SYMPOSIUM NN
Biomaterials for Drug Delivery
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SESSION NNL: STIMULI-SENSITIVE POLYMERS AND PHASE BEHAVIOR RELATED TO DRUG DELIVERY - WHAT WE LEARNED WITH TRICYCLIC ANTIDEPRESSANTS. Edward W. Merrill, MT, Dept. of Chem. Eng., Cambridge, MA; Cynthia Sung, Human Genome Sciences, Bethesda, MD; Edward Ellis, Vista Scientific, Inc, Andover, MA.

A copolymer of dimethyl siloxane and glycidoxypropylmethyloxiloxane having about six epoxy groups per molecule, hereafter designated PSX, was used to end link polyethylene glycol of 2000, 8000, or 20000 Dalton mol. wt. under cationic initiation. The PSX also polymerized with itself forming a cross-linked hydrophobic phase co-continuous with the hydrophilic PEG phase. The mass ratio of PEG to PSX was varied from 1/4 to 2. Equilibrium water content varied from 20 to 80 percent by weight. Two single phase networks were made as extreme limits: pure PSX via cationic initiation and pure PEG by radiation cross-linking. The uptake and release of five tricyclic antidepressants were determined as a function of network composition and of the relative hydrophobicity of each TCA. Principal findings were: (1) the two phase PEG-PSX networks take up more TCA than either limiting single phase network; (2) the more hydrophobic the TCA, the higher its partition into a PEG-PSX network; (3) the higher the PSX content in the network, the greater was the retention of the TCA. Because of these uptake/release characteristics, the PEG-PSX network is being evaluated as a conjunctival insert to release psychiatric drugs, such as the polycyclic antidepressants.

New complexation copolymer networks of polymethacrylic acid) grafted with poly(ethylene glycol) have been shown to be excellent carriers for protein delivery due to their pH-sensitive swelling behavior as a result of the formation of reversible interpolymer complexes stabilized by hydrogen bonding between the carboxylic acid proton and the ethyleneglycol on the grafted chains. Additionally, the presence of the PEG grafts serves as a stabilizer for entrapped peptides and proteins. Because of the complexation phenomena in these networks, the characteristic pore size in these gels is an order of magnitude greater in the uncomplexed state than in the complexed state. Because of their oscillatory swelling behavior, these gels have been used as oral carriers for insulin and calcitonin where the release of the bioactive agent in the intestine is necessary. Upon oral administration of insulin loaded gels, the blood glucose levels in rats were significantly reduced due to release of insulin in the upper small intestine. Most recently, the cytocompatibility of the P( MAA-g-EG) hydrogels was evaluated in Caco-2 cells which have been used as an intestinal epithelial cell model for drug absorption studies. The powdered hydrogels exhibited no significant cytotoxic effect at a dose of 10 mg/mL. On the other hand, the transmembrane electrical resistance of the Caco-2 cell monolayers showed a reversible drop during exposure to the hydrogels at the same dose, suggesting that these hydrogels may bring about an opening of the tight junctional paracellular pathway which is a major permenation route for the protein drugs.

9:30 AM *NN1.3 DESIGN OF pH-SENSITIVE POLYMERS TO ENHANCE INTRACELLULAR TARGETING: CD44, PROTEINS, ODNs & DNA. Allen Hoffman, Niren Murthy, Chuck Cheung, Chantal Leduc, Sue Stacey, University of Washington, Bioengineering Department, Seattle, WA; Oliver Press, Nelson Prossio, Jean Campbell, University of Washington, School of Medicine, Seattle, WA.

The intracellular trafficking of drugs is a critical barrier to the efficacy of drugs that are degraded by lysosomal enzymes. Such drugs include peptides, proteins, oligonucleotides and DNA. The design and synthesis of carriers which can enhance the transport of endocytosed drugs from the endosomal compartments into the cytoplasm is therefore an important goal. The pH of an endosome is lower than that of the cytosol by 1-2 pH units, depending on the stage of endosomal development. This pH gradient is a key factor in the design of membrane-disruptive polymers which could enhance the endosomal release of drugs. Such polymers should disrupt lipid bilayer membranes at pH 6.5 and below, but should be non-disruptive at pH 7.4. In addition, they should be capable of carrying targeting moieties to localize the therapeutics to specific cells. We will present our current approach to the design of pH-sensitive polymers and present new polymeric compositions that we have developed to deliver gene and protein therapeutics.

10:30 AM NNL.4 SYNTHESIS AND CHARACTERIZATION OF ENVIRONMENTALLY RESPONSIVE ORGANIC-SILICA HYDROGEL NANOPEARLS. Clinton D. Jones, Christina Baker, L. Andrew Lyon, Georgia Institute of Technology, School of Chemistry and Biochemistry, Atlanta, GA.

We report the synthesis of environmentally responsive hydrogels as nanosized (30-300 nm) particles with core-shell morphologies. Composed of co-polymers of N-isopropylacrylamide with various co-monomers, these materials can be designed to render the core and shell responsive to different stimuli or to different magnitudes of the same stimulus. The measured phase transitions reflect the degree to which the two materials interact and thereby modulate the responsivity of the particle as a whole. Characterization of these materials is accomplished via dynamic light scattering, differential scanning calorimetry, electron microscopy, and fluorescence spectroscopy. Prospects for the use of these particles in the assembly of new biomaterials is discussed.

10:45 AM NNL.5 PHOTOINDUCED RELEASE OF STERICALLY STABILIZED LIPOSOMES CONTENTS. Anja Mueller, Bruce B. Bundrant, Paul A. Sprunt, David F. O'Brien, University of Arizona, Dept. of Chemistry, Tucson, AZ.

Liposomes are useful for delivery and buffering of drugs in the body. Liposomes that are sterically stabilized with poly(ethylene glycol) (PEG-liposomes) have an increased circulation time and are therefore more effective in delivering therapeutic agents to the interstitium of the tumor site. During circulation PEG-liposomes must not release the drug. After accumulation of the liposomes in the interstitium of the tumor site a trigger for release is desirable. An attractive trigger is light, because methods for the delivery of light to tumor cells have already been developed for photodynamic therapy. Therefore, the photoinduced destabilization of liposomes offers an attractive method to couple the temporal and spatial control of light to drug delivery.

11:00 AM NNL.6 ELASTIN-LIKE POLYPEPTIDES AS THERMALLY TARGETED DRUG CARRIERS. Dan Meyer, Ashutosh Chilkoti, Duke Univ, Dept of Biomedical Engineering, Durham, NC; Michael Zalutsky, Duke Univ Medical Center, Dept of Radiology, Durham, NC.

Elastin-like polypeptides (ELPs) are polymers of the pentapeptide sequence Val-Pro-Gly-Xaa-Gly (where the "xaa residue" Xaa can be any amino acid, in any order, except pro). ELPs are an interesting class of polypeptides because they are soluble in aqueous solutions below a specific transition temperature (Tt), but, upon heating above Tt, they undergo a phase transition that results in their hydrophobic collapse and aggregation. To investigate thermal targeting of conjugated drugs to solid tumors, we synthesized a SI-3 ELP with a Tt of 40°C, which was specified by adjusting the identity and fraction of guest residues. Because the Tt of this polypeptide is greater than normal body temperature, we hypothesized that, as a drug carrier, it will remain soluble when injected systemically. However, upon vascular transport to a solid tumor that is externally heated to Ttumor > Tt, by focused ultrasound or microwave energy, the ELP carrier will undergo its transition and accumulate through hydrophobic interactions. Here, we present results of tissue distribution studies for radiolabeled ELP carriercarriers that were injected
into nude mice with implanted tumors (human glioma D54MG). We observed a two-fold increase in ELP accumulation versus untreated animals when the tumor-bearing line was hatched by immersion in a temperature-controlled water bath. Significant contralateral effects that the observed enhancement is largely caused by the phase transition of the ELP carrier rather than by non-specific effects of hyperthermia (e.g., increased vascular permeability). Ongoing optimization studies seek to determine the effect of ELP MW, concentration, and administration protocol (e.g., bolus vs. low-level infusion) on targeting efficiency.

11:15 AM N11.7 WATER SOLUBLE COPOLYMERS CONSISTING OF TERTIARY AMINE AND CARBOXYLIC ACID PENTANT GROUPS
Mohammad M Baru, Chengju Ju, Temple University, School of Pharmacy, Philadelphia, PA.

This study was to synthesize new water soluble copolymers, composing of tertiary amine and carboxylic acid pendant groups, for oral drug delivery systems. The copolymers prepared with different ratios of tertiary amine (i.e., dimethylaminoethyl methacrylate, diethylaminoethyl methacrylate) and carboxylic acid (i.e., acrylic acid, methacrylic acid) were swollen in de-ionized water and freeze-dried before obtaining fine powders. Drug release experiments with various drugs were carried out with compressed tablets in pHs of 1.5 and 7. Effects of various variations of drug carriers and drug properties on drug release kinetics were evaluated: drug solubility, drug loading, ion type of drugs, polymer composition, types of monomers, etc. In general, zero-order release kinetics were obtained in both pH 1.5 and 7 for a long period of time. The release of drugs in pH 1.5 is not significantly different even with varying solubility and ion type of drugs. However, different drug release profiles in pH 7 were observed with different types of drug and solubility. Molar ratios of monomer composition and types of tertiary amine and carboxylic acid significantly influence drug release kinetics.

11:30 AM N11.8 MODIFIED POLYAMER POLYMERS FOR pH-SENSITIVE DRUG DELIVERY
Briana C Anderson, Surya K Mulpuru, Virginia Commonwealth University, Richmond, VA.

Polymers [poly (ethylene oxide)]b-poly [poly (propylene oxide)]b-poly [ethylene oxide)] have been investigated in recent years for drug delivery applications due to their zero order dissolution kinetics in an aqueous gel state and drug solubility capabilities. Polymers undergo thermo-reversible gelation at moderate temperatures, making them responsive to temperature changes in their surroundings. Polymers with similar gel-forming characteristics were synthesized that also contain an ionic monomer to make the gels responsive to pH changes in addition to temperature changes. This increases the gel dissolution at lower pH levels. These polymers were characterized both for physical properties and drug delivery potential and were compared to poloxamer polymers to investigate the influence of the amount of ionic monomer and ionic groups on the properties of the resulting materials.

11:45 AM N11.9 TEMPERATURE-SENSITIVE POLYMER NANOSHELL COMPOSITES FOR PHOTOTHERMALLY MODULATED DRUG DELIVERY
Scott R Senden, Jennifer L West, Rice University, Department of Chemistry, Houston, TX.

Composites of thermally-sensitive hydrogels and optically active nanoparticles have been developed for photothermally modulated drug delivery. Copolymers of N-isopropylacrylamide (NIPAAm) and acrylic acid (AAm) exhibit a lower critical solution temperature (LCST) that decreases with increasing body temperature. When the temperature exceeds the LCST, the hydrogel collapses, causing a burst release of any soluble material held within the hydrogel matrix. Gold-gold sulfide nanoshells, a new class of nanoparticles designed to strongly absorb infrared light and convert it to heat, have been incorporated into poly[NIPAAm-co-AAm] hydrogels to initiate a temperature change with light. The nanoshells consist of thin layers of gold (~4 nm in thickness) surrounding a gold sulfide core (~40 nm in diameter), and when the core/silica ratio is high enough, the silica phase is not visible by TEM. Light in the near infrared region (700-1000 nm) can be applied externally, pass through tissue, and then be converted to heat, causing the temperature of the nanoshell itself to increase and consequently causing the hydrogel to collapse. This process releases the drug from the polymer matrix.

1:30 PM N22.1 CONTROLLED RELEASE OF PROTEINS FROM EXTRUDED RODS
Jorge Heller, John Barr, Steve Y. Ng, Hui-Rong Shen, Advanced Polymer Systems, Redwood City, CA (California State University, Sacramento, CA).

The need to develop delivery systems for proteins and peptides where full protein activity is preserved is not well recognized. However, the development of such systems in fraught with difficulties, and dominant among these is the instability of proteins to maintain full activity when exposed to an organic solvent/water interface. Because conventional microencapsulation methods are based on the use of organic solvents and water, such methods are not generally useful for proteins that must retain their tertiary structures to preserve biological activity and specialized microencapsulation methods that avoid an aqueous phase have been developed.

Since many dry proteins have excellent thermal stability, a viable fabrication method is extrusion of intimate mixtures of microporous protein and finely powdered polymer. This method avoids exposure of the protein to organic solvents and especially to an organic solvent/water interface. However, to be generally useful, this method needs a polymer where softening temperatures and erosion rates can be accurately adjusted to the desired values. We have described such a polymer and by proper choice of monomers, polymers that can be extruded at temperatures no higher than 70°C and where erosion rates can be adjusted to the desired values can be prepared. We have studied the in vitro release of a model protein, FITC-BSA, from 1 mm diameter rods cut to 10 mm lengths. Results of these studies indicate that FITC-BSA is released at linear rates with concomitant weight loss indicating that BSA release is completely erosion controlled and that the erosion process occurs by surface erosion. There was, however, a significant induction period before the release began and we will describe methods that decrease, or eliminate this induction period.

2:00 PM N22.2 LIPID COMPOSITE MATERIALS FOR NANOPARTICLES DELIVERY SYSTEMS
Pierandra Esposto, Istituto di Ricerche C. Serono - Drug Delivery System, Colleterre Ginocchio, Turin, ITALY.

The use of lipids as materials for matrix type, nanoparticulate carriers manufactured has gained considerable interest in the pharmaceutical field. They are in general GRAS materials of low or medium cost, low toxicity, and high bioavailability. Lipids occur in a variety of compositions which influence their physicochemical characteristics as well as biopharmaceutical properties. Lipid blends, prepared in controlled conditions, can further expand the potential of application of such materials to nanoparticles formulation development. Such blends, at defined compositions, can originate from lipid material surface and bulk properties. Lipid nanoparticles based on such compositions may find favourable applications in specific drug delivery applications (i.e. oral delivery of peptides). Objective of the work are to characterize the surface and bulk properties of the lipid blends used for nanoparticles preparation. To study how such characteristics would affect the nanoparticles properties. To investigate the potential of lipid nanoparticles as a carrier for peptide drugs for the oral route delivery and to evaluate the impact of the above parameters on the properties of the nanoparticles. A study of calcium liposomes was also studied by mean of polarized light spectrofluorimetry and THF analysis analysis evidenced the differences in nanoparticles morphology. Salmon calcitonin (sCT) was incorporated into nanoparticles prepared using lipid blends of different compositions. sCT-Nanoparticles suspensions were orally administered in vivo to Rh monkeys, at a single dose of 80 µg/kg. Significant peptide amounts were found in plasma up to 7 hours after dosing, with corresponding reductions in total and ionized calcium concentrations. The results show that the
oral absorption of a peptide drug can be favoured by incorporating it into lipid nanoparticles. Furthermore, the modification of the surface properties of the nanoparticles towards the decrease of total surface free energy, and the increase of surface polarity seems to enhance the absorption of salmon calcitonin.

References:

Work performed at Vectorpharma International SpA, Business Innovation Center, Via del Polloficio 12, 34148 Trieste, Italy.

2:30 PM *NN2.5 BIODEROGRADEABLE POLYMERS, AND ENVIROMENTALLY SENSITIVE HYDROGELS FOR THE CONTROLLED DELIVERY AND SURRELIZATION OF PROTEINS, VACCINES AND CONVENTIONAL DRUG MOLECULES. Gaylen Zentner, Micromed Inc., Salt Lake City, UT.

Controlled release drug delivery systems (DDS) based on biodegradable polymers in the form of environmentally sensitive gels and microspheres will be presented. Polymer technologies that effectively solubilize poorly soluble drugs are included. The PK/PD and in vitro properties of DDS for cancer (paclitaxel, hormones, cytokines), growth promotion (HGH, pGh), and vaccine (hepatitis B) therapies are the focus of this presentation. Safety/toxicity data on key polymeric components of these DDS are included.

3:30 PM *NN2.4 BIOMATERIALS FOR TISSUE ENGINEERING AND REGENERATIVE MEDICINE. Michael Lyons, Brown University, Providence, RI.

Tissue engineering appears likely to represent the next generation of substitutive medical devices. It relies upon devices and therapies which utilize living cells as therapeutic regents and combine living cells with synthetic or naturally occurring biomaterials. Applications may involve replacement or regeneration of structural body components (eg, skin, cartilage, bone) or substitution of the function of a metabolic organ with a biologic equivalent (eg, pancreas, liver). Biomaterials for tissue engineering and regenerative medicine may be hydrophilic or hydrophobic, permanent or temporary, biodegradable or degradable. Although numerous candidate biomaterials have been proposed and investigated, those applications which have reached the clinic rely upon relatively few biomaterials (~15 in aggregate), most of which have a successful history in earlier medical applications.

4:00 PM NN2.5 SUBCUTANEOUS ADMINISTRATION OF INSULIN LOADED MICROSPHERES FOR SUSTAINED DELIVERY. Danielle Abrahamson, Amit Ayer, Edith Mathiowetz, Brown University, Department of Molecular Pharmacology, Physiology and Biotechnology, Providence, RI.

Current treatment for type I diabetes includes multiple subcutaneous (SQ) injections of unencapsulated insulin, which provides an initial therapeutic dose, but is short lasting. The insulin bypasses the liver, going directly into the systemic circulation to enter peripheral tissues, exposing them to high insulin levels. A large amount of this insulin is degraded and unavailable for use. In order to mitigate some of the problems associated with unencapsulated insulin, we have developed a sustained biodegradable delivery system. Studying various types of insulin loaded microspheres (ILMS) invitro and in-vivo, we were able to find a system that provides an initial therapeutic dose of insulin followed by a sustained stable insulin level. The most effective SQ delivery system will deliver the highest percentage of active insulin to target tissues at a rate which insulin can be utilized. Poly[(fumaric-co-sebacic) P(F-SA) (200k)] microspheres (MW = 1.5µm) were prepared by the PIN technique. Microspheres were loaded at various insulin loadings with either micromized insulin or regular insulin crystals. Rats (205 ± 10g male, CD strain) were fasted overnight and allowed free access to water. The rats were anesthetized using an ioflurane gas chamber. Blood was collected via tail bleeding. After the initial blood was collected, a SQ injection with either ILMS or unencapsulated insulin suspended in 1.8mL of saline was administered. Blood was collected for up to nine hours. Plasma samples were analyzed for both glucose and insulin levels. The P(F-SA) microspheres loaded with 3% insulin showed a large burst effect, which corresponded to a quick drop in glucose levels followed by a slow rise to initial fasting glucose levels. Microspheres made from P(F-SA) loaded with micromized insulin at 2% loading, exhibited no glucose drop in initial levels, but instead a slow steady release of insulin corresponding to a slow drop in glucose level for up to nine hours. The micronization of insulin facilitates efficient encapsulation within the microspheres, thus reducing the burst effect and establishing a sustained release delivery system. We were successful in fabricating a sustained-release subcutaneous system that increased the duration of insulin action beyond that of conventional insulin injections while reducing the negative large burst effect. Future work on enteral release will be started to try to establish bioavailability parameters for the same microspheres.

4:15 PM *NN2.6 USING A COMBINATORIAL LIBRARY OF DEGRADABLE POLYDIARYLATES TO OPTIMIZE PEPTIDE MATRIX INTERACTIONS IN DRUG DELIVERY SYSTEMS. Debbie M. Schachtier, Joshua Simon, Joanne Kehr, Rutgers University, Dept. of Chemistry, Piscataway, NJ. Smaller Therapeutics, Advanced Materials Design, LLC, Piscataway, NJ.

Delivery systems based on degradable polymeric matrices that can release high payloads of watersoluble peptides with reproducibly programmable delay times have been formulated using a combinatorially designed library of polycrylates in which the material properties of the polymers can be varied in a predictable and systematic fashion. Tyrrosine-derived polycrylates are alternating copolymers of a diphenyl and dioxyclic linkerester bonds. These polymers are readily processable, biocompatible and degrade in vivo. We had shown previously that high payloads of INTEGRILIN, a watersoluble cyclic heptapeptide (used clinically as an antithrombotic drug) can be incorporated into various polycrylates and that hydrogen bonding interactions between the peptide and the polymer can prevent the release of the peptide from the matrix. Following up on this initial observation, we now show that it is possible to vary the degree of hydrogen bonding by small changes in the polymer structure. Using the available library of polycrylates, a wide range of delay-release profiles were obtained, including delayed release and pulsatile release profiles. Specifically, it was possible to formulate burst-free matrix systems with loadings of peptide as high as 50% (w/w) of the water-soluble INTEGRILIN. Choosing appropriate polycrylates from the library, high-load systems were prepared that triggered the peptide within the matrix so that only a trace of peptide was released even after 77 days. In contrast, other members of the polycrylate library provided formulations that released the peptide with a controllable delay time. The length of the delay was clearly related to the molecular composition of the release matrix and ranged from no delay to a delay of over 60 days before release was observed. The precise control over the length of the lag time allows the design of a pulsatile delivery system using combinations of different polymers.

4:45 PM *NN2.7 PROTEIN RELEASE FROM MULTI-LAYERED POLYMER MICROSPHERES FABRICATED VIA SOLVENT REMOVAL. J. Godbee, D. Vázquez and E. Mathiowetz, Department of Molecular Pharmacology, Physiology & Biotechnology, Brown University, Providence, RI.

Introduction: Previous research in our lab has shown multi-layered microspheres to have a lower initial burst of drug than the release obtained from single-layered microspheres of the same polymer. Solvent removal is a method that provides us with a controlled and controllable way to encapsulate proteins without exposure to a aqueous environment, which reduces protein losses to the non-solvent during encapsulation. The purpose of this study is to investigate the effects of polymer solution concentration and drug loading on the release profiles from multi-layered microspheres fabricated via solvent removal. In the interest of having controlled release over several months, poly L-lactic acid (PLLA), and poly (fumaric-co-sebacic) acid (200k) (PFSA), were selected for these studies. These two polymers readily phase separate, which is a prerequisite for the one-step multi-layered fabrication method. Method: We used polymer solutions of varying concentrations (5%, 10%, and 15% w/v). Spray-dried FITC-labeled bovine serum albumin (BSA) was used as the model protein which was loaded into the PFSA at varying concentrations (5%, 10%, 15%, and 20% w/v). The FITC-BSA-containing solution was sonicated to create an emulsion, the two polymer solutions were then mixed into one vial, shaken vigorously and poured into the stirring non-solvent solution. Petroleum ether was added immediately to complete the removal of the organic solvent from the polymer solution droplets and Guardian into microspheres of protein. The protein concentration had a large effect on the initial burst. The 15% solutions had initial bursts at 24% and 5% of the theoretical value and the 10% solutions had greater than 3 times more burst at 15% and 22% of the theoretical value. The drug loading did not have much of an effect on the initial burst between the 10%, 15%, and 20% loaded spheres. However, the spheres with 5% drug loading had an initial burst at least twice the value of the 10%, 15%, and 20% spheres after 3 minutes. Additionally, the release profiles for 15% and 20% samples varied: decreasing release with increasing drug loading. Discussion: Based on our findings we conclude that the lowest burst will be achieved from spheres fabricated from 15% solutions. The drug loading should be between 10% and 20% of the desired protein profile.
SESSION NN3: TISSUE AND GENE DELIVERY
Chair: Richard Korinek
Tuesday Morning, November 28, 2000
Republic A (Sheraton)
8:30 AM *NN3.1
MICROENCAPSULATION OF CELLS USING SYNTHETIC POLYMERS. Michael V. Sefton, University of Toronto, Institute of Biomaterials and Biomedical Engineering, Toronto, CANADA.

Microencapsulation in a polymer membrane is a means of isolating cells from the immune system, thereby enabling the transplantation of mammalian cells without immunosuppression and the use of xenogenic or genetically engineered cells. The cells are encapsulated to correct a disease state by the delivery of a cell product, typically a protein. Insulin from pancreatic islets is an example of this mode of therapy. Unlike conventional drug delivery devices, the cells have an inextricable supply of the protein (pulsed cell viability) in an intrinsically stable form and without the problem of expense and protein purification. Furthermore, the protein is delivered at a rate determined by the normal physiology of the cells which might involve regulation by glucose level (lactate or potassium concentration [dopamine secreting cells] or cytokine levels [antitrypsin]). Successful microencapsulation and cell transplantation requires (1) high cell number and viability (2) control of cell function (through the extracellular matrix, for example) and (3) maintenance of function for extended duration. These properties of encapsulated cells are illustrated with the use of hydroxystylyl methacrylate-methyl methacrylate copolymer (HEMA-MMA). This presentation will focus on the material problems associated with this type of tissue engineering.

9:00 AM NN3.2
INCREASING GENE EXPRESSION LEVEL WITH ENGINEERED PEPTIDES FOR NON-VIRAL GENE TRANSFER TO NON.
DIVIDING ENDOTHELIUM. Huchang Ma, Jinyun Zhu and Scott L. Diamond, Institute for Medicine and Engineering, Dept of Chemical Engineering, University of Pennsylvania, Philadelphia, PA.

The largest obstacle toward therapeutic applications of non-viral gene therapy is their poor gene delivery efficiency. This is especially true in non-dividing cells such as those in or near the endothelium. In general, there are three major steps that affect the gene delivery efficiency: endocytosis, endosome escaping and nuclear targeting, in which the last step is often the rate-limiting step. Unlike the dividing cell, the low division rate of endothelium makes them a difficult target for nonviral gene transfer. To overcome this, we tested the nuclear import driving function of non-classical nuclear localization signal peptide, MB sequence of hTFP-1 [38 amino acid] in confluent bovine aortic endothelial cells (BAEC). The full length MB peptide alone has very low plasmid binding activity and can only slightly increase marker gene expression. After linking the MB peptide with a citrnic tail, the chimeric MB-citrine peptide DNA complexes at 1:1 (v/v) ratio, which is able to protect plasmid DNA from DNase digestion at a 10 min reaction of 0.1 unit DNase I in 37°C. This citrnic peptide could improve the transfection particles formed between plasmid and liposome both in size and particle distribution. Such as, by using vector of pcMV5GFP (4.7kb), the average size of liposome/peptide complexes are 101 ± 93 nm, but liposome/peptide complexes are 162 ± 24.7 nm. Lipofection with citrnic MB complexes also dramatically increased marker gene's expression in highly confluent BAEC. With standard GFP assay, the total GFP gene expression level (ng/assay) could be easily increased more than 616 fold to levels up to 80 nm / 2g2 BAEC. This citrnic nuclear targeting system may eventually used in other genetic targeting delivery, such as plasmids, intramucosal oligos, RNA-DNA chimeras and peptide nucleic acids.

9:15 AM NN3.3
THE MOLECULAR BASIS OF ENGINEERED IN VITRO HEPATOCYTOGENESIS. Erin R. Orshick, Massachusetts General Hospital, Dept of Pathology, Boston, MA; Toshihiko Ito, Dept of Transplantation and Immunology, Faculty of Medicine, Kyoto University, Kyoto, JAPAN; Joseph W. Carbone, Harvard/MIT Division of Health Sciences and Technology, Boston, MA; Joseph P. Vacanti, Massachusetts General Hospital, Dept of Surgery, Boston, MA.

We employ in situ hybridization to describe a liver engineering process at the molecular level and evaluate a strategy for engineering human replacement livers. We employ 3DPE™ printing technology to create a biofunctional polymer scaffold contoured to the 100 µm scale. Mimicking liver vascularization, this 3D scaffold contains an inlet “artery” which branches to smaller vessels feeding a liver “parenchyma”, and an outlet “vein.” Onto this scaffold we seed isolated highly proliferative hepatocytes, then culture tissue-engineered livers in a dynamic bioreactor. Eventually, vascularized tissue-engineered liver will be constructed from a human patient’s donor hepatocytes then transplanted to the patient’s portal vein and induced to grow at the expense of diseased native liver while maintaining integrity of liver function and avoiding transplant rejection. Underlying this strategy is the hypothesis that, given adequate culture conditions, diseased liver cells will spontaneously reiterate in situ organogenesis. The in situ process has been studied by molecular biologists using in situ hybridization, which employs digoxigenin-labeled RNA probes to detect the presence or absence of individual genetic transcription factors in a liver at a given time. As each factor is expressed in the developing liver, it activates other regulating factors whose complex interactions control organogenesis. We have synthesized probes with appropriate controls to detect for each of the transcription factors which are most important to hepatogenesis: HNF-3β, HNF-6, mHGF, eTFAT, IFG-1, KER-1, GATA-2, Hix, and JNK-1. For each probe twenty-five rat liver biopsies are tested at each of three gestational points. The same probes will be used for 25 tissue-engineered rat livers at each of three time points. We expect our data to show donor hepatocytes undergoing a genetic pattern transition and then a pattern restoration, indicating that the active culture phase of the engineering process mimics in situ hepatogenesis at the molecular level.

9:30 AM NN3.4
NOVEL POLY(ETHYLENE GLYCOL)-CONJUGATED DENDRIMER FOR BIOPATIBLE, HIGH EFFICIENT, AND LOW COST DNA DELIVERY. Dan Luo, Nadya Belchica, Ernest Han and W. Mark Saltzman, Cornell University, School of Chemical Engineering, Ithaca, NY.

Starburst polyamidoamine dendrimer (PAMAM) is a DNA delivery agent with high efficiency, which has been the most popular gene delivery reagent. In this study, we developed new dendrimer with biocompatible poly(ethylene glycol) chains would have several potential advantages: 1) Voids created on the dendrimer surface via PEGylation could increase the flexibility of dendrimers and accommodate the DNA helixes without creating strong electronic interactions; 2) Biocompatibility of the molecule should increase due to the reduction in generation of PAMAM and addition of PEG branches; 3) Intracellular release of DNA molecules should be more efficient due to the presence of fewer tertiary amino groups. Here, we report on the synthesis and characterization of a novel PEG-PAMAM conjugate that increases transfection up to 20 fold compared with partially degraded dendrimer controls. This extremely efficient, highly biocompatible, and low cost DNA system can be readily used in basic research laboratories and may find future clinical applications.

9:45 AM NN3.5
ELECTROSTATIC SELF-ASSEMBLY OF ACTIN-MEMBRANE TUBULAR CAPSULES. Gerard C.L. Wong, University of Illinois at Urbana-Champaign, Materials Dept, Physics Dept; Jay X. Tang, Indiana University, Physics Dept; Youli Li, Alisa Lin, University of California at Santa Barbara, MBI, Paul Janeway, University of Pennsylvania, Institute for Medicine and Engineering; Cyrus R. Safinya, University of California at Santa Barbara, Materials Dept, Physics Dept, Biochemistry and Molecular Biology Program.

We describe a distinct new type of spontaneous hierarchical self assembly comprised of cytoskeletal filamental actin (F-actin), a highly charged polyelectrolyte, and citiucic lipid membranes, using entropically modulated electrostatic interactions. Unexpectedly, on the mesoscopic length scale, confocal microscopy reveals a ribbon-like tubule structure which connect to form a network of tubules on the micrometer scale. Within the tubules, on the 0.5 to 50 nanometer scale, x-ray diffraction reveals a structure consisting of coasotically swollen stacks of composite membranes with no direct analog in simple amphiphilic systems. The composite membrane is comprised of three layers, a middle lipid bilayer sandwiched between two layers of actin, and a reminiscent of multi-layered bacterial cell walls which exist far from equilibrium. Electron microscopy reveals that the actin layer consists of laterally locked F-actin filaments forming an anisotropic 3-dimensional tethered crystal which appears to be the origin of the tubule formation. The open, nested structure of these self-assembled rigid-walled tubules suggests possible applications in drug delivery. [1] G.C.L. Wong, J.X. Tang, A. Lin, Y. Li, P.A. Janeway, and C.R. Safinya, SCIENCE, in press.

10:30 AM *NN3.6
PHOTODYNAMIC CONTROLLED DELIVERY FOR GENE DELIVERY AND IMMUNOTHERAPY. Kwan W. Leong, Dept of Biomedical Eng, Johns Hopkins School of Medicine, Baltimore, MD.
Non-viral vectors are increasingly being proposed as alternatives to viral vectors for in vivo gene transfer because of their potential advantages in addressing the pharmacological issues of applying gene as a drug. We have studied the complexation of DNA with natural or synthetic polymers in forming nanopores. In addition to benefits common to other non-viral gene delivery systems of protecting the DNA from nucleic degradation and allowing active targeting, characteristics unique to these biodegradable DNA nanoparticles include co-macroporation of bioactive agents and sustained release of the DNA. Phase-transfer gene transfer has been observed in vivo in the lung, muscle, and gastrointestinal tissues in animal models. While the transfection efficiency of these DNA nanoparticles remain low, their application in DNA vaccination, where high antigen expression may not be required, is promising because of their ability to encapsulate and deliver cytokines in a local and sustained manner to stimulate the infiltrating immune cells.

11:00 AM *N3.7
CONTROLLED RELEASE OF BONE GROWTH FACTORS FROM INJECTABLE BIODEGRADABLE POLYMER SCAFFOLDS FOR BONE TISSUE ENGINEERING
Elizabeth L. Heschong and Antonios G. Mikos, Rice University, Department of Bioengineering, Houston, TX.

We seek to develop injectable, in situ polymerizable, biodegradable materials for treating skeletal defects with guided bone regeneration. At a minimum, the biomaterial should serve as a scaffold for cell adhesion and migration. Regeneration may be enhanced, however, through the incorporation of bioactive molecules. To that end, the injectable polymer (poly(propylene fumarate) (PF) was loaded with poly(lactic-co-glycolic acid) (PLGA) microparticles carrying FITC-Dextran and then co-crosslinked with N- vinyl pyrollidone in the presence of a benzyl nitrite as an initiator and sodium chloride (NaCl) as a levelling porogen. The encapsulation of the growth factor in microparticles was necessary to minimize denaturing of the growth factor during scaffold crosslinking. The FITC-Dextran is used as a co-factor to test in the release of the growth factor. Modulation of the release of FITC-Dextran will in turn lead to modulation of the release of the growth factor. PLGA microparticles were incorporated into composites of varying NaCl weight percent and the effects on FITC-Dextran release kinetics was determined in vitro for cylinders of diameter 0.5 mm and height 13.0 mm. FITC-Dextran was incorporated into the biodegradable microparticles at 10 mg FITC-Dextran/1 mg microparticles. PLGA microparticles were incorporated into the composites at 40 mg microparticles/g PF. The FITC-Dextran loaded microparticles alone exhibited a large initial burst effect, while the composite materials displayed a smaller burst effect and a longer linear region of release. At day 1, 43.81%, 2.88.0.5%, and 8.30.7% of loaded FITC-Dextran was released into pH 7.4 phosphate buffered saline from the microparticles, the 50% NaCl, and the 70% NaCl composites, respectively. By day 28, 90.96%, 12.71%, and 34.40% of loaded FITC-Dextran was released. Our results demonstrate that PLGA microparticles that can successfully be added to PF composites and that the release kinetics of FITC-Dextran can be systematically manipulated through alterations of the composite material properties.

11:15 AM *N3.8
AN AQUEOUS SOL-GELOT PROCESS FOR CAPSULATION OF PROTEINS AND CELLS FOR BIOSENSORS APPLICATIONS
Amir K. Singhsingh, G. Gunina, Sandia National Laboratory, Livermore, CA; Ashok Malchandani, Dept. of Chemical and Environmental Engineering, Univ. of California, Riverside, CA; Rimple B. Bhutia, Carol S. Ashley, C. Jeffrey Brinker, Univ. of New Mexico/Laboratory for Microengineered Materials, Albuquerque, NM and Sandia National Laboratory, Albuquerque, NM.

Porous silica materials made by low temperature sol-gel process are promising hosts for encapsulation of biomolecules. Their mechanical strength, chemical inertness, hydrophilic nature, and above all, their optical transparency makes them an exciting platform for development of biosensors. To date, researchers have focused on sol-gel routes using alkoxides such as tetramethyl orthosilicate (TMOS) and tetraethyl orthosilicate (TEOS) for encapsulation of biomolecules. These routes lead to formation of alcohol as a byproduct that can have detrimental effect on the activity of entrapped biomolecules. We have developed a novel sol-gel process to encapsulate biological molecules [such as enzymes, antibodies and cells] that uses neutral pH, room temperature, and does not generate alcohol as a byproduct. The process uses sodium silicate as precursor and is carried in two-step, pH-controlled procedure. It may result in a low pH silicate sol followed by gelation at neutral pH in a buffer containing biomolecules. Two enzymes widely used in biosensing applications- horseradish peroxidase (HRP) and glucose-6-phosphate dehydrogenase (G6PDH), were used to probe silica coated silica monoliths to investigate the effect of silica as host matrix on enzyme kinetics. We also developed a novel homogeneous immunoassay for 2,4,6-trinitrotoluene (TNT), and encapsulated the immunoassay reagents in sol-gel matrices to produce disposable biosensors for the detection of TNT. Using the solgel material doped with immunoassay reagents, TNT at low pgm levels in water could be detected. We also report encapsulation of E. coli cells expressing the enzyme arachidonic acid hydrolase (APH) in the cell surface in sol-gel material to be used to develop biosensors for detection of organophosphorous compounds such as insecticides and chemical warfare agents.

1:30 PM *N4.1
THE DYNAMICS OF PHASE INVERSION RELATED TO INJECTABLE DRUG DELIVERY
Anthony McCarthy, Uchicago, Dept. of Chemical Engineering, Urbana, IL.

An alternative to the use of preformed polymeric membranes for controlled delivery of peptide and protein therapies is that of polymer solution injection. In this case, protein particles are suspended in a solution of a biodegradable polymer in a biocompatible solvent and injected subcutaneously. Contact with the aqueous-based physiologic surroundings causes liquid demixing and gelation of the polymer solution (phase inversion), thereby forming the membrane carrier invivo, simultaneously with the release of the entrapped drug. The dynamic of the membrane formation reflect the thermodynamic and mass transfer interactions in the system and, in turn, profoundly influence the drug release characteristics. Selection of solution formulations for optimal release profile thus requires an understanding of the role of phase inversion in the process. This talk will review recent studies that are addressing these issues. We employ dark ground imaging to visualize the phase inversion dynamics of several injectable delivery systems. These measurements are related to invivo drug release profiles obtained using standard techniques and, together, provide fundamental insights on the role of the key variables affecting the process. The latter may be relevant for the pharmaceutical design of optimized drug delivery systems.

SESSION N4A: PHASE SEPARATION AND CHARACTERIZATION OF DELIVERY SYSTEMS
Chair: Balaji Narasimhan
Tuesday Afternoon, November 28, 2000

President: Sheraton
2:00 PM **NN4.2**

**SURFACE-TOLERABLE POLYANHYDRIDE COPOLYMERS AND BLENDS FOR DRUG DELIVERY APPLICATIONS.** Elizabeth Shen, Briamie Dietrich, Mee-Kyoung Lim, Balaji Narasimhan.

Biodegradable controlled release systems hold significant advantages over other controlled release systems since the need to surgically remove the device is obviated. An understanding of the complex relationship between the polymer microstructure and drug distribution/release would pave the way for a systematic engineering approach to designing controlled drug delivery systems. It is our hypothesis that drugs thermodynamically partition themselves into regions of similar hydrophobicity when loaded into microphase-separated heterogeneous polymers. We synthesized copolymers and blends of polyanhydrides based on 1,6-bis-carboxyphenoxy hexanoic (CPH) and sebacic acid (SA). We examined the polymer microstructure and the effects of loading these polymers with two model drugs, hydrophilic brilliant blue and hydrophobic potentiometer.

**Morphological characterization** was carried out using differential scanning calorimetry (DSC) and wide-angle X-ray diffraction (WAXD). These methods showed that brilliant blue had no effect on the crystalline structure of the polymer while potentiometer disrupted the crystalline structure, causing loading-dependent melting point depression. Surface microstructure was examined using atomic force microscopy (AFM) and small angle X-ray scattering (SAXS). These techniques provided evidence of microphase separation in copolymer compositions exceeding 75% of one component. Kinetics studies were carried out to obtain drug and monomer release profiles. Significant correlations between the polymer microstructure and the drug/monomer release kinetics emerge, depending on the copolymer composition and the drug hydrophobicity. By examining fundamental monomer- and polymer-drug interactions, we hope to better predict and design controlled drug delivery systems for specific applications.

3:15 PM **NN4.3**

**DIRECT MEASUREMENT OF INTERACTIONS BETWEEN TETHERED PEG CHAINS AND ADSORBED MUCIN LAYERS BY SURFACE FORCE APPARATUS.** Yienhon Huang, School of Chemical Engineering, Purdue University, West Lafayette, IN; Nadezhda Efremova, Deborah E. Lockwood, Department of Chemical Engineering, University of Illinois, Urbana, IL; Nicholas A. Peppas, School of Chemical Engineering, Purdue University, West Lafayette, IN.

We used surface force apparatus (SFA) to make direct force measurement between tethered poly(ethylene glycol) (PEG) chains and an adsorbed mucin layer. The mucins were adsorbed on the mixed microsurfaces of PEG chains and on the hydrophilic force measurements were made in pH 7.2 and 4.0 buffer solutions, and the results showed that there was no notable interaction between the two surfaces. The in-situ mucin adsorption experiments were done at pH 7.2 by using surface force microscopy (SFM) and the measurements, and it was found that there was no permanent binding of mucins on the PEG-tethered surface. However, the adsorption experiment of mucins on self-assembled PEG monolayers in pH 2.0 buffer solutions showed permanent and stable interactions in the solution. We suggest that there are some attractions between PEG and mucins at this low pH condition. This work showed that SFA could provide information of molecular interaction between polymers and simulated mucous layers, which is essential for the design of new transdermal drug delivery systems.

3:30 PM **NN4.4**

**SMALL MOLECULE DIFFUSION AND SOLUBILITY IN ADHESIVES USED FOR TRANSDERMAL DRUG DELIVERY: INFRARED-ATTENUATED TOTAL REFLECTANCE (IR-ATR) STUDIES.** Adam S. Centor, 3M Drug Delivery Systems Division, St. Paul, MN.

A key factor in designing a drug-in-adhesive transdermal drug delivery system is to understand the rate at which the drug and small-molecule excipients can diffuse in the adhesive matrix. The solubility of these components in the adhesive matrix is of great importance. Results will be presented discussing the use of infrared-attenuated total reflectance (IR-ATR) spectroscopy as a method to measure diffusion and solubility of small molecules in adhesives. In this method, the donor layer is either a doped adhesive or a free liquid that is placed in contact with a receptor layer which is an undoped adhesive in contact with an IR-ATR crystal. The IR-ATR crystal detects the presence of time-averaged diffuse from the donor layer into and through the receptor layer. Examples will be discussed of several different experiments that can be performed with this technique. Using a doped adhesive layer, diffusion coefficients have been determined for testosterone and terpinen-4-ol in an acrylic acid matrix-based adhesive. Diffusion studies of several adhesives has been determined using the experiment where a free liquid is used as the donor. Diffusion from a doped layer containing dispersed, as well as solubilized salve has also been performed with terpinen-4-ol to simultaneously determine solubility and diffusion coefficient of a solid solute. Finally diffusion from a doped layer of one adhesive to an undoped layer of a different adhesive can be used as a partition measurement. The parameters can be extracted from each of these experiments, as well as the limitations of such type of experiment will be discussed.

3:45 PM **NN4.5**

**PHASE SEPARATION IN POLY(PSEUDO AMINO ACID) - PEG BLENDS AND COPOLYMERS.** M Libern, Stevens Institute of Technology, Hoboken, NJ; M Jaffe, Medical Device Concept Laboratory, Newark, NJ; J. Kohn, Rutgers University, Piscataway, NJ.

The hydrophilic properties of resorbable polymers for drug-delivery and other biomaterials applications are often controlled by combining poly(ethylene glycol) (PEG) with a more hydrophobic polymer phase. Relatively little is known about the local morphology and nature of phase separation in such PEG-modified systems, however. This research studies the development of phase-separated morphology in blends and random-multi-block copolymers of a tyrosine-based poly(pseudo amino acid) [poly(DTE carbonate)] and PEG 1000. This system exhibits attractive biocompatibility, strength and modulus, and resorption behavior which can be controlled by main-chain and copolymer main chain moieties. The samples were studied at high spatial resolution by transmission electron microscopy (TEM) using solvent-cast thin films. The various films display qualitatively different phase-separation behavior with morphological features having characteristic length scales ranging from 1 to 10 mm. These length scales are comparable to those characteristic of proteins and of cells and the nature of phase separation can be anticipated to influence both protein and cell adhesion phenomena. Co-continuous morphologies may be possible in blends of appropriate composition and using various processing strategies. For high-PEG concentrations, cryo-electron microscopy shows that these systems can form water soluble micelles with characteristic length scales of order 50 nm depending on polymer molecular weight.

3:45 PM **NN4.6**

**BIOMOLECULAR MATERIALS CHARACTERIZATION USING STATIC AND DYNAMIC LASER LIGHT SCATTERING DETECTION TECHNOLOGIES.** John P. Hellrich, Life Science Group, Precision Detectors, Inc., Franklin, MA.

Rugged characterization methods for new therapeutic and diagnostic biomaterials [proteins, antibodies and polymeric formulations] is a fundamental task for the successful submission of data for regulatory approval and proper quality control documentation. A key component of this data set is the determination of molecular weight and/or molecular weight distribution or aggregation state. Most bio-macromolecules can aggregate as a function of temperature, pH, ionic strength and concentration. Even small amounts of aggregation (dimer, trimer, etc.) can significantly affect the intended function as an effective therapeutic or diagnostic agent. Monitoring these understandings is an important aspect of process development and quality control requirements.

Laser light scattering (LLS) detectors have been used for over a decade to determine the molecular weight characteristics of industrial polymers. Recent innovations in modern high speed electronic components such as high performance diode lasers, high-speed digital signal processors and modern monochrome photodiode detectors has lead to the evolution of a new combined static and dynamic laser light scattering detector. This detector has a 10 L/s flow cell design and is capable of characterizing both molecular weight and size for biomolecules when coupled to modern HPLC/SEC instruments. This detector and associated software provides: absolute molecular weight data for each eluting component in the range of 1 kD to 5 million daltons and hydrodynamic radius (R_h) measurements for biomolecules in the range of 1 nm to 10 nm. This paper will outline the design and applications of this unique detection system for "well-characterized" biomolecules and their controlled release formulations.

**5:45 PM **NN4.7**

**CHARACTERIZATION AND BIOPATIBILITY STUDIES OF LAYER-BY-LAYER SELF-ASSEMBLED HAMIC ACID/P** 3 FILMS. Izabela Galasik, Fotios Papamatthopoulou, Dept. of Chemistry, Polymer Sci Program, Nanomaterials Optoelectronics Lab, Inc. of Missouri. St. Louis University, St. Louis, MO; Christopher Hickey, Ms. Mousay, Ctr for Biomaterials & Surgical Research Center, Univ of Connecticut Health Center, Farmington, CT.
A stable, soft, semipermeable and non-inflammatory membrane is a prerequisite for the development of an implantable glucose biosensor for continuous pain free monitoring of glucose levels in vivo. Humic acids have been reported to have therapeutically relevant in vivo characteristics such as anti-oxidative and anti-inflammatory. This encouraged us to test in vivo biocompatibility of Humic acid based multilayered films as a potential membrane material for the implantable glucose sensors. Humic Acids (HA) are naturally occurring biopolymers found in soil, sediments, waters and some plants like pine needle samples. Electron spin resonance (ESR) and layer self-assembly technique of HA with oppositely charged ferric ions was utilized to grow films, which could potentially be used as the outer semi-permeable protective layer for the glucose sensor. The gross characteristics of these assemblies exhibits strong dependence on the pH and the ion strength of HA solution and can be correlated with the degree of ionization of carboxyl groups and the neutralization induced by ESR analysis. Quantum chemical calculations of the solubility and ellipticities studies have shown repeatable, stepwise increase in mass and in film thickness during the self-assembly. Importantly these films exhibit reversible swelling in water and have a shear modulus of about 50 GPa which implies stability on implantation. The biocompatibility of these films were studied by implanting HA/Fe\textsuperscript{3+} coated siliastic tubing in rats and comparing the tissue response to a medical grade siliastic tubing under the same conditions. The tissue response of these films compares favorably with the siliastic tubing after 4 weeks of implantation.

4:00 PM NN4.8

A NOVEL POLYETHYLENE DEPOT DEVICE FOR THE STUDY OF PLGA NANOSPHERES IN VIVO. Maryellen Sandler, Joshua H. Harris, Edith Markowitz, Brown University, Dept of Molecular Pharmacology, Physiology, and Biotechnology, Providence, RI.

Polymer nanospheres are difficult to characterize in vivo due to their tendency to degrade, migrate, and be endocytosed. A novel polyethylene mesh device which contains nanospheres in vivo allowed for retrieval of degraded products from rats. Passage through the body, PLGA in nanospheres were implanted intramuscularly, subcutaneously, and intraperitoneally for 3 days, 1, 2, or 4 weeks. Explants were photographed, analyzed by GPC, and measured for mass loss. Devices tested in vitro were compared to naked nanospheres to determine device effect on degradation rates. In vitro, capped and naked nanospheres exhibited very similar degradation profiles, indicating no interference by the device itself. Devices implanted in vivo behaved differently from those tested in vitro for the first 2 weeks, after which in vivo and in vitro results converged. In vitro, MW decreased immediately to 51.1% and 28.67% of the original value by 72 hours and 1 week, respectively. In vivo, the decrease in MW lagged initially, with no change from the original value at 72 hours for subcutaneous and intraperitoneal implants, and a decrease to 61.9% and 81.9% for those implanted 1 week. Conversely, simple samples subcutaneously and intraperitoneally began to lose mass immediately, dropping to 76.9% and 75.5% of the mass by 1 week, whereas those tested in vitro had only decreased to 93.00% and did not begin to lose mass appreciably until after 1 week. Intramuscular implants behaved more like in vitro samples decreasing in MW immediately (79.2% and 72.10% by 3 days and 1 week) and lagging in mass loss (89.50% and 80.00% by 3 days and 1 week). These results suggest that mass loss, which is usually preceded by and dependent on MW loss in vitro, may initially be directly due to enzymatic, rather than hydrolytic, degradation subcutaneously and intraperitoneally. Intramuscular implants may undergo a different mechanism of degradation.

4:15 PM NN4.9

ADHESION OF PRESSURE SENSITIVE ADHESIVES WITH APPLICATIONS IN TRANSDERMAL DRUG DELIVERY. Marc B. Taub and Reinhold H. Dauskardt, Stanford University, Department of Materials Science and Engineering, Stanford, CA.

The development and implementation of successful transdermal devices for drug delivery requires an understanding of the adhesion occurring between the device and the soft dermal layer. The trend towards increasingly complex and novel patch designs further necessitates the development of a systematic approach to quantify this adhesion. Pressure sensitive adhesives (PSAs) are used as the adhesive due to their desirable properties of good initial and long-term adhesion, clean removability, and skin and drug compatibility. In addition, their viscoelastic properties are necessary prerequisites to be converted to soft tissue. However, the adhesion of PSAs is not well understood with almost no reproducible test methods or quantitative adhesion data. This study utilizes a mechanics approach to quantify the adhesive properties of representative adhesives for transdermal drug administration. An investigation of PSAs is comprised by cavitation in the PSA and the formation of an extensive cohesive zone containing the debond tip. The presence of such a large-scale bridging

provides significant energy dissipation and increased resistance to delamination. The strain energy release rate (G) during debonding of a transverse-beam sample, containing cavitation in the PSA, was utilized to quantify the adhesion of the PSA. The analysis accounts for both the work of adhesion as well as the viscoelastic constitutive behavior of the soft adhesive layer. Effects of adhesive layer thickness, strain rate, and physiological environment, and permeation-enhancement additions will be discussed.

4:30 PM NN4.10

BIOENGINEERING 3D NANOSTRUCTURES CHARACTERIZATION. Aleksandra B. Bezdudna, St. Petersburg State Technical University, St. Petersburg, RUSSIA.

Static and dynamic light scattering can provide further progress in on-line control of complex 3D dispersive systems such as liposomes carrying various substances (enzymes, viruses, etc.), blood substitutes and other bioengineering structures. They are also compatible with the nondestructive analysis of dispersive systems by other optical methods: refractometry, absorption and fluorescence. Our research has investigated different dispersive systems: liposomes, blood substitutes, proteins, nucleoglycans, viruses, lipoglycans, lip emulsions, etc. and mixtures - liposomes and viruses, blood substitutes with blood serum, etc. by static light scattering (integral and differential, unpolarized and polarized) and dynamic light scattering. For the solution of inverse physical problem of static light scattering we used the fitting method with approximation of particles as homogeneous spheres, core-shell structured spheres, oblate and prolate ellipsoids of revolution and regulation procedure for inverse problem of dynamic light scattering have been applied. By optical methods it is possible to determine parameters of dispersive systems state (mean equivalent diameter and number of particles, mean refractive index and mass of dispersive phase, number and mass distributions) and parameters of particles structure form and thickness of shell.

4:45 PM NN4.11

THERMO-MECHANICAL PROPERTIES OF GELS: STATIC AND DYNAMIC MEASUREMENTS. M. Naci ficin, Burak Emre, Faculty of Engineering and Natural Sciences, Sabanci University, Orhan, Istanbul, TURKEY; Selma Durmus, Oguz Okay, TUBITAK Marmara Research Center, Kocaeli, TURKEY.

Highly swollen gels used in drug delivery technology and related areas are strongly controlled by their thermo-mechanical properties. Among these is the elastic modulus of the gel as a semi-open system, where the gel moves in and out depending on the state of stress and environmental thermodynamic conditions. In the present study, elastic modulus of cross-linked swollen poly(acrylamide) gels and films are studied by monitoring deformations under stress, using an optical microscope. The gels are prepared by suspension polymerization. Stress relaxation in beads of about 1-2 mm in diameter is studied by uniminiically compressing a bead between two walls and characterizing their instantaneous modulus as a function of time. A simple constitutive equation is proposed that relates the amount of solvent in a compressed gel to time, stress and thermodynamic and structural variables.

SESSION N5 POSTER SESSION

BIOMATERIALS FOR DRUG DELIVERY

Chair: Edith Markowitz

Tuesday Evening, November 28, 2000

4:00 PM

Exhibition Hall D (Hynes)

N5-1

MORPHOLOGY AND RELEASE PROFILE OF ACTIVELY LOADED POLYHYDROXYALKANOATE MICROSPHERES. Teresa Eligio, Ruben Sanchez, Polymer Section, Advanced Material Laboratory, North Fluminense State University, UENF, Campus, R.J., BRAZIL.

The poly-3-hydroxyalkanoates (PHAs) are biocompatible and biodegradable polymers family suitable for biomedical purposes. In this work are presented a preliminary study to establish a morphologic and release profile difference between two membrane poly-3-hydroxybutyrate/PHB, a high crystallinity polymer, and the poly-3-hydroxyoctanoate, PHO, amorphous material in order to encapsulate two different loaded: a low molecular weight and relative high molecular weight drugs, both hydrophilic materials. Two kinds of polymeric devices were obtained: reservoirs (capsules) and monolithic (matrix) produced by different techniques; oil in water emulsion (-o-w), water-oil-water double emulsion (-w-o-w) and spray dryer. The external and internal microparticles morphology studied by Scanning Electron Microscopy (SEM) and Transmission Electronic Microscopy (TEM) techniques showed differences in the internal distribution of the drug on the microparticles associated to encapsulation techniques. The external texture, independent of preparation techniques, indicates
a rough surface morphology, sphericity and diameters ranging between 5.10 mm. The porosity and tortuosity of the polymeric devices are good characteristics in general, for the emulsion techniques the release pattern is zero or first order and for the spier drier techniques the Higuchi’s ‘n’ dependence were observed.

NN3.2 A NOVEL CARBOXYLIC CARBOHYDRATE-BASED LIPID FOR GENE DELIVERY. Keenan S. Sajadi, Geoffrey S. Hird, Mark W. Grinstaff, Duke Univ, Dept of Chemistry, Durham, NC.

Cationic lipid based gene delivery systems such as DOTMA (N,N,N',N'-tetradecyl-N,N',N'-trimethylammonium chloride)/DOPE (dioctadecylphosphatidylethanolamine) micelles have been used for both in vivo and in vitro transfection of nucleic acids. The basic components of a cationic lipid are the hydrophobic lipid group that aids in interactions with the cell membrane, the positively charged lipid group with biologically relevant phosphatidylcholine and a linker group between the two which is important for both biodegradability and chemical stability of the compound. Currently there is an intensive research effort in optimizing the transfection efficiency by altering the cationic head group, the hydrophobic lipid group, and the linker. We have synthesized and characterized a novel cationic lipid containing ribose in the biocompatible and biodegradable linker (1-methyl-2,3-hexanediyl-5-ribo-5-lactone). The ability of these novel molecules to transfect DNA in vitro is underway.

NN3.3 A QUANTITATIVE TECHNIQUE FOR DETERMINING THE EXTENT OF POLYMER UPTAKE. Chris Thomas, Edith Mathiozieta, Brown University, Department of Molecular Pharmacology, Physiology, and Biotechnology, Providence, RI.

Microspheres of varying size cross the mucosal lining of the small intestine and enter systemic and lymphatic circulation within less than an hour. Although the exact mechanism has yet to be elucidated, it has been speculated that uptake can occur via the gut-associated lymphoid tissue (GALT), across the apical membrane of absorptive epithelium, and through paracellular routes. Previous work has concentrated on histological analysis of tissue including confocal microscopy and TEM, however the results have served primarily as qualitative characterization. In this study, biodegradable polymers, including PLLA, PAA, and PCL were blended with a polystyrene-linked fluorescein dye into particles ranging from 200 nm to 5 microns in diameter and incubated in rabbit jejenum for 1 hour. Following tissue excision and fixation for histology, tissue was vigorously rinsed to remove particles on the surface and aliquoted for fluorescence analysis. This tissue was subsequently obtained to obtain dry weights, incubated in 8% KOH for 24 hours at 60°C, and put through a series of microcentrifugal separation techniques at various molecular weight membrane cutoffs to obtain a layer of polystyrene-linked dye. KOH digests the tissue components along with the polystyrene and polyester microspheres used in this study, hence the final component in the extraction includes only the polystyrene and fluorescent dye which is easily quantified without background interference from cellular and polyelectrolyte elements. This material is resuspended in aqueous solution and fluorometric analysis is used comparing the samples to standards prepared from stock beads in aqueous suspension. This method can be used to quantitatively provide the loading of dye linked to the fluorescein polystyrene beads, which are uniformly labeled, and was used to validate the results of confocal experiments comparing the aforementioned biodegradable polymers.

NN5.4 HIGH-PRESSURE INFLUENCED LIQUID CRYSTAL PHASES MAINTAINED IN NON-MESOGENIC POLYMERS AT AMBIENT TEMPERATURE AND PRESSURE. Edwin Edwards, Edith Mathiozieta, Brown University, Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI.

lipids (no long-range order), and crystals with long-range three-dimensional order. These phase called mesophases, are created by unique rigid molecular structures called mesogens, which are generally rod-shaped disk like. These mesogens can be individual low molecular weight molecules or part of repeats in a polymer chain (polymeric liquid crystals). The self-assembly behavior is based on subjecting the material to a combination of temperature and pressure conditions and appears to be maintained at ambient conditions for extended periods of time. However, when the material is reheat beyond a critical temperature the phase is removed and the material returns to its native state. These novel liquid crystal materials could be used as safer hip replacement polymers or in drug delivery devices.

NN5.5 SEGMENTED POLYURETHANES FOR CONTROLLED DRUG DELIVERY. Erkesh O. Buyrakov, Rimat M. Isakov, Balint A. Zlabarsov, Institute for Chemical Sciences, Almory, KAZAKHSTAN.

The segmented polyurethanes with different soft and hard segments have been studied as drug carriers for controlled delivery applications. Biodegradable polyurethanes were obtained by means of a two step procedure using different polyisocyanates, diisocyanates and branching agents. Drugs such as antibiotics and antimicrobial agents can be incorporated into the structure of the polyurethanes or as preadsorbed on the surface. The successful application of polyurethane Drug Delivery Systems for the treatment of tuberculosis, esophagus burn, gastric and some dental diseases was shown.

NN5.6 Abstract Withdrawn.

NN5.7 A POLY CARBONATE OF GLYCEROL. William C. Ray III and Mark W. Grinstaff, Duke Univ, Depts of Chemistry and Ophthalmology, Durham, NC.

New biopolymers are needed to meet the current challenges in orthopaedics, dentistry, cardiovascular surgery, and ophthalmology. Polycarbonates are one class of polymer being investigated, and polymers of 5-hydroxyethyl-1,3-dioxan-2-one are known. However, no polymers of its 6-membered cyclic isomer, 5-hydroxy-1,3-dioxan-2-one, have been made. The cyclic carbonate 6-benzyl-1,3-dioxan-2-one has been synthesized from glycerol and polymerized. Following cleavage of the benzyl group by catalytic hydrolysis, the resulting polymer is a novel polycarbonate of glycerol. The benzyl protected and free hydroxy polymers have been characterized by GPC, NMR, IR, DSC, and contact angle. This glycerol polycarbonate is a potentially useful biomaterial since it is expected to hydrolyze in vivo to glycerol and carbon dioxide. The pendant hydroxyl groups of the (5-hydroxy-1,3-dioxan-2-one) also provide a site for post-polymerization modification (i.e. attachment of additional functional molecules).

NN5.8 BIODENDRIMERS FOR DRUG DELIVERY. Michael Carnahan, Mark W. Grinstaff, Duke Univ, Dept of Chemistry and Ophthalmology, Durham, NC.

Dendrimers are monodisperse spherical macromolecules in which all bonds converge to a focal point or core. In contrast to linear polymers, dendrimers possess a large number of controllable terminal functionalities and exhibit low viscosities, high solubility, miscibility, and unique properties. One class of dendrimers is the class of hydrophilic aliphatic polystyrene dendrimers containing glyceral and succinimide acid. These dendrimers contain a teta-functional core, synthesized from one succinic acid and two glycerol units, and an AB2 monomer, synthesized from one succinic acid and one glycerol unit. To date, the G1 biodendrimer, [G1]-P(2Glu), has been synthesized and fully characterized by 1H-NMR, 13C-NMR, IR, MS, and elemental analysis. Further generations of this biodendrimer will be synthesized and biocompatibility will be determined through generation. Drug encapsulation studies are ongoing to assess the efficiency of this novel biocompatible macromolecule for drug delivery applications.

NN5.9 CARBOHYDRASES: A NEW CLASS OF POTENTIAL DRUG DELIVERY VESICLES. Geoffrey S. Hird, Duke University, Dept of Chemistry, Durham, NC; Thomas J. McIntosh, Duke University Medical Center, Dept of Cell Biology, Durham, NC; Mark W. Grinstaff, Duke University, Dept of Chemistry, Durham, NC.

Spherical self-closed structures called liposomes self-assemble from conventional glycerol based phospholipids, such as phosphatidylcholines. Naturally occurring phosphoglycerides are composed of a glycerol backbone, two hydrophobic hydrocarbon chains and a polar head group, that is often a choline. Current research in this field focuses on altering the head group and hydrophobic tails to tailor the desired physical properties of liposomes for drug delivery. We are
manipulating the backbone as a new means to optimize the chemical and physical properties for biomedical applications and to assess supramolecular structure formation. Selecting ribose as the new backbone, we have termed these novel carbohydrate three-dimensional supramolecular structures "carbohydrosome". The ribose backbone analog of dimyristoylphosphatidyl choline (DLPC), 1-methoxy-2,3-dimyristoylphosphatidylcholine (DMPC) as well as the ribose backbone analog of dimyristoylphosphatidyl choline (DMPC), 1-methoxy-2,3-dimyristoylphosphatidylcholine (DMPC) were synthesized. The resulting carbohydrosomes were characterized by optical microscopy, utilizing differential scanning calorimetry (DSC) and X-ray diffraction. Mixtures of cholesterol and DLPC were extruded and 200 nm liposomes containing the water-soluble dye 5(6)-carboxyfluorescein were formed. The synthesis of DLPC, its ability to form stable supramolecular structures, and the ability to derive DLPC provides a unique opportunity to synthesize and engineer vesicles for specific biomedical applications.

**NN5.10**

**SYNTHESIS AND CHARACTERIZATION OF CORALLINE HYDROXYAPATITE - GELATIN COMPOSITE MICROSPHERES FOR ORTHOPAEDIC APPLICATIONS**

M. Sivakumar and K. Panduranga Rao, Biomaterials Laboratory, Central Leather Research Institute, Adyar, Chennai, INDIA.

Calcium phosphates in the form of hydroxyapatite (HA), have been widely used for bone implant material. These materials exhibit several problems of handling and fabrication, which can be overcome by mixing with a suitable binder. Recently, a great interest has been shown for the use of composites of HA with proteins such as fibrin, collagen, gelatin, chitosan and alginate, with inorganic powders, as bone fillers. Owing to their physiochemical and biological properties, calcium phosphates have recently been considered as a potential material for bone defect drug delivery systems. In this study, composite microspheres of coralline hydroxyapatite (CHA) granules with gelatin, prepared by dispersion polymerization technique, are reported. These composite microspheres were characterized by various techniques such as FT-IR, TGA, DSC. The particle size and size distribution of the composite microspheres was analyzed using particle size analyzer and the average size was found to be 16 microns. The optical micrographs clearly indicated that the microspheres are spherical and uniform in size. These CHA-gelatin composite microspheres were also loaded with antibiotic drug such as gentamycin and its in vitro drug release profiles in phosphate buffer were evaluated.

**SESSION NN5: NOVEL APPROACHES TO DRUG DELIVERY SYSTEMS**

Chair: Edith Mathiews

Wednesday Morning, November 29, 2000

Republic A (Sheraton)

**8:30 AM #NN5.1**

**DEVELOPMENT OF BIODEGRADABLE POLILACTATE MICROSPHERE (PACLIERTM) FOR SITE SPECIFIC CANCER THERAPY**

Wenbin Deng, Zhong Zaho, Stephen Dordunou, Guilford Pharmaceuticals Inc, Baltimore, MD.

The advances in the field of controlled drug delivery have been continually fueled by the desire to improve the therapeutic effects of existing pharmaceutical substances (EAS). The key to achieve the desired improvement is to deliver the drug in an efficacious concentration directly to the site of action for a prolonged period of time so the pharmacological effects are maximized while the side effects are minimized for the drug. Biodegradable polymers such as PLGA are frequently used to engineer such controlled drug delivery systems. For certain highly insoluble chemotherapeutical agents such as paclitaxel the desired efficacious results are achieved by maintaining a continuous supply of the drug from the degrading polymer matrix. We have developed a new synthetic biodegradable polylactide [polylactate] for such drug delivery applications. Polylactate comprises mainly of lactic acid oligomers which are separated by ethyl phosphaester bonds. One major potential advantage of polylactate is that it is minimally compatible with living tissues, which is approved by FDA and has an excellent safety record, while the interpolymer ethyl phosphaester groups make the final polymer more hydrophilic and degrade more evenly. The final polymer polylactate has been proven biocompatible in various animal models. The overall degradation rate of the polymer may be further modified by varying the ratio between the lactide and the phosphaester segments. The relatively rapid degradation of the polymer matrix is desired for applications such as local chemotherapy combined with repeated dosing of the drug is critical to the treatment. The development of a targeted cancer therapy using polylactate PACLIERTM microspheres will be highlighted as an example in this presentation. PACLIERTM microspheres are polylactate microspheres containing 1% paclitaxel. PACLIERTM microspheres has been demonstrated to release paclitaxel continuously for over three months in vivo. The synthesis, in vitro and in vivo degradation, and the degradation mechanism will be discussed. The preclinical results including the efficacy studies of PACLIERTM microspheres in various preclinical animal cancer models such as ovarian cancer and non-small cell lung cancer will also be presented.

**9:00 AM NN6.2**

**A NANOTECHNOLOGICAL APPROACH TO OSMOTIC CONTROLLED LOCAL DRUG DELIVERY DEVICES**

Thibaut Szwarczowski, Wulff Fischer, Anja Fischer, Guenter Schmid, Univ of Essen, Essen, GERMANY.

Local drug delivery is up to now based on two general approaches. On the one hand a drug containing polymeric material is (chemically in solution) dissolved in contact with body liquids. On the other hand a mechanically operating device made of a reservoir (and a counterbalance) is implanted in the body to deliver the drug over time. In both cases the advantage of the local delivered drugs are less side effects and low dosage needed for therapy. The disadvantage of the chemically driven polymeric devices is the low amount of drug which can be delivered and problems related to the delivery kinetics which is preferred to be of zero order with respect to time. For the built in devices their size is very often a problem. Here we report on a new technology which is based on chemically modified nanoporous membranes which enables us to vary the delivery rate easily. The basic material is a nanoporous ceramic membrane which is produced by an electrochemically oxidation process. The pore size of those membranes can be varied between 20 nm and 250 nm while the thickness can be as high as 1 mm. Those ceramic layers are then inserted in order to change the surface polarity or to anchor specific moieties to the surface. This leads to a change in the interaction between the pore structure and the delivered substance. Both the pore size and the surface chemistry can be tuned to adjust the delivery rate to the drug and the therapy. We report on results for the delivery of insulin-loaded Oestradiol which is a Somatostatin analogue used in cancer therapy. This oligopeptide consists of 8 amino acids linked by a disulfide bridge. For this rather small molecule we can show large variations of the delivery rate. Changing the pore size from 50 nm to 80 nm leads to strong increase in the rate. In addition if all 4 chains of different length are chemically bound to the pore surface the delivery rate can be reduced. In all cases the zero order dependency of the delivery rate is observed. Because the variable size those membranes can be produced we believe that implants can be built as small as possible. This opens up new ways for local drug delivery therapy like minimal invasive therapy of tumors.

**9:15 AM NN6.3**

**DIFFUSION OF DENDRITIC POLYMERS THROUGH CONCENTRATED POLYMER SOLUTIONS**

James L. Thomas, Columbia University, Departments of Chemical and Biomedical Engineering, NY.

Diffusional dynamics of polymers are very sensitive to polymer architecture. For example, Wood and Lodge have shown that "arm restriction" can be an entropy-rate limiting step for diffusion of small polymers. Unusual diffusional dynamics can result if the controlled release of therapeutic compounds from gels or concentrated polymer solutions with potentially novel, useful kinetics. Towards this end, we have been studying the diffusion of model dendrimeric polymers in concentrated solutions of "nuclear" polymers, using in-situ laser scanning photobleaching and reactivation. The self-similar polymidoamine dendrimers grow exponentially in size with generation (number of synthetic cycles). High generation dendrimers (> 6) are rather compact and their diffusion behavior depends only on the ratio of their hydrodynamic size to the matrix mesh size. Lower generation dendrimers are capable of partial entanglement with the matrix itself; the consequences of this entanglement will be presented.

**9:30 AM NN6.4**

**ELECTROKINETICALLY BUILT MICRO HEAD AND CELL ARRAYS FOR DRUG DISCOVERY PRACTICE**

Maimunah Ozturk, Brian Esner, Electrical and Computer Engineering Department, University of California at San Diego, San Diego, CA; Sangeet A. Bhatn, Bioengineering Department, University of California at San Diego, San Diego, CA.

We have developed a novel electrochemical system for field assisted, fluidic assembly of objects on a microfabricated silicon substrate by means of electrical and optical addressing. The principle of our technique is the movement of a charged species in solution to oppositely charged electrodes, as seen commonly in electrophoresis. Here, charged species such as beads and cells are moved electrokinetically through an aqueous solution towards a charged electrode. Microstreaming of the electrode allows localization of charged species which has been previously utilized extensively for localizing DNA. Here we first demonstrate the localization of negatively charged polystyrene
Wang, University of Strathclyde, Dept of Pharmaceutical Sciences, Glasgow, UNITED KINGDOM; Lawrence Tetley, University of Glasgow, Institute of Biomedical and Life Sciences, Glasgow, UNITED KINGDOM.

Nanoparticles and polymeric vesicles for drug delivery and other industrial applications have been prepared by simply sonicing specially designed poly-L-lysine graft copolymer amphiphiles in aqueous media. Amphiphiles which have a poly-L-lysine backbone and varied levels of both hydrophilic methacryloyl glycol [Mr ~2x10^4] and hydrophobic cholesterol [Mr ~4x10^4] were prepared from 2 different molecular weight poly-L-lysine hydrobromide samples (~4,000 and ~20,000 respectively). These amphiphilic polymers [PLAs] were characterised using light scattering, 1H NMR and mmsy for the level of free amino groups. Steric factors appear to limit the final level of lysine group modification that can be achieved and even an excess amount of grafting reagents still resulted in the protection of polymers (71% - 72% mole %) and all terminal amino groups remain unsubstituted. Probe sonication of an aqueous dispersion of PLP samples resulted in the production of stable nanoparticles (80 - 170nm in diameter) as imaged by electron microscopy. Nanoparticles were able to encapsulate the hydrophilic fluorescent FITC-dextran and encapsulation increased as the level of unretracted lysine terminal amino groups in PLP increased, indicating the presence of hydrophilic microdomains. Polymeric unilamellar vesicles (220 - 570 nm in diameter) imaged by electron microscopy were produced by probe sonication of PLP. cholesterol. Vesicle formation was possible over a narrow spectrum of polymer architecture and was favoured by a low molecular weight and a low level of hydrophobic substitution. A vesicle formation mechanism has been derived. The size of both the nanoparticles and the vesicles was directly influenced by the molecular weight of PLP. PLPs of molecular weight 32,000 - 48,000 and 80,000 - 140,000 resulted in nanoparticles of ~140 nm in diameter respectively and PLP of molecular weight 25,000 and 89,000 gave rise to polymeric vesicles of 252 nm and 570 nm in diameter respectively.

11:00 AM NGN.9 ENGINEERING LARGE MONODISPERSE UNILAMELLAR VESICLES WITH HIGH ENCAPSULATION YIELD. Sophie Parot, David A. Weitz, Harvard University, Dept. of Physics and DEAS, Cambridge, MA.

A vesicle is a membrane closed on itself to form a big that delimits two volumes of the same fluid: an inner volume, and an inner volume. The advantage of this structure is that the inner fluid can contain soluble components: ions, vitamins, proteins, and polymer like DNA which are then separated and protected from the outer fluid. The membrane is composed of a lipid bilayer and these structures are called liposomes. They have been extensively used for transdermal and injectable delivery of bioactive molecules. We have developed a novel emulsion technique which allows one to produce controlled monodisperse vesicles not only with lipids but also with food substrates, and polymer emulsions. In such systems we can define the size distribution from 200nm up to 2um, control the lipid composition of each layer of the bilayer independently and achieve an encapsulation yield close to 100%. This technique is based on a variation of an inverted technique that involves the formation of complex droplets of aqueous solution in an organic phase. We first prepare an inverted emulsion with the aqueous solution we want to encapsulate. This is emulsified in an organic continuous phase using surfactant like molecules to stabilize the emulsion. At this step, we can control the size and the emulsion as we can control the size of the emulsion and the encapsulation yield. To complete the bilayer we let the inverted emulsion droplets sediment across a surfactant layer at the oil/water interface. The droplets take with them the second lipid layer to complete the lipid bilayer.

11:15 AM NGN.10 PHASE COMPOSITION DETERMINATION IN PLA-PLGA DOUBLE WALLED MICROSPHERES. Nasheen Rahman, Edith Mathiowitz, Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI.

We have demonstrated the fabrication of double walled microspheres from a mixture of two polymers poly-(l-lactide) [PLLA] and poly-(L-lactide-co-glycolide) 50:50 [PLGA 50:50] resulting in a core of polymer A rich phase and a shell of polymer B rich phase. It is important to obtain a composition profile of these spheres so that we can evaluate the arrangement of the two phases and eventually manipulate these phases to design improved double walled systems. So far it has been a difficult task due to inherent problems with determining the composition of the spheres but with the current technique described in this paper some of the problems have been overcome. In addition PLLA and PLGA are chemically PLAs and it is not always easy to identify and separate the different peaks in characterization techniques such as the fourier transform infrared

9:45 AM NGN.5 VITAMIN E TPGS ENCAPSULATED IN MESOPOROUS ALUMINA: A NOVEL ORAL DRUG DELIVERY SYSTEM. Ying Ma, Kenneth J. Balkus, Jr., University of Texas at Dallas, Department of Chemistry, Richardson, TX.

Vitamin E TPGS, a modified form of the natural source of vitamin E containing a hydrophilic PEG chain, has been successfully immobilized inside of a novel mesoporous alumina using a templating synthesis method. Free flowing powders were obtained, which are referred to as ALDAM1 (Dallas Amorphous Materials). These powders overcome the difficulty in directly handling and delivery of the sticky vitamin E TPGS. Upon exposure to simulated gastric fluid, the A503 host molecular sieve is dissolved while vitamin E TPGS is released. Through this synthesis method, as much as 0.6 of vitamin E TPGS can be immobilized into 1 gram of A503. Details of the synthesis and characterization of ALDAM1 will be presented. Preliminary results for using ALDAM1 for oral delivery of other drugs will be presented as well.

10:15 AM NGN.6 MICRO-TRIENAILS AND THERAPEUTIC ELEMENT DELIVERY FROM A BIODEGRADABLE SEMICONDUCTOR: MESOPOROUS SILICON. L.T. Carah, C.L. Reeves, P.J. Wright, T.I. Cox, Sensors and Electronics Division, DERA Malvern, UNITED KINGDOM.

The introduction of porosity at the nm scale into silicon renders the semiconductor bioactive and biodegradable [1]. We describe here one area of drug delivery which aims to exploit the bioavailability, purity and high temperature processing capability of porous silicon. Many elements of the periodic table (e.g. Se, Cr, Mn, Mo) are needed by the body at extremely low levels (‘trace elements’ or ‘micronutrients’) and yet deficiency effects are well documented. This is often simply due to diet inadequacy and because only a small and highly variable fraction of orally ingested microminerals are absorbed. Other elements (e.g. Li, Au, Ag) have widespread use clinically for therapeutic purposes. We have started to investigate the use of microporous silicon as a new drug delivery vehicle for elements such as gold which has recently been developed technique of core impregnation and high temperature anneal. By distributing the element within the Si skeleton itself we hope to eliminate the common ‘burst effect’ seen with porous silicon, and achieve controlled precise delivery over tunable timescales of months to years. [1] L.T. Carah Adv. Mater. 7,1033 (1995).

10:30 AM NGN.7 CYCLODEXTRIN POLYMERS FOR ABSORPTION AND RELEASE OF ORGANIC MOLECULES. DeQuan Li and Jason Han, Department of Chemistry and Materials Research Center, Washington State University, Pullman, WA.

Key requirements in designing nanostructured materials with abilities to absorb or release organic molecules include suitable nanostructures to dock target molecules, optimum molecular interactions, and triggering mechanisms to alter interaction strength. A class of enzymatic compounds, cycloexetrins, have received great attention as such candidates because they have hydrophilic cores suitable for inclusion of many organic molecules. Currently, we employ cycloexetrins and disaccharides to synthesize a class of polymers with nanostructured pores. The results are a class of materials that have nanoparticles with great affinity to organic molecules. Indeed, cycloexetrin-based polymers have such high affinity for organic molecules in an aqueous environment that they effectively scavenge even trace amount of organic molecules down to concentration levels of parts-per-billion. In this contribution, we will provide an account of our continuing efforts, especially the absorption/release of organic molecules using cycloexetrin-based nanostructured materials.

10:45 AM NGN.8 NANOAPARTICLES AND POLYMERIC VESICLES FROM NEW POLY-L-LYSINE BASED AMPHIPHILES. Jecma F. Uchebgu, Wei
spectroscopy. Therefore we had to resort to the differential scanning calorimetry to quantify the amounts of PLLA and PLGA 50:50 in our double walled spheres. The composition profiles of the microspheres were compared to compositions of phase separated polymer mixtures at different concentrations in an attempt to understand the thermodynamics behind the fabrication of double walled spheres from such polymer mixtures. In addition we wanted to determine the effects of drug incorporation on both the compositions and the arrangements of the different phases in the spheres. If phase arrangement and drug localization are indeed related in double walled spheres, we can try manipulating the phase arrangements to control the layer in which the drug is encapsulated. This would have a tremendous impact on the drug release profile using double walled spheres.

11:30 AM NN6.11
Abstract Withdrawn.

11:45 AM NN6.12
NEW POLYMER SYSTEMS WITH CONTROLLED RELEASE ACTION. Apostoles K. Rizos1, John Alifrangis1, Aristidis M. Tatsakis2, Manolis Tatsakis2, Michail Shilman3. 1University of Crete, Department of Chemistry, Heraklion, GREECE. 2University of Crete, The School of Health Science, Heraklion, GREECE. 3Mendelev University of Chemical Technology, Moscow, RUSSIA.

The last few decades have witnessed concerted efforts to enhance the effectiveness of drugs used in therapeutic, diagnostic and preventive medicine. Many of the problems associated with conventional drug therapy may be circumvented by the use of delivery systems which in a variety of ways will optimize drug action. The concept of targeted drug delivery was first aired early this century and entails the use of carrier systems to deliver drugs to where they are needed or facilitate their release there. In the present work we employed dynamic light scattering to obtain a comprehensive dynamical model of a series of polymeric derivatives that are able to release a bioactive compound at a certain rate. Our new biocompatible polymeric systems inhibit fungal growth and mycotoxin formation.