SYMPOSIUM NN
Biomaterials for Drug Delivery

November 27 – 29, 2000

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SESSION NN1: STIMULI-SENSITIVE POLYMERS AND PHASE BEHAVIOR RELATED TO DRUG DELIVERY - WHAT WE LEARNED WITH TRICYCLIC ANTIDEPRESSANTS. Edward W. Merrill, MT, Dept. of Chem. Engr., Cambridge, MA; Cynthia Sung, Human Genome Sciences, Bethesda, MD; Edward Ellis, Vitta Scientific, Inc., Andover, MA.

A copolymer of dimethyl siloxane and glyceroxipropylmethoxiloxane 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/s 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 tricyclic antidepressants were determined as functions 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 hydrophilic the TCA, the higher is its partition into a PEG-PSX network; (3) the higher the PSX fraction in a 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 lipid-soluble drugs, such as the polyvalent anti-inflammatory and psychopharmaceuticals. With an equilibrium water content of about 50%, a PEG-PSX network readily conforms to the eye.

9:00 AM *NN1.2 NEW COMPLEXATION-SENSITIVE HYDROGELS FOR ORAL PROTEIN DELIVERY. Nicholas A. Pappas, Madeline Torres-Lugo, Aaron C. Fox, Daghtje Robinson, Cristina Donini, Marcos Garcia, Purdue University, School of Chemical Engineering, West Lafayette, IN.

New complexation copolymer networks of poly(methacrylic 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 amine groups 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 biactive agent in the intestine is preferable. 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 cytocompatiblity 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 significant cytotoxic effect at the dose of 10 mg/mL. On the other hand, the transmembraneous electrical resistance of the Caco-2 cells 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 permeation route for the protein drugs.

9:30 AM *NN1.3 DESIGN OF pH-SENSITIVE POLYMERS TO ENHANCE INTRACELLULAR TARGETING IN MEVER PEPTIDES, PROTEINS, ODN'S AND DNA. Allen Hoffman, Niren Murthy, Chuck Cheung, Chantal Leduc, Sue Skoglund, University of Washington, Bioengineering Department, Seattle, WA; Oliver Press, Nelson Pasto, 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 endocyted drugs from the endosomal compartments into the cytoplasam is therefore an important goal. The pH of an endosome is lower than that of the cytosol by 1.2-2.0 pH units, depending on the stage of endosomal development. This pH gradient is a key factor in the design of monovalent-dissociative polymers which could enhance the endosomal release of drugs. Such polymers should disrupt lipid bilayer membranes at pH 6.5 and below, but should not be non-dissociative at pH 7.4. In addition, they should be capable of carrying targeting moieties to recognize the therapeutics to specific cells. We present here different approaches to the design of pH-sensitive polymers and present the new polymeric compositions that we have developed to deliver gene and protein therapeutics.

10:00 AM *NN1.4 SYNTHESIS AND CHARACTERIZATION OF ENVIRONMENTS-RESPONSIVE CO-QUEL-HYDROGEL, NANOPARTICLES. 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-isopropyllacrylamide 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 transition reflect the degree to which the two materials interact and thereby modulate the responsiveness 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 *NN1.5 PHOTODEDUCTED RELEASE OF STERICALLY STABILIZED LIPOSOMES CONTENTS. Anja Mueller, Brice B. Boudrant, 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 intracellular site of the tumor site. During circulation PEG-liposomes must not release the drug. After accumulation of the liposomes in the extracellular site 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. Boudrant and O'Brien (J. Am. Chem. Soc. 1998, 120, 13545-13549) showed that UV induced crosslinking of lipids could destabilize certain PEG-liposomes. With an appropriate choice of bilayer components the release of the PEG-liposomes contents is efficient and fast. Visible light would be more useful, though, since it is less toxic and penetrates deeper than UV light. Here we show that photochemically induced destabilization of PEG-liposomes can be sensitized to visible light by the incorporation of a cyanine dye into the bilayer wall of PEG-liposomes. Two-photon dyes which absorb at longer wavelengths are also being examined as sensitizers for PEG-liposome destabilization.

11:00 AM *NN1.6 ELASIN-LIKE POLYPEPTIDES AS THERMALLY TARGETED DRUG CARRIERS. Dan Meyer, Ashutosh Chilkoti, Duke Univ, Dept of Biomedical Engineering, Durham, NC; Michael Zalusky, Duke Univ Medical Center, Dept of Radiology, Durham, NC.

Elasmin-like polypeptides (ELPs) are polymers of the pentapeptide sequence Val-Pro-Gln-Glu-Xaa-Gly (where the “guest 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, when 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 50:50 ELP with a Tt of 48°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 carriers that were injected...
into mice with implanted tumors (human glioma D553MG). We observed a two-fold increase in ELP accumulation versus un.injected animals. The same treatment was repeated in a second group of mice. Mice were injected with ELP in a temperature-controlled water bath. Statistical analysis showed that the observed enhancement is largely driven by the time dependence of the ELP activity in vivo. Our results suggest that ELP therapy may be a promising approach for cancer treatment.}

**SESSION NN2: PROTEIN AND PEPTIDE DELIVERY**

**Chair:** Mark A. Tracy

**Monday Afternoon, November 27, 2000**

**Republic A (Sheraton)**

**1:30 PM NN2.1 CONTROLLED RELEASE OF PROTEINS FROM EXTRUDED RODS.** Jorge Heller, John Barr, Steve Y. Ng, Hui-Rong Shen, Advanced Polymer Systems, Redwood City, CA; Alexandra Retten-Meinholt, Robert Gurny, University of Geneva, School of Pharmacy, Geneva, SWITZERLAND.

The need to deliver delivery systems for peptides and proteins where full protein activity is preserved is still not well recognized. However, the development of such systems is fraught with difficulties, and dominant among these is the inability 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 maintain 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 microcrystalline protein and finely powdered polymer. This method avoids exposure of the protein to organic solvents and especially to an organic solvent/water interface. However, as 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 short induction period before the erosion phase begins and we will describe methods that decrease, or eliminate this induction period.

**2:00 PM NN2.2 LIPID COMPOSITE MATERIALS FOR NANOPARTICLES DELIVERY SYSTEMS.** Pierandrea Esposito, Istituto di Ricercan C. Serono - Drug Delivery System, Collegio Ginoss, Turin, ITALY.

The use of lipids as materials for matrix type, nanoparticles carriers manufacturing has gained considerable interest in the pharmaceutical field. They are in general GRAS materials of low or medium cost, low toxicity, and high biocompatibility. Lipids occur in a variety of compositions which influence their biological properties and biopharmaceutical properties. Lipid blends, prepared in controlled conditions, can further expand the potential of application of such materials to nanoparticles formulation development. Such blends, defined compositions, can originate from different surface properties, core properties, 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 such as fatty acids, phospholipids, triglycerides, PEG-ylated glycerides can be used. The type of lipids which are used are determined by the angle method: surface free energy, surface polarity or surface fractions of components were used, according to Gibbs or Cassie-Baxter methods. Phase diagrams of significant blends were constructed by DSC analysis, supported by hot stage microscopy observations. Lipids were characterized by photometric spectroscopy methods and XRD analysis. The differences in the nanoparticles morphology were also studied by means of polarized light spectroscopy. TEM analysis evidenced the differences in nanoparticles morphology.
oral absorption of a peptide drug can be favoured by incorporating it into lipid nanoparticles. Furthermore, the modification of the surface properties of liposomes 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 Pollacio 12, 34148 Trieste, Italy.

2:30 PM *NN2.3
BIODEGRADABLE POLYMERS, AND ENVIRONMENTALLY SENSITIVE HYDROGELS FOR THE CONTROLLED DELIVERY AND SOLUBILIZATION 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 (bGH, pGH), and vaccine (hemagglutinin 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 reconstructive medicine. It relies upon devices and therapies which utilize living cells as therapeutic reagents and combine living cells with synthetic or naturally-occurring biomaterials. Applications may involve replacement or regeneration of structural body components (e.g., skin, cartilage, bone) or substitution of the function of a metabolic organ with a biologic equivalent (e.g., pancreas, liver). Biomaterials for tissue engineering and regenerative medicine may be hydrophilic or hydrophobic, permanent or temporary, bioactive or inert. Although numerous candidates have been proposed and investigated, those applications which have reached the clinic rely upon a 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 Abramson, Amit Ayer, Edith Mathiowitz, 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, entering portal 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) invivo 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) (PFS) microspheres (Mw=1-5μm) were prepared by the Pin technique. Microspheres were loaded at various insulin loadings with or without micronsized insulin or regular insulin crystals. Rats (205±20g male, CD strain) were fasted overnight and allowed free access to water. The rats were anesthetized using an isoflurane gas chamber. Blood was collected via tail bleeding. After the initial blood was cold, a SQ injection with either ILMS or unencapsulated insulin suspended in 1.0ml of saline was administered. Blood was collected for up to nine hours. Plasma samples were analyzed for both glucose and insulin levels. The PFS microspheres loaded with 30% 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 PFS loaded with micronsized insulin at 2% loading, exhibited no glucose drop in glucose levels, but instead a slow steady release of insulin corresponding to a slow drop in glucose level for up to nine hours. The micronsized insulin facilitates efficient encapsulation within the microspheres, thus reducing the burst effect and establishing a sustained release system. We were successful in fabricating a sustained-release subcutaneous system that incrased the duration of insulin action beyond that of conventional insulin injections while reducing the negative large burst effect.

4:15 PM *NN2.6
USING A COMBINATORIAL LIBRARY OF DEGRADABLE POLYARYLATES TO OPTIMIZE PEPTIDE MATRIX INTERACTIONS IN DRUG DELIVERY SYSTEMS, Debbie M. Schachtner, Joshua Simon, Joanne Kehs, Rutgers University, Dept. of Chemistry, Piscataway, NJ; SmithKline Beecham Advanced Materials Design, LLC, Piscataway, NJ.

Delivery systems based on degradable polymeric matrices that can release high payloads of water-soluble peptides with reproducibly programmable delay times have been formulated using a combinatorially designed library of polyarylates in which the material properties of the polymers can be varied in a predictable systematic fashion. Tyrosine-derived polyarylates are alternating copolymers of a diphenyl and dioxindilid derivative linked by ester bonds. These polymers are readily processable, biocompatible and degrade in vivo. We have shown previously that high payloads of INTEGRILIN, a water-soluble cyclic heptapeptide (used clinically as an antithrombotic drug) can be incorporated into various polyarylates 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 polyarylates, a wide range of different release profiles were obtained, including delayed release and pulskate 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 polyarylate from the library, highly controlled systems were prepared that tripped the peptide within the matrix so that only a trace of peptide was released even after 77 days. In contrast, other members of the polyarylate 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 pulsate delivery system using combinations of different polyarylates.

4:45 PM NN2.7
PROTEIN RELEASE FROM MULTILAYERED POLYMER MICROSPHERES FABRICATED VIA SOLVENT REMOVAL, J. Godbee, D. Valezquez and E. Mathiowitz, 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 way to encapsulate proteins without exposure to an 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-actic (PGLA), and poly (fumaric-co-sebacic) (PFS) (PFS) were selected for these studies. These two polymers readily phase separate, which is a prerequisite for the one-step multi-layered fabrication method.

Methods: 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 PFS at varying concentrations (5%, 10%, 15%, and 20% w/w). 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 drawn them into microspheres. 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 three times as high of a burst at 15% and 28% 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% samples, at 3 minutes. Additionally, the release profiles of the 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%, depending on the desired release profile.

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SESSION N3: TISSUE AND GENE DELIVERY
Chair: Richard Korenney
Tuesday Morning, November 28, 2000
Republic A (Sheraton)

8:30 AM *N3.1
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 xenogeneic or syngeneic engineered cells. The cells are encapsulated in a matrix that can regulate in vitro the release of cell products.

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9:00 AM NN3.2
INCREASING GENE EXPRESSION LEVEL WITH ENGINEERED PEPTIDES FOR NON-VIRAL GENE TRANSFER TO NON.
DIVIDING ENDO THELIUM. Hauing Ma, Jingyin 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 found in 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 importation function of non-classical nuclear localization signal peptide, Mβ sequence of hNUP-A1 (38 amino acid) in confluent bovine aortic endothelial cells (BAEC).

9:15 AM NN3.3
THE MOLECULAR BASIS OF ENGINEERED IN VITRO HEPATOCYPINOSIS. Erin R. Orlich, Massachusetts General Hospital, Dept of Pathology, Boston, MA; Robert G. Green, Dept of Transplantation and Immunology, Faculty of Medicine, Kyoto University, Kyoto, JAPAN; Joseph W. Carlson, 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 3D photolithography printing technology to create a biodegradable polymer scaffold connected to the 3D perfusion culture. 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.

9:30 AM N3.4
NOVEL POLY(ETHYLENE GLYCOL)-CONJUGATED DEN DRIMER FOR BIOM I-COMPATIBLE, HIGH EFFICIENT, AND LOW COST DNA DELIVERY. Dan Lu, Nadya Belchenko, 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, when used in combination with other chemical transfection reagents. Partially degraded dendrimer offers even higher efficiency, presumably due to enhanced flexibility of the rigid dendrimer. Based on the current understanding of DNA delivery, we hypothesized that chemical modification of low-generation 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 helices 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. Wang, University of Illinois at Urbana-Champaign, Materials Dept, Physics Dept; Jay X. Tang, Indiana University, Physics Dept; Youyi Li, Alison Lin, University of California at Santa Barbara, MIR, 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 cytokeratin filament-actin (F-actin), a highly charged polyelectrolyte, and actin and 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 macroscopic > 100 micron scale. Within the tubules, on the 0.5 to 50 nm micron length scale, x-ray diffraction reveals a composition consisting of coatomically 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 reminder 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 tethred crystal which appears to be the origin of the tubule formation. The open, nested structure of these self-assembled rigid-tubule tubes suggests possible applications in drug delivery.

10:30 AM *N3.6
PHOTODYNAMIC CONTROLLED DELIVERY FOR GENE DELIVERY AND IMMUNOTHERAPY. K. W. Leong, Dept of Biomedical Engr, 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 pharmacokinetic issues of applying gene as a drug. We have studied the complexation of DNA with natural or synthetic polycations in forming nanoparticles. In addition to benefits common to other non-viral gene delivery systems of protecting the DNA from nucleosome degradation and allowing active targeting, characteristics unique to these biodegradable DNA nanoparticles include co-encapsulation of bioactive agents and sustained release of the DNA. Non-viral gene transfer has been observed in vivo in the lung, muscle, and gastrointestinal tissue in animal models. While the transfection efficiency of these DNA nanoparticles remains 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 N3N.7
CONTROLLED RELEASE OF BONE GROWTH FACTORS FROM INJECTABLE BIODEGRADABLE POLYMER SCAFFOLDS FOR BONE TISSUE ENGINEERING
Elizabeth L. Hedin 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) (PPF) was loaded with poly(3-hydroxy-6-lysine-co-glycidylic acid) (PLGA) microparticles carrying FITC-Dextran and then crosslinked with N-vinyl pyrrolidone in the presence of a benzyl derivative as a scavenger and sodium chloride (NaCl) as a leachable 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 assist 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/p PPF. 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%, 2.86%, and 1.76%, of loaded FITC-Dextran was released into phosphate buffered saline from the microparticles, the 50 wt % NaCl, and the 70 wt % NaCl composites, respectively. By day 28, 90.96%, 12.71%, and 34.40% of loaded FITC-Dextran was released.

SESSION N4A: PHASE SEPARATION AND CHARACTERIZATION OF DELIVERY SYSTEMS
Chair: Balaji Narasimhan
Tuesday Afternoon, November 28, 2000
Republic A (Sheraton)

11:15 AM N3N.8
AN AQUEOUS SOL- GEL PROCESS FOR ENCAPSULATION OF PROTEINS AND CELLS FOR BIOSENSORS APPLICATIONS
Anshu K. Singhai, Sudipta, Sundar Laboratory, Livermore, CA, Ashok Mahandran, Dept. of Chemical and Environmental Engineering, Univ. of California, Riverside, CA; Rimple B. Bhutia, Carol S. Adley, and Jeffrey Brinker, Univ. of New Mexico/Center for Microengineered Materials, Albuquerque, NM and Sandia National Laboratory, Albuquerque, NM

Porous silicate materials made by low temperature sol-gel process are promising hosts for encapsulation of biomolecules because of 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 alcohols such as tetramethyl orthosilicate (TMOS) and tetraethyl orthosilicate (TEOS) for encapsulation of biomolecules. These routes lead to formation of a lyotropic gel that can then be dried out to form an amorphous gel. We have developed a novel sol-gel process to encapsulate biological molecules (such as enzymes, antibodies and cells) that use neutral pH, room temperature, and does not generate alcohol as a byproduct. The process uses sodium silicate as precursor and is carried out in two steps: preparation of a low pH sodium silicate solution followed by gelation at neutral pH in a buffer containing biomolecules. Two enzymes widely used in biosensor applications- horseradish peroxidase (HRP) and glucose-6-phosphate dehydrogenase (G6PDH), were used to test the encapsulated enzyme 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 organophosphorous hydrolase (OPH) on the cell surface in sol-gel matrices. The colloidal sol-gel material can be used to develop biosensors for detection of organophosphorous compounds such as insecticides and chemical warfare agents.

11:30 AM *N3N.9
ANALYSIS OF ELECTROSTATIC EFFECTS ON THE SUCCESS OF RETROVIRAL-MEDIATED GENE DELIVERY
Howard E. Davis, Harvard M.T. Division of Health Sciences and Technology, Cambridge, MA; Jeffrey R. Morgan, Martin L. Yarmush, Center for Engineering in Medicine and Surgical Services, Massachusetts General Hospital, Harvard Medical School and Shriners Burns Hospital, Boston, MA.

Recombinant retroviruses are a commonly used gene delivery tool in human gene therapy clinical trials as they permanently integrate the therapeutic DNA into the genome of the target cell. Despite their widespread use, however, retroviral gene transfer efficiencies remain disappointingly low. In the years since their initial development as vectors, it has become clear that the physicochemical properties of the recombinant retrovirus, as well as the properties of the target tissues, have a major impact on the success of gene transfer. In particular, the interaction between the native negative charge present on the vector and target cell membranes results in a significant electrostatic barrier which must be overcome in order for the transduction to begin. Using a recently developed retrovirus adsorption assay, we have demonstrated that this electrostatic interaction is the dominant interaction during the initial steps of transduction. We have also established that this electrostatic adsorption, and exogenously transduction, by neutralizing this electrostatic barrier. Interestingly, we also found that this enhanced adsorption could be visualized even in the absence of a cellular receptor for the virus, suggesting that this step does not involve binding of the virus to currently identified receptors, but is rather a non-specific adsorption process or involves binding to an as yet unidentified class of receptor. Based upon our findings, we propose a new physical model of retrovirus adsorption, which is diffusion-limited, for the interaction of the virus to cellular membranes and demonstrate that this model gives a simple and quantitative method to determine the rate constants for the formation of the vector to cell membrane interaction. These findings imply that any process that reduces the negative charges on the vector, or enhances the negative charge on the cell membrane, will enhance the rate of retroviral transduction.

1:30 PM *N4N.1
THE DYNAMICS OF PHASE INVERSION RELATED TO INJECTABLE DRUG DELIVERY
Anthony McGuff, Univ. of Illinois, 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 de-mixing and gelation of the polymer solution (phase inversion), thereby forming the membrane carrier in vivo, simultaneously with the release of the entrapped drug. The dynamics of the membrane formation reflect the thermodynamic and mass transfer interactions in the system and these, in turn, profoundly influence the drug release characteristics. Selection of solution formulations for optimal release profiles 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 dielectric imaging to visualize the phase inversion dynamics of several injectable delivery systems. These measurements are related to in-vivo drug release profiles obtained using standard techniques and, together, provide fundamental insights on the role of the key variables affecting the process. The latter has profound impact on the drug release characteristics. Selection of formulation can provide an efficient means to control release rates. Both in-vitro and in-vivo studies have demonstrated that extended-release profiles and significantly reduced bursts result when the aqueous affinity of the depot is reduced. The uniform gel morphology
that results lacks the highly porous structure characteristic of rapid precipitation systems that also exhibit a strong burst effect. This suggests that the fast polymerization mechanism is not a major contribution to the protein through a homogeneously formed polymer matrix.

2:00 PM NN4.2
SURFACE-SENSITIVE POLYANHYDROIDE COPOLYMERS AND BLENDS FOR DRUG DELIVERY APPLICATIONS. Elisabeth Shen, Brianne Dzhukh, Mee-Kyoung Lim, Bahji Nascimento.

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 polyanhydroides based on 1,6-bis-carboxyphenoxy hexane (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 pimozidine.

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 pimozidine 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 upon the copolymer composition and the drug hydrophobicity. By examining fundamental monomer–monomer and polymer–drug interactions, we hope to better predict and design controlled drug delivery systems for specific applications.

2:15 PM NN4.3
DIRECT MEASUREMENT OF INTERACTIONS BETWEEN TETHERED PEG CHAINS AND ADSORBED MUCIN LAYERS BY SURFACE FORCE APPARATUS. Ysuhin Huang, School of Chemical Engineering, Purdue University, West Lafayette, IN; Nadezhda Efremova, Deborah E. Leckband, 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 mild surface of the PEG chains and on the adsorbed mucin layer. Force measurements were made in pH 7.2 and 4.0 buffer solutions, and the results showed that there was no notable attraction between the two surfaces. The in situ mucin adsorption experiments were done at pH 7.2 by using surface force microscopy (SFM) and measurements, and it was found that there was no permanent binding of mucins on the PEG-tethered surface. However, the adhesion experiment of mucins on a free-assembled PEG monolayers in pH 2.0 buffer solutions showed permanent binding, and hence it was suggested there were some attractions between PEG and mucins in this low pH condition. This work showed that SFA could provide information of molecular interaction between polymers and simulated mucin layers, which is essential for the design of new microdevice drug delivery systems.

2:30 PM *NN4.4
SMALL ANGLE X-RAY DIFFUSION AND SOLUBILITY OF ADHESIVES USED FOR TRANSDERMAL DRUG DELIVERY: INFRARED-AATTENUATED TOTAL REFLECTANCE (IRRATR) STUDIES. Adam S. Conner, MJ 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 the two components in the adhesive matrix is of great importance. Results will be presented discussing the use of infrared-attenuated total reflectance (IRRATR) 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 IRRATR crystal. The IRRATR crystal detects the time of transfer of this sample 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 terpinol in an acrylic network-based adhesive. Diffusion and solubility 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 dissolved solute has also been performed with testosterone 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 each type of experiment will be discussed.

3:15 PM NN4.5
PHASE SEPARATION IN POLY(PSEUDO AMINO ACID) - PEG BLENDS AND COPOLYMERS. M. Libner, Stevens Institute of Technology, Hoboken, NJ; M. Jaffe, Medical Device Concept Laboratory, Newark, NJ; J. Kohan, 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-multiblock copolymers of a tyrosine-based poly(proline 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 side-chain chemical structure. The system was studied at high spatial resolution by transmission electron microscopy (TEM) using solvent-cast thin films. The various films display qualitatively different phase-separation behaviors with morphological features having characteristic linear sizes ranging from 1 to 10 μm. These scale lengths are comparable to those characteristic of proteins and 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 show that these systems can form water soluble micelles with characteristic linear scales of order 50 nm depending on polymer molecular weight.

3:30 PM NN4.6
BIOMOLECULAR MATERIALS CHARACTERIZATION USING STATIC AND DYNAMIC LASER LIGHT SCATTERING DETECTION TECHNOLOGIES. John P. Helfrich, Life Science Group, Precision Detectors, Inc., Franklin, MA.

Rugged characterization means for new therapeutic and diagnostic biomarkers (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 is the control 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 aggregates (dimer, trimer, etc.) can be significant in biological systems. Aggregates may also cause conformational shifts in the molecular structure that can alter the intended function of an effective therapeutic or diagnostic agent. Monitoring and understanding these phenomena are fundamental for process development and quality control requirements.

Laser light scattering (LDS) 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 and miniaturized photodiode detectors has led to the evolution of a new combined static and dynamic laser light scattering detector. This detector has a 10 μL 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 kDa to 10 million daltons and hydrodynamic radius (Rg) measurements for biomolecules in the range of 1 nm to 1000 nm. This paper will outline the design and applications of this unique detection system for ‘well-characterized’ biomolecules and their controlled release formulations.

3:45 PM NX4.7
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-oxidant and anti-inflammatory. This encouraged us to examine the behavior of humic acid based multilayer films as a potential membrane material for the implantable glucose sensors. Humic Acids (HA) are naturally occurring biopolymers found in soil, sediments, water, and some plants like pine bark. Properties of polyelectrolyte layer by layer self-assembly technique of HA with oppositely charged ferric ions was utilized to grow films, which could potentially be used as the outer semipermeable protective layer for the glucose sensor. The growth characteristics of these assemblies exhibits strong dependence on the pH and the ionic strength of HA solution and can be correlated with the degree of ionization of carboxyl groups and the neutralization induced by the polyelectrolytes. Quantum chemical calculations and ellipsometric 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/Bi2O3 coated silastic tubing in rats and comparing the tissue response to a medical grade silastic tubing under the same conditions. The tissue response of these films compares favorably with the silastic 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 Sandoz, Joshua H. Harris, Edith Mielowicz, Brown University, Dept of Molecular Pharmacology, Physiology, and Biotechnology, Providence, RI.

Polymer nanoparticles are difficult to characterize in vivo due to their tendency to degrade, migrate, and be endocytosed. A novel polyethylene mesh device which contains nanoparticles in vivo allowed for retrieval of degraded products from rats. Protease containing PLGA nanoparticles 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 nanoparticles to determine device effect on degradation rates. In vitro, encased and naked nanoparticles 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 561.7% 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 64.8% and 84.1% for those implanted 1 week. Conversely, simple spheres subcutaneously and intraperitoneally began to lose mass immediately, dropping to 76.4% and 65.9% of the original mass by 1 week, while those tested in vitro had only decreased to 94.00% and did not begin to lose mass appreciably until after 1 week. Intramuscular implants behaved more like in vitro samples decreasing in MW immediately (79.4% and 57.0% by 3 days and 1 week) and lagging in mass loss (98.50% 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. Tsai and Reinhold H. Dussek, 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 for adhesive tape. 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 compared to soft tissues. Moreover, the adhesion of PSAs 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 response of physiological environment, and permeation-enhancement additions will be discussed.

4:30 PM NN4.10
BIOENGINEERING 3D NANOSTRUCTURES CHARACTERIZATION. Alexandria G. Bezrukova, St. Petersburg State Technological 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 others bioengineering constructs. These methods are also compatible with the nondestructive analysis of dispersive systems by other optical methods: refractometry, absorbency and fluorescence. Our research has investigated different dispersive systems: liposomes, blood substitutes, proteins, nucleic acids, vitamins, lipoproteins, lipid 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 the fitting method with approximation of particles as homogeneous, core-shell structured spheres, oblate and prolate ellipsoids of rotation and regularization procedure for inverse problem of dynamic light scattering have been applied. By optical methods it is possible to determine the 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 OF N-iDoci-1, Brunel University, Faculty of Engineering and Natural Sciences, Sarben University, Orhanli, Istanbul, TURKEY; Selin Duruma, Ozgur Kay, TUBITAK Marmara Research Center, Komel, 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 in a semi- open system, where the solvent moves in and out of the gel depending on the state of stress and environmental thermodynamic conditions. In the present study, elastic moduli of cross-linked swollen poly(acrylamidine) spheres 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 uniaxially compressing a bead between two walls and characterizing their instantaneous moduli 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 NN5 POSTER SESSION
BIOMATERIALS FOR DRUG DELIVERY
Chirag Edith Mielowicz
Tuesday Evening, November 30, 2000
4:00 PM
Exhibition Hall D (Hynes)

NN5.1
MORPHOLOGY AND RELEASE PROFILE OF ACTIVE-LOADED POLYHYDROXYALKANOATE MICROPARTICLES. 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 family members: poly-3-hydroxybutyrate (PHB), a high crystallinity polymer, and the poly-3-hydroxyoctanoate (PHO), amorphi 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-in-oil double emulsion (w/o/w) and spray dryer. The external and internal microparticles morphology studied by Scanning Electron Microscopy (SEM) and Transmission Electron 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 5.1 µm. The porosity and tortuosity of the polymeric
delivery matrix had a profound impact on the release characteris.
In general, for the emulsion techniques the release pattern is zero or first
order and for the sprier drier techniques the Higuchi 0.5 n dependence
were observed.

**NNS.2**

**A NOVEL CATIONIC CARBOHYDRATE-BASED LIPID FOR
GENE DELIVERY.** Keswani S. Sujitj, Geoffrey S. Hind, Mark W.
Grinstaff, Duke Univ, Dept of Chemistry, Durham, NC.

Cationic lipid based gene delivery systems such as DOTMA
(N-[1-(2,3-dioleyloxy)propane]-N,N,N-trimethylammonium chloride)/
DOPE (dioleoylphosphatidylethanolamine) micelles have been used
for both in vivo and in vitro transfection of nucleic acids. The basic
components of a cationic lipid are the hydrophilic lipid group that
ails in interactions with the cell membrane, the positively charged
hydrophobic group, and non-polar core containing cholesterol and
phospholipid 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
caracterized a novel cationic lipid containing ribose in the
bicompartmental and biodegradable linker (1-mercapto-3,4-dihydroxy-
ribosyl-5-lysinyl). The ability of these novel molecules to transfect DNA
in vitro is underway.

**NNS.3**

**A QUANTITATIVE TECHNIQUE FOR DETERMINING THE
EXTENT OF POLYMER UPTAKE.** Chris Thomas, Edith
Mathiowitz, 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
colfocal microscopy and TEM, however the results have served
primarily as qualitative characterization. In this study, biodegradable
polymers, including PLLA, PPSA, and PCL were blended with a
polyethylene-linked fluoresecce dye into particles ranging from
200 nm to 5 microns in diameter and incubated in rabbit jejunum
for 1 hour. Following tissue excision and fixation for histology, tissue was
rigorously flushed to remove particles on the surface and aliquoted for
fluorescence microscopy. This tissue was homogenized 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 polysulfone-linked dye.
KOH digests the tissue components along with the polyethylene and
polyester microspheres used in this study, hence the final component
in the extraction includes only the polysulfone and fluorescent dye
which is easily quantified without background interference from
cellular and polymer elements. This material is resuspended in
aqueous solution and fluorescence microscopy is used comparing the
samples to standards prepared from stock beads in aqueous
suspension. This method can be used to quantify uptake provided the
loading of dye is constant and the fluorescent microspheres are
uniformly labeled, and was used to validate the results of confocal
microscopy comparing the aforementioned biodegradable polymers.

**NNS.4**

**HIGH-PRESSURE INDUCED LIQUID CRYSTAL PHASES
MAINTAINED IN NON-MESOGENIC POLYMERS AT AMBIENT
TEMPERATURE AND PRESSURE.** Edwin Edens, Edith
Mathiowitz, Brown University, Department of Molecular
Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI.

liquids (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 or disk-like. These mesogens can be individual
inorganic or organic molecules or part of repents in a polymer chain
(polymer liquid crystal). The reining philosophy has been that liquid
molecular crystals can only occur in mesogenic materials however
recent discoveries indicate the potential of inducing these phases in
non-mesogenic materials by subjecting the material to a combination of
temperature and pressure conditions and appears to be maintained at ambient conditions for extended periods of
the time. However, when the material is reheat back a critical temperature the crystal 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.

**NNS.5**

**SEGMENTED POLYURETHANES FOR CONTROLLED DRUG
DELIVERY.** Erkesh O. Bazarbekov, Rimat M. Isakov, Bulat A.
Zhumabai, Institute for Chemical Sciences, Almty, KAZAKHSTAN.

The segmented polyurethanes with different soft and hard
segments have been studied as drug carriers for controlled delivery
application. Biodegradable polyurethanes were obtained by means of a
two step procedure using different polyisocyanates, diols and
blending agents. Drugs such as antibiotics and antitumor agents are
expected to be incorporated in the polyurethane matrix via the
polyurethane synthesis or adsorption from aqueous solutions.

The influence of different factors such as the chemical structure and
loading of the drugs, nature of polyurethanes, the supramolecular
structure and morphology of polyurethanes on the drug release rate
were investigated. It was shown that the microdomain structure of polyurethanes play a significant role in the drug transport.
The successful application of Polyurethane Drug Delivery Systems for
the treatment of tuberculosis, esophagus burn, glaucoma and some
dental diseases was shown.

**NNS.6**

Abstract Withdrawn.

**NNS.7**

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

New biopolymers are needed to meet the current challenges in
orthopedics, dentistry, cardiovascular surgery, and ophthalmology.
Polyurethanes are one class of polymer being investigated, and
polymers of 1,4-dihydroxyphenyl-1,3-dioxolane-2-one are known. However,
no polymers of its 6-membered cyclic isomer, 5,6,6-dioxan-2-one have been
made. The cyclic carbonate 6-benzzyloxy-1,3-dioxolane-2-one has been synthesized from glycol and polymerized.

Following cleavage of the benzyl group by catalytic hydrolysis, the resulting polymer is a 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 glycol and carbon dioxide. The pentad hydroxyl groups of
tpycyl (5,6-dihydroxy-1,3-dioxolane-2-one) also provide a site
for post-polymerization modification (i.e., attachment of additional
functional molecules).

**NNS.8**

**BIONDEINERIERS 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 numbers of controllable terminal functionality and exhibit low viscosities, high solubility, miscibility,
and unusual properties. One can display a variety of physical properties desirable for industrial and biomedical applications.

For example, dendrimers have shown significant potential as drug delivery agents by physical entrapment or covalent attachment of drugs. The phase is in synthesizing phosphorylated, aliphatic polyester biodendrimers containing glycol and succinic acid. These
biodendrimers contain a tetra-functional core, synthesized from one
succinic acid and two glycolic units, and an AB2 monomer,
synthesized from one succinic acid and one glycolic unit. To date, the
G1 biodendrimer, [G1]-PGlu, has been synthesized and fully
carbohydrated by H-NMR, 13C-NMR, IR, MS, and elemental analysis.

Further generations of this biodendrimer will be synthesized and biocompatibility will be determined. Generation
Drug encapsulation studies are ongoing to assess the efficacy of this
novel biocompatible macromolecule for drug delivery applications.

**NNS.9**

**CARBOHYDROSES: 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 closed structures called liposomes self-assemble from
conventional glycol based phospholipids, such as phosphatidyl-
diacylcholines. Naturally occurring phospholipids are composed of a
glycol backbone, two hydrophilic hydrogen groups and a polar head
group, that is often a choline. Current research in this field focuses on altering the head group and hydrophilic tail to obtain
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 biotechnological applications and to assess supramolecular structure formation. Selecting ribose as the new backbone, we have termed these novel carbohydrate three-dimensional supramolecular structures “carbohydrose.” The ribose backbone analog of dl-myo-inositol hexaphosphate (InP), L-methoxy-2,3-dihydroxy-6-PO4-phosphate [DLRIPC] as well as the ribose analog of dl-myo-inositol triphosphate (dl-MPTC), L-methoxy-2,3-dimyristoyl-6-phosphate (DLRIP) were synthesized. The resulting carbohydrates were characterized by optical microscopy, modulated differential scanning calorimetry (MDSC), and X-ray diffraction. Mixtures of cholesterol and DLRIPC were extruded and 200 nm liposomes containing the water-soluble dye 5(6)-carboxyfluorescein were formed. The synthesis of DLRIPC, its ability to form stable supramolecular structures, and the ability to derive DLRIPC 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 in the use of mixtures of hydroxyapatite as fibrin, collagen, gelatin, chitosan and alginate, with inorganic powders, as bone fillers. Owing to their physicochemical and biological properties, calcium phosphates have recently been considered as a potential matrix for bone grafting. In this paper, 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 XRD, FT-IR. The particle 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 were spherical in size. These CHA-gelatin composite microspheres were also loaded with antibiotics such as gentamicin and its in-vitro drug release profiles in phosphate buffer were evaluated.

SESSION NN6: NOVEL APPROACHES TO DRUG DELIVERY SYSTEMS
Chair: Edith Mathiowetz
Wednesday Morning, November 29, 2000
Republic A (Sheraton)

8:30 AM *NN6.1 DEVELOPMENT OF BIODEGRADABLE POLYLACTATE MICROSPHERE (PAEMLERTM) FOR SITE SPECIFIC CANCER THERAPY. Wenbin Deng, Zhong Zhao, Stephen Dordunoo, 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 of 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 PGA and PLGA are extensively used to engineer such controlled drug delivery systems. For certain highly insoluble chemotherapeutic 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 polyphosphoester [polylactate] for such drug delivery applications. Polylactate comprises mainly of lactic acid oligomers which are separated by ethyl phosphpaheter bonds. One major potential advantage of polylactate is that it is currently approved for clinical use, which is approved by FDA and has an excellent safety record, while the interpenetrating ethyl phosphate groups make the final polymer more hydrophilic and degrade more evenly. The final polylactate polymer 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 phosphate 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 PAEMLERTM microspheres will be highlighted as an example in this presentation. PAEMLERTM microspheres are polylactate microspheres containing 1% paclitaxel. PAEMLERTM microspheres have 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 PAEMLERTM 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 SYSTEMS. Thomas Swiatkowski, W.T. Starche, Andreas 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) dissolved in contact with body liquids. On the other hand a mechanically operating device made of a reservoir (and a catheter) is implanted in the body to deliver drugs over time. Both cases provide 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 preferable to be 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 nanomoporous membranes which enables us to vary the delivery rate easily. The basic material is a nanomoporous ceramic membrane which is produced by an electrochemically oxidation process. The pore size of these membranes can be varied between 20 nm and 250 nm while the thickness can be as high as 100-300 microns. Ceramic layers are deposited 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 are used to control and adjust the delivery rate to the drug and the therapy. We report on results for the delivery of [11] In labeled Octreotide which is a Somatostatin analogue used in cancer therapy. This choleopeptide 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 alky chains of different lengths are chemically bound to the pore surface the delivery rate can be reduced to almost zero. In all cases a zero order time dependency of the delivery rate is observed. Because of the variable sizes 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, Wen and Lodge have shown that “arm retraction” can be an entropy-rate-limiting step for diffusion of small polymers. Unusual diffusional behaviors occurs for highly concentrated polymeric solutions with potentially novel, useful kinetics. Towards this end, we have been studying the diffusion of model dendritic polymers in concentrated solutions of “linear” polymers, using small laser-scanning photobleaching and recovery. The self-similar polyamidoamine 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. Mallriniq Ozdemir, Steven F. Essner, Electrical and Computer Engineering Department, University of California at San Diego, San Diego, CA, Sangeet A. Bhatin, Bioengineering Department, University of California at San Diego, San Diego, CA.

We have developed a new 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 charged objects 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. Microscanning of the electrodes allows localization of charged species and the technique has been previously utilized extensively for localizing DNA. Here we first demonstrate the localization of negatively charged polystyrene
bends as model cells of various sizes (10-20 μm in diameter) on micro-patterned substrates. In addition, light emitting diodes (50 μm diameter) and interconnects (100 μm) have been fabricated to demonstrate the general utility of this technique as a tool to interface disparate materials. Finally, 2640 μm diameter live mammalian cells were patterned on regular arrays by means of electrical addressing. Our results indicate that cell survival was sufficient for subsequent attachment, spreading, mitosis, and passage of 3T3 fibroblasts. For applications in high-throughput phenotyping, neural stem cells were also studied. Single cell patterning was achieved on an agarose patterned, optically transparent, semiconductor. This experiment demonstrates the feasibility of microscopic monitoring of many live cells in real-time, in parallel. This technique has applications in certain other cellular arrays for cell biology research, drug discovery, and tissue engineering.

09:45 AM N6G.5

Wang, University of Strathclyde, Dept of Pharmaceutical Sciences, Glasgow, UNITED KINGDOM; Lawrence Tseley, 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 sonicating 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 methoxy polyethylene glycol (Mr ~3000) and hydrophobic poly(l-lysine), were derived from 2 different molecular weight poly-L-lysine hydrobromide samples (~4000 and ~20,000 respectively). These amphiphilic polymers (PLS) were characterised using light scattering, 1H NMR and afm 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 presence of polymers of poly-L-lysine (PL) 22 - 26 mole % of which 22 - 25 mole % of lysine groups remain unmodified. Probe sonication of an aqueous dispersion of PLS samples resulted in the production of stable nanoparticles (80 - 170nm in diameter) as imaged by electron microscopy. Nanoparticles were able to encapsulate the hydrophilic fluorophore FITC-dextran and encapsulation increased as the level of unreacted lysine terminal amino groups in PLS increased, indicating the presence of hydrophilic microdomains. Polymeric unilamellar vesicles (220 - 570nm in diameter) imaged by electron microscopy were produced by probe sonication of PLS, 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 palmitic substitution on the lysine group. A method has been derived. The size of both the nanoparticles and the vesicles was directly influenced by the molecular weight of PLS. PLSs of molecular weight 32,000 - 48,000 and 89,000 - 140,000 resulted in nanoparticles of 80 - 140 nm and 125 - 167 nm in diameter respectively and PLS 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 N6G.9

ENGINEERING LARGE MONODISPERSE UNILAMELLAR VESICLES WITH HIGH ENCAPSULATION YIELD. Sophie Patout, David A. Weitz, Harvard University, Dept. of Physics and DEAS, Cambridge, MA.

A vesicle is a membrane closed on itself to form a bag 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 foodstuff ingredients, and polymer emulsion. To achieve this we define the size distribution from 200nm up to 2μm, 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 dispenses liposomes and aqueous 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, using statistical emulsion techniques 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 N6G.10

PHASE COMPOSITION DETERMINATION IN PLGA-DUAL WALLED MICROSOPHERES. Nasimina Rahman, Edith Mathiowitz, Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI.

We have demonstrated the fabrication of dual 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 performance 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 similar so that it is not always easy to identify and separate the different peaks in characterization techniques such as the Fourier transform infrared
spectroscopy. Therefore we had to resort to the differential scanning calorimetry to quantify the amounts of PLLA and PLAGA 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, Apostolos K. Rizos1, John Alifragis1, Aristidis M. Tzianakis2, Manolis Tzianakis2, Michael Shtilman3. 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 measure 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.