air-water Interfaces
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The in vitro adsorption kinetics of lung surfactant at air-water interfaces is affected by both the composition of the surfactant preparations and the conditions under which the assessment is conducted. Relevant experimental conditions are surfactant concentration, temperature, subphase pH, electrolyte concentration, humidity and gas composition of the atmosphere exposed to the interface. The effect of humidity on the adsorption kinetics of a therapeutic lung surfactant preparation, Bovine Lipid Extract Surfactant (BLES), was studied by measuring the dynamic surface tension (DST). Axisymmetric Drop Shape Analysis (ADSA) was used in conjunction with three different experimental methodologies, i.e. captive bubble (CB), pendant drop (PD), and constrained sessile drop (CSD), to measure the DST. The experimental results obtained from these three methodologies show that for 100% relative humidity (RH) at 37°C the rate of adsorption of BLES at an air-water interface is substantially slower than for low humidity. These experimental results agree well with an adsorption model that considers the combined effects of entropic force, electrostatic interaction, and gravity. These findings have implications for the development and evaluation of new formulations for surfactant replacement therapy.

7-33
Flow and Particle Transport in a Human Nasal System
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In this paper a 3D computational model for studying the flow and nano-size particle transport and deposition in a human nasal passage was developed. The nose cavity was constructed using a series of pictures of coronal sections of a nose of a human subject. For several breathing rates associated with low or moderate activities, the steady state flows in the nasal passage were simulated numerically. The airflow simulation results were compared favorably with the available experimental data for the nasal passages.

Deposition and transport of ultra fine 1 to 100 nm particles in the cavity for different breathing rates was also simulated. The simulation results for the nasal capture efficiency were found to be in reasonable agreement with the available experimental data for a number of human subjects despite anatomical differences. The computational results for the nasal capture efficiency for nanoparticles of different sizes and various breathing rate in a laminar regime were found to correlate with the ratio of particle diffusivity to the breathing rate, or the nose Peclet number. An improved empirical model for the nose capture efficiency was proposed.
Accurate prediction of micro-scale particle behavior in human upper airway is one of the prerequisites for effective design of inhalation drug delivery devices. It also could provide insight into the deposition of contaminants in human respiratory tracks and the nature of personal exposure. In the past very few works employed 3-D asymmetric model to study the airflow through human lung, although natural tracheobronchial branching is generally asymmetric, and such an asymmetry has profound effect on the subsequent flow fields. Also limited work was devoted to the study of particle depositions in upper airways where the effect of turbulence on particle depositions is important. This work approaches three of the underlying components to provide a realistic computational model for lung deposition. The new study include: a realistic 3-D asymmetric bifurcation representation of human upper trachea-bronchial tree; simulation of airflow field characterizing the inspiratory flow conditions in these branches with turbulence Reynolds stress transport model; and lastly a particle transport model for identifying particle deposition pattern as well as deposition mechanism in the upper tracheobronchial tree.