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Dr. Jay serves as the Director of the Center for Pharmaceutical Science and Technology (CPST). The CPST is a fully integrated analytical and formulation development and FDA-registered pharmaceutical manufacturing facility utilizing current Good Manufacturing Practices (cGMPs). The facility employs 20 trained professionals and occupies approximately 3,700 square feet on the first floor of the College of Pharmacy Building. The CPST has four primary missions: (1) to enrich the education of the University's students through specialized educational and training programs related to pharmaceutical technologies, (2) to provide expertise to students and faculty involved in translational research requiring the manufacture of pharmaceutical products under cGMP, and (3) to support the extensive infrastructure required to manufacture drug products for clinical trials through grants and contracts with academic institutions, biotechnology and pharmaceutical companies, and federal agencies such as the National Institutes of Health, and (4) to enhance economic development in the Commonwealth. Additional information may be obtained from the CPST's web page: <http://www.uky.edu/Pharmacy/cpst/>

Dr. Jay is also a Professor of Pharmaceutical Sciences with a joint appointment in the Department of Diagnostic Radiology. He is a member of the *Pharmaceutics, Drug Delivery and Analysis* Area of Graduate Study (AGS) and has on-going collaborations with faculty within and outside of the College.

Dr. Jay is also a co-founder, along with Dr. Russ Mumper, of NanoMed Pharmaceuticals, Inc., an early-stage advanced drug delivery company using nanotechnology, thin film composites, and film-forming gels to enable the development of new drugs and vaccines, and improve existing drugs. (<http://www.nanomedpharm.com/index.htm>)

Dr. Jay's research projects include:

1. NanoScintillation Systems for Aqueous-Based Liquid Scintillation Counting.

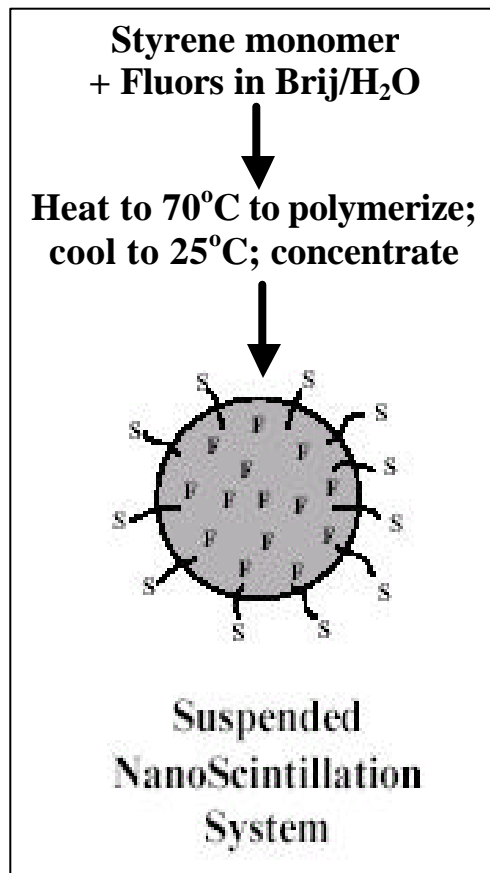
This project is being conducted in collaboration with **Dr. Russ Mumper** and is being executed by a Pharmaceutical Sciences graduate student, **Mr. Jim Weekley**. Jim has been ably assisted by two summer research students, **Mr. Paul Rosenstiel** (Duke University) and **Ms. Sara Wuenschel** (LaTourneau University), both of whom were supported by an REU (Research Experience for Undergraduates) grant from the National Science Foundation.

Liquid Scintillation (LS) counting involves the addition of radioactive samples to a fluor-containing organic solvent; interaction of emitted β^- particle with fluor produces light that is quantified in an LS counter. This system is highly efficient, but results in the generation of large amounts of mixed (organic-radioactive) waste. The goal of this project is to develop an *aqueous-based* NanoScintillation system that may serve as an alternative to organic solvent-based liquid scintillation cocktails.

The NanoScintillation system is produced by initially forming a styrene-in-water microemulsion using Brij-78 as the surfactant and pentanol as co-surfactant. Fluor molecules (PPO and bis-MSB) were solubilized in the styrene phase. The styrene was polymerized using sodium persulfate and heat which resulted in the formation of a nanoparticle suspension. ^{14}C -acetic acid (50 μL ~83,600 dpm) was added to 1 mL samples ($n = 3$) that were subsequently counted in a liquid scintillation counter. Monte Carlo calculations determined that there was a high probability that an emitted β^- particle would interact with a nanoparticle in suspension.

The results of the counting experiments showed that the NanoScintillation system was capable of quantifying the amount of ^{14}C in a sample at greater than 50% of the efficiency of a conventional (organic) scintillation cocktail (see Table below). Thus, the NanoScintillation system has the capability of quantifying the amount of ^{14}C in a sample at a sufficient detection efficiency without generating mixed waste. This is expected to have significant environmental and economic advantages.

This research was supported by a grant from the National Science Foundation (NanoScintillation Systems for Aqueous-Based Liquid Scintillation Counting. (P.I.: RJ Mumper) \$79,656. 7/1/01 – 6/30/02.).



	CPM	Relative Counting Efficiency	Absolute Counting Efficiency
Conventional LSC Cocktail	75,310 ± 195	-	90.1%
NanoScintillation System	37,735 ± 706	50.1%	45.1%
NanoScintillation System – no ¹⁴ C-acetic acid added	13 ± 1.3	0.018%	0.016%
Water	26 ± 4.5	0.035%	0.031%

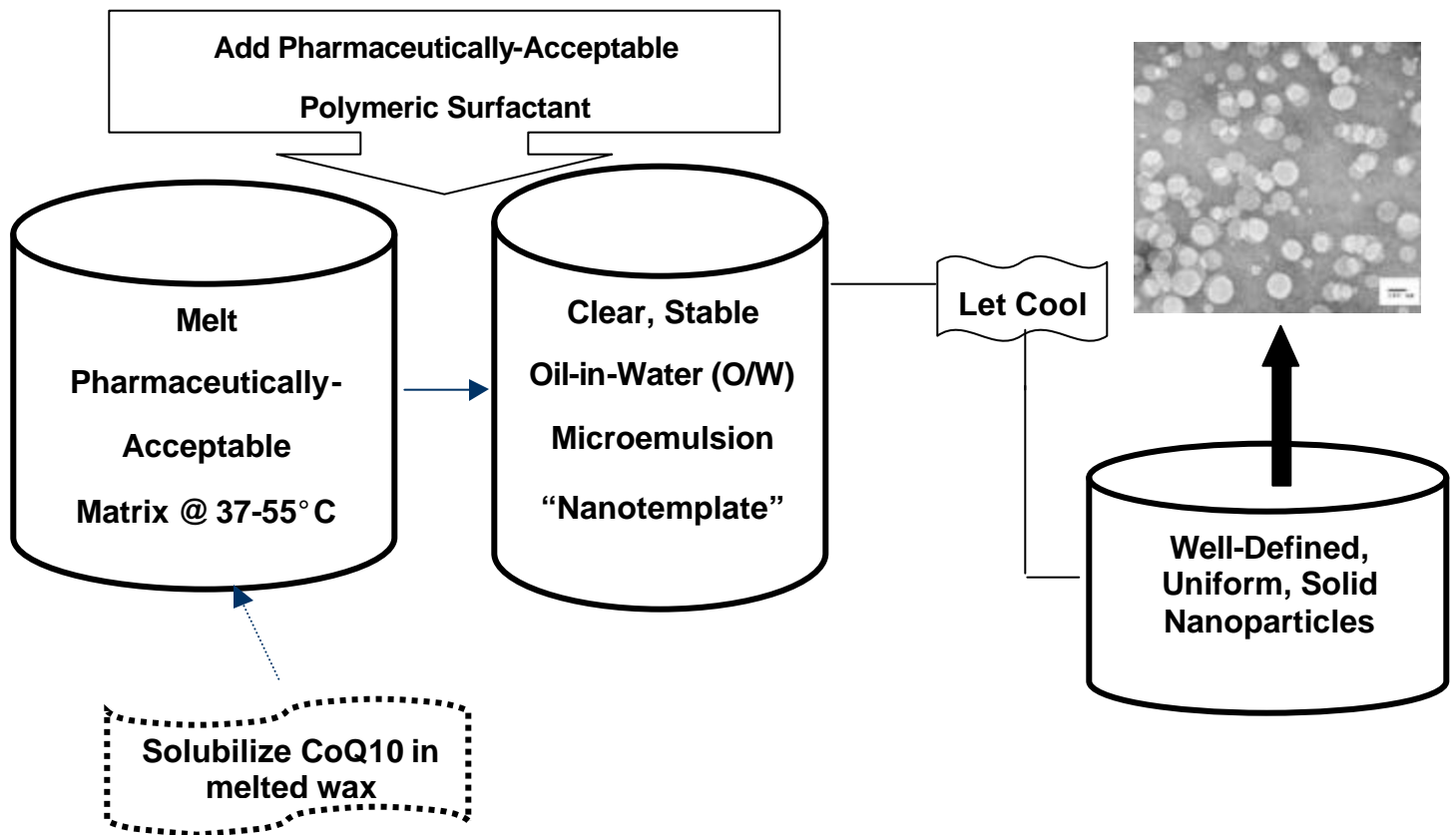
2. Nanoparticles Engineered from Microemulsion Precursors for Coenzyme Q10 (CoQ10) Delivery

This project is being conducted in collaboration with **Dr. Russ Mumper** and is being executed by a Pharmaceutical Sciences graduate student, **Ms. Cheng-Hsuan (Sherry) Hsu**.

CoQ10, a poorly water-soluble compound exhibiting low oral bioavailability, is a physiological antioxidant and has been used in the treatment of cardiovascular disorders. It has been hypothesized that its bioavailability can be improved by incorporating the compound into sub-micron particles. The purpose of these studies was to prepare and characterize a CoQ10 nanoparticles using a simple, scalable method.

CoQ10-incorporated nanoparticles were prepared by cooling warm microemulsion precursors comprised of emulsifying wax, CoQ10, Brij 78 and/or Tween 20. The nanoparticles were characterized by particle size analysis, TEM, and DSC. The incorporation efficiency was determined by ultrafiltration. The stability of CoQ10-nanoparticle in aqueous suspension and simulated GI media was monitored at 37°C. The release of CoQ10 from the nanoparticles was investigated at 37°C. Finally, an *in-vitro* cell uptake of CoQ10-nanoparticles by mouse macrophage, J774A.1, was completed.

CoQ10-incorporated nanoparticles (d~70 nm) were successfully engineered. The incorporation efficiency of CoQ10 was approximately 74±5%. The CoQ10-nanoparticles were spherical and uniformly distributed under TEM. The DSC thermograms of CoQ10 and emulsifying wax exhibited sharp endothermic peaks, corresponding to the melting points of each compound. However, the thermograph of CoQ10-incorporated nanoparticles showed a broad peak around 40°C, which was different from those of CoQ10, emulsifying wax, and the physical mixture of both compounds. Short-term stability studies showed the nanoparticles increased in size in both aqueous suspension and simulated GI media, demonstrating that alternative ways to storage conditions were needed. The *in-vitro* release profile of CoQ10 from the nanoparticles showed a faster release in the first 9 hours followed by a period of slower and extended release. The uptake of CoQ10-nanoparticles by the J774A.1 cells was over 4-fold higher than that of the CoQ10-free nanoparticles (P < 0.05).

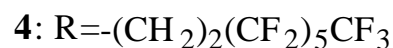
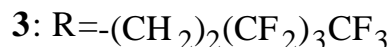
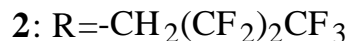
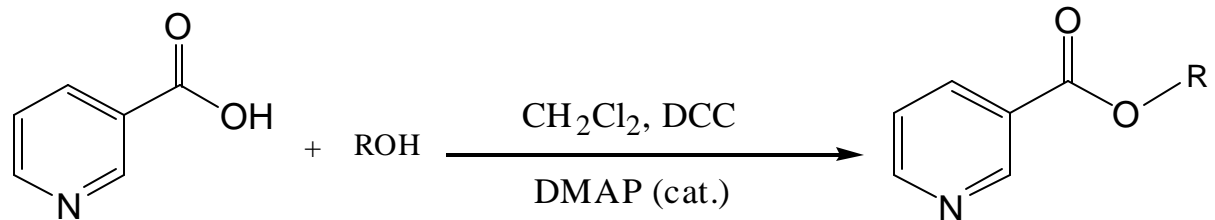


This research is being supported in part by a grant from the National Institutes of Health (Nanotemplate Engineering of Cell-Specific Nanoparticles. National Institutes of Health Technology Development for Biomedical Applications: Phased Innovation Award - R21/R33). (P.I.: RJ Mumper). \$1,919,393. 2/1/02 – 1/31/07.

3. Synthesis, Chemical Stability and *in vitro* Cytotoxicity of Ester Prodrugs of Nicotinic Acid for Pulmonary Liquid Ventilation

This project is being conducted in collaboration with **Dr. Hans Lehmler** (Graduate Center for Toxicology) and **Dr. Paul Bummer** (Pharmaceutical Sciences) and was being executed by a Pharmaceutical Sciences graduate student, **Ms. Cheng-Hsuan (Sherry) Hsu**.

It has been proposed that fluorinated ester prodrugs could improve the solubility of nicotinic acid (NA) in a perfluorocarbon solvent (e.g. perflubron) for drug delivery via pulmonary liquid ventilation. The solubility and stability of a series of fluorinated NA prodrugs were evaluated in perflubron and aqueous media. The *in vitro* cytotoxicity of these prodrugs and their corresponding alcohols were assessed in human non-small-cell lung cancer (NSCLC) cell line.



The solubility of nonfluorinated and fluorinated NA ester prodrugs was determined by adding excess amounts of the compounds to perflubron and different buffer solutions in the range of pH 2-8 at 25°C for 12 hours. The apparent partition coefficient ($\log P_{\text{app}}$) were evaluated in 1-octanol/pH 7.4 phosphate buffer at 25°C. The degradation of the esters was investigated in different buffer solutions in the pH range of 2-8 at 60°C, and the appearance of degradation products was monitored by HPLC. The prodrugs and their corresponding alcohols were coincubated with NSCLC cell line (H522) for 24 and 72 hours. The resazurin assay was used to assess in-vitro cytotoxicity.

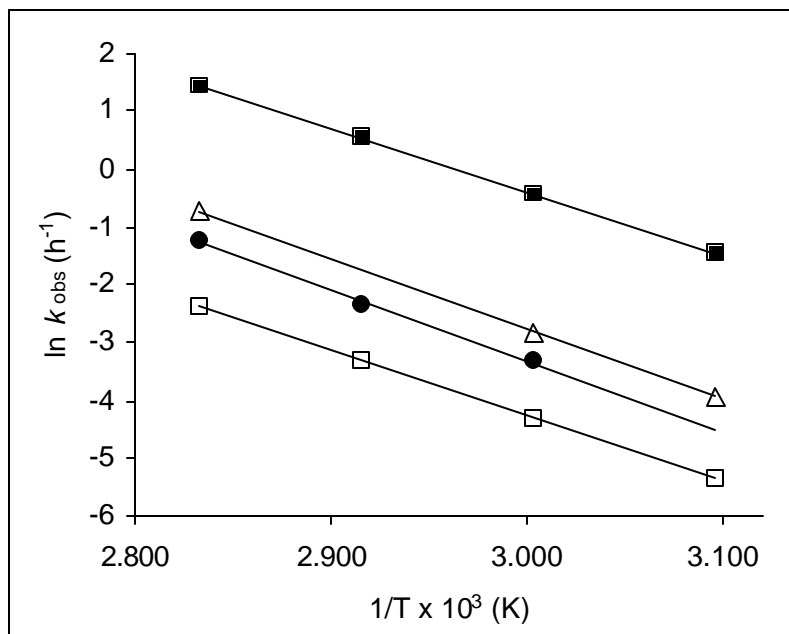
In perflubron, the fluorinated butyl nicotinate is 3.5-fold more soluble than butyl nicotinate. The order of the solubility of fluorinated prodrugs in perflubron was octyl > hexyl > butyl nicotinate. The aqueous solubility of the prodrugs increased with decreasing buffer pH. The lipophilicity of these prodrugs increased with increasing chain length. The toxicity results showed the LC_{50} value of the fluorinated nicotinate decreased with increasing carbon chain length. The nonfluorinated prodrugs have higher LC_{50} values compared to those of the corresponding fluorinated prodrugs. However, at the concentrations tested, these prodrugs and their corresponding alcohols exhibited no significant cytotoxicity.

Chemical and enzymatic stability of Compounds 1-4

Esters	$t_{1/2}$	
	pH 7.4 buffer ^a (h)	Esterase (100 U/L) (min)
1	646	170
2	12	3
3	178	163
4	316	- ^b

^a $t_{1/2}$ was calculated by the extrapolation of the Arrhenius plot at 37°C.

^b $t_{1/2} > 24$ h.



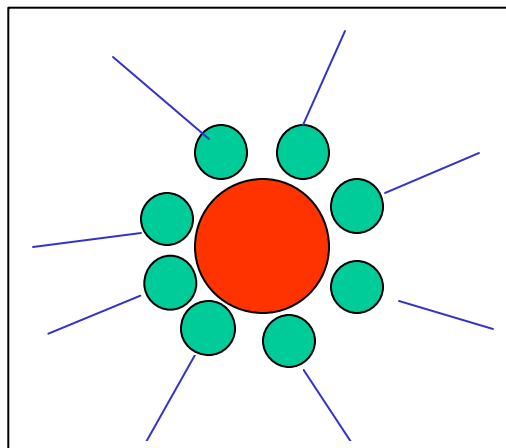
Arrhenius plot for prodrugs **1** (■); **2** (△); **3** (●); **4** (□) in 0.02M phosphate buffer pH 7.4 ($\mu=0.1$).

Thus, it appears that the prodrug approach can enhance the solubility of NA in perflubron, and initial screening showed that these prodrugs and their corresponding alcohols do not cause cytotoxicity. This approach has potential for the pulmonary delivery of water-soluble compounds via liquid ventilation.

4. Water-in-Fluorocarbon Microemulsions for Pulmonary Drug Delivery

This project is being conducted in collaboration with **Dr. Hans Lehmler** (Graduate Center for Toxicology) and **Dr. Paul Bummer** (Pharmaceutical Sciences) and is the Ph.D. thesis project of a Pharmaceutical Sciences graduate student, **Mr. Michael Clark**.

Another approach that we have undertaken to enhance drug solubility in perflubron has been to prepare inverse micelles and microemulsions with the aid of fluorinated and partially-fluorinated surfactants. A water-in-perfluorocarbon emulsion can contain clinically useful concentrations of a water-soluble drug dissolved in the aqueous interior of the emulsion and, thus, facilitate the pulmonary administration of drugs with liquid ventilation. The thermodynamic stability of microemulsions makes them attractive for this application. A microemulsion system composed of perflubron, perfluoroheptanoic acid and water was prepared in

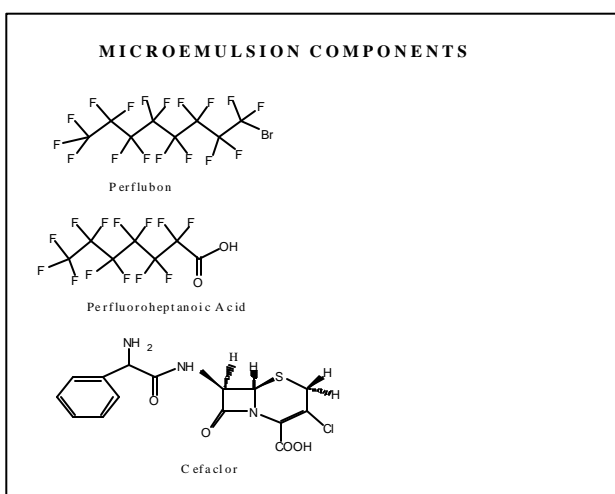


Water in PFOB Microemulsion at 10%, 20% and 30% Surfactant (35°C)

Label	10%	20%	30%
Perflubron wt%	82.8	66.4	57
Surfactant wt%	9.2	16.5	23.9
Aqueous wt%	8	17.1	19.1
W/S Molar Ratio	18 +/- 2.8	21 +/- 0.2	16 +/- 1.1
Aqueous (mL)	16 mL	30 mL	40 mL

which phase diagrams were constructed to determine the appropriate component ratios for maximizing the water content. From the table, it can be seen that significant quantities of water can be incorporated while retaining a stable microemulsion system. This allows the possibility of significant solubilization of water soluble drugs into perflubron, expanding the therapeutic capabilities of

this approach. Since inverse microemulsions have polar functional head groups, one concern involves the stability of drug molecules incorporated into the aqueous phase. Unstable compounds may be subjected to enhanced degradation in the environment of the aqueous core of an inverse microemulsion. A model compound, cefaclor, is being used to study the effect of various surfactant head groups on its rate of degradation in a water-in-perflubron microemulsion. Preliminary studies have revealed that the presence of cefaclor in the aqueous has a demonstrable effect on the droplet size.



Apparent Droplet Size (nm)			
Surfactant Concentration	10%	20%	30%
Water	42-55	5-7	5-7
Buffer	9-14	4-9	9-11
Buffer + Drug	25-32	4-9	5-7

5. Purification by Foam Fractionation.

Foam fractionation is a separation process based on the selective adsorption of a surface active species to a gas-liquid interface. We are currently exploring the potential of foam fractionation as a low-cost, high-volume protein purification method. Gamma scintigraphy is being employed to acquire data to be used in the development of a mathematical model that can be used to determine the effect of column parameters on protein separation and enrichment. Dr. Jay and **Dr. Paul Bummer** have previously described the use of foam fractionation to separate protein mixtures based on their relative affinities for a gas-liquid interface. This was the Ph.D. thesis project of **Dr. Christopher Lockwood** who is currently employed at Boehringer-Ingelheim Corp. Drs. Jay and Bummer are also working with **Dr. Czarena Crofcheck** (Dept. of Biosystems and Agricultural Engineering) on the use of foam

fractionation to purify proteins that have been recombinantly produced in tobacco plants by enhancing the affinity of a protein of interest for a gas-liquid interface with the assistance of novel surfactants. Another project involves the use of foam fractionation to economically isolate expensive lipid components from drug-lipid mixtures. This project was the subject of the Ph.D. thesis of **Mr. David Worthen**.

A schematic diagram of a batch-type foam fractionation device is shown in Figure. 1. The device is characterized by simple glass construction and lack of chromatographic matrix.

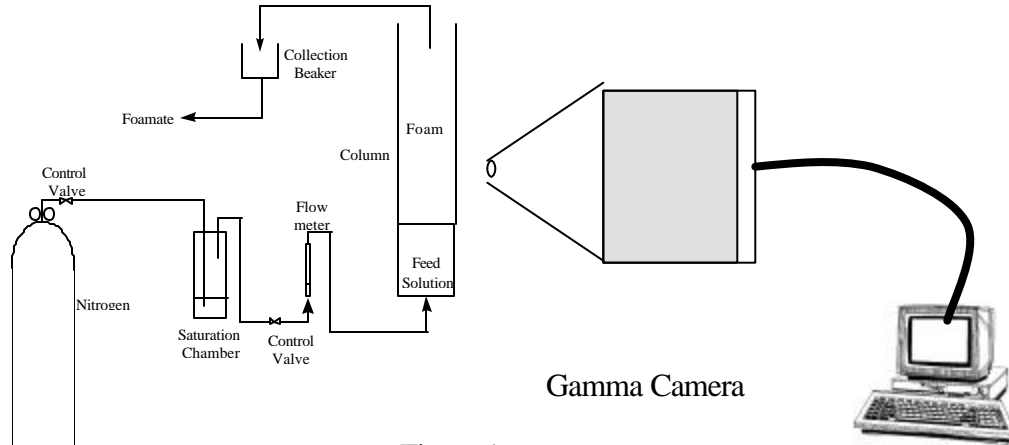


Figure 1

Illustrated in Figure 2 are the important phenomena occurring in a simple foam fractionation unit. At the bottom of the glass column, individual bubbles are produced by introducing an inert gas, pre-saturated with water, into the feed solution through a sintered glass frit or other porous device. As the bubbles rise through the feed solution, surface active species (A) in the feed solution adsorb to the gas-liquid interface, the surface being dominated by those molecules with a greater rate and extent of adsorption. Bubbles leave the surface of the feed liquid pool, entraining both adsorbed solute and bulk liquid (in the interstitium between bubbles) into the rising column of foam. The interstitial liquid drains slowly through the lamella between the individual bubbles returning any unadsorbed solute (U) to the feed solution. Drainage results in a thinning lamella which causes the gas bubbles to undergo

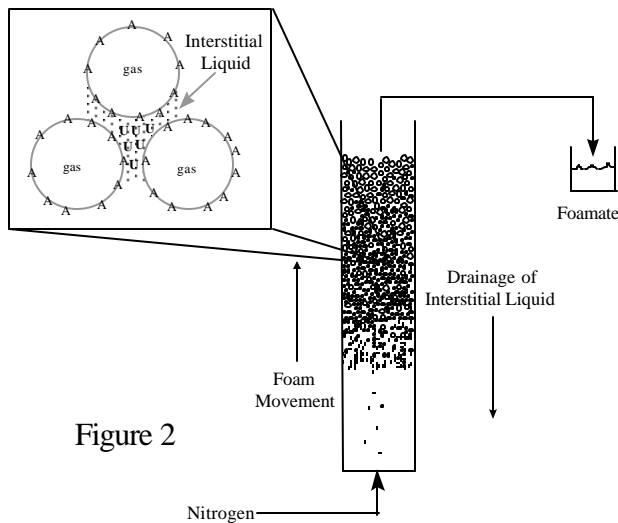


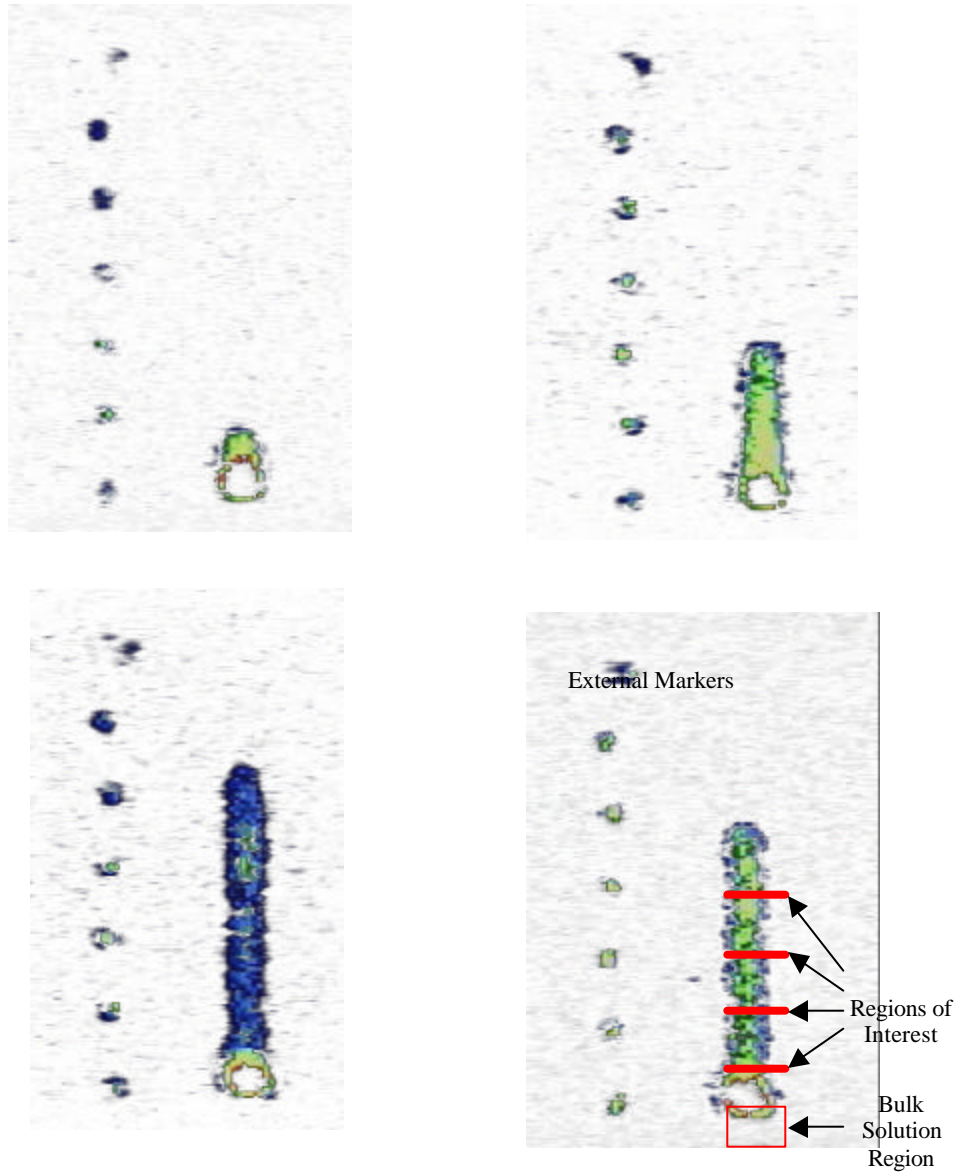
Figure 2

coalescence and interbubble gas diffusion. At the exit point, foam is collected and collapsed, forming the foamate liquid enriched in the surface active component.

Foam fractionation has many advantages over other more traditional separation methods for use in the separation and recovery of biological products such as proteins and enzymes. Besides low capital and operational costs, the application to dilute protein solutions would be advantageous because separation efficiency generally increases with a decrease in species concentration. Foam fractionation is also fast, and should be easily scaled for industrial use.

Dr. Jay's lab has employed gamma scintigraphy to measure the volume of liquid holdup in foam fractionation columns. The radionuclide ^{99m}Tc -pertechnetate ($^{99m}\text{TcO}_4^-$) was added to the bulk solution as a marker of the aqueous phase, and images were obtained using a scintigraphic imaging device.

Serial scintiphotos were obtained which reflected the water content in the interstitial lamellae of the bubbles as they moved up the column. A dedicated software program was used to flag thin Regions-of-Interest (ROIs) at various column heights. Comparing radioactive counts in these ROIs to a ROI of similar size in the bulk solution provided a measure of the liquid holdup at the various heights above the bulk liquid-foam interface.



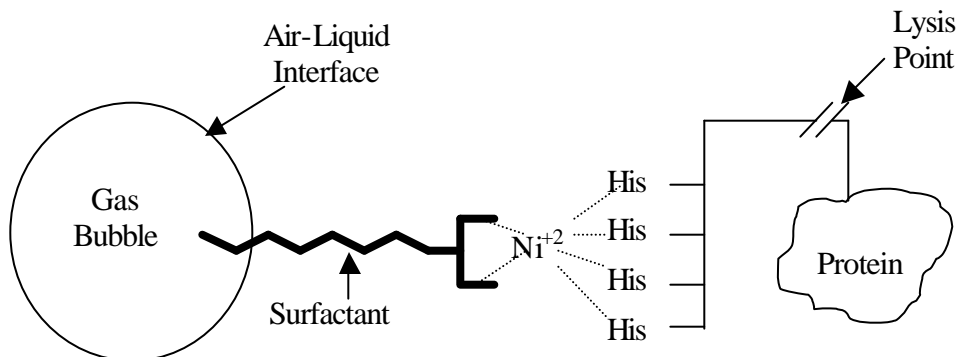
This work was presented at 17th Pharmaceutical Technology Conference and Exhibition in Dublin, Ireland (March 24-26, 1998) and earned the **Mendell Award** as the outstanding presentation of the conference

Improved Recovery of Engineered Pharmaceutical Proteins from Tobacco Plant Extract

Czarena Crofcheck, Michael Jay and Paul Bummer

Recently there have been significant advances in the development of transgenic tobacco, which can be used as a solar powered bioreactor, producing commercially attractive pharmaceuticals or enzymes. Several plant biotech companies have identified valuable product targets, but there is a need for acceptable production practices and industrial scale process development before transgenic plants can provide a new market for growers. The cost of protein recovery and purification may be the determining factor in whether a product is economically viable. One economically viable recovery process that has received new interest is foam fractionation, where a gas is bubbled through a dilute protein solution, the proteins adsorb to the water-gas interface, rise to the top of the solution, and can be collected as a protein enriched foam. This project focuses on the use of foam fractionation to separate engineered pharmaceutical proteins from tobacco. One disadvantage of foaming is its potential to denature the protein when the protein adsorbs to the bubble surface. It has been hypothesized that a protein can be engineered to favor binding to surfactant instead of to the bubble surface, and then the surfactant adsorbs to the bubble and facilitates removal by foaming. The protein is then removed with little exposure to the bubble surface, minimizing denaturation and maximizing protein recovery. In this study, the engineered protein will be added to tobacco extract and then appropriately preconditioned before addition to the foam fractionation column. Subsequently we will determine if the protein retains its structure and function following the foam fractionation separation process; adjust the solution and column parameters to optimize the recovery of the engineered protein; and develop a model to aid in further analysis and scale-up. The work proposed here is a necessary step before attempting to produce the engineered protein in tobacco.

We have proposed to engineer a peptide sequence into the protein structure that would chelate Ni^{2+} ions, e.g., a histidine “tag” (His). This engineered protein could be complexed with a specifically-designed surfactant that is expected to accumulate at gas-liquid interfaces like those occurring in a foam. Thus, the surfactant would adsorb to the gas-interface instead of the protein of interest (Figure 3). In this way, the protein would be located away from the gas-liquid interface and hopefully limit the extent of denaturation. After separation, the histidine tag could be easily cleaved from the protein of interest. This methodology is also attractive because, the optimum foaming conditions would be the same for any protein of interest; may allow for separation by foam fractionation even when the protein of interest is not easily foamed; and allow for selective separation of the protein of interest, leaving behind surface-active by-products.



This work is being supported by the following grants:

Foam Fractionation of Engineered Proteins from Tobacco Plant Extract. Tobacco and Health Research Institute. (P.I.: C. Crofcheck). \$37,000. 10/1/01 – 9/30/02.

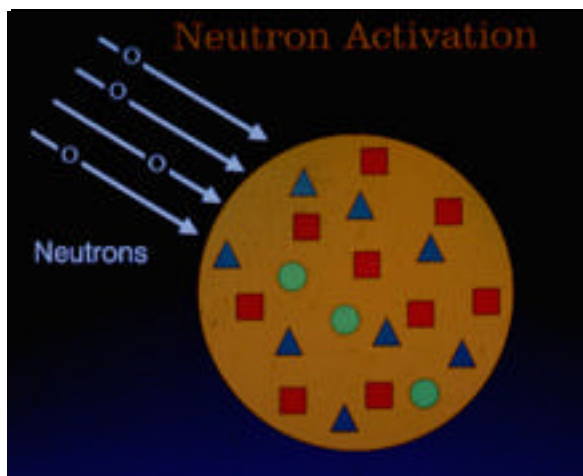
Improved Recovery of Engineered Pharmaceutical Proteins from Tobacco Plant Extract. Kentucky Science & Engineering Foundation. (P.I.: C. Crofcheck). \$56,069. 2/01/02–1/31/04.

PREVIOUS RESEARCH ACTIVITIES

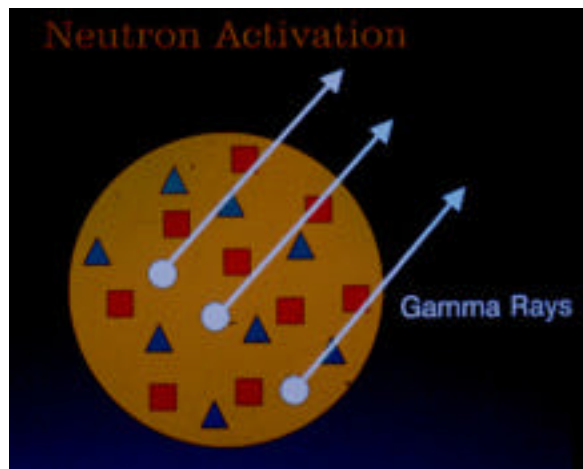
1. **Gamma Scintigraphy.** This involves the labelling of pharmaceutical dosage forms with gamma-emitting radionuclides and monitoring their biodisposition with a gamma camera following administration to human volunteers.



A gamma camera is capable of acquiring images in a static or dynamic mode, and is interfaced with a computer for data storage and subsequent image analysis. The quantities of radioactivity administered to human subjects is 100-500 fold lower than those routinely administered to patients undergoing a diagnostic nuclear medicine procedure. All human scintigraphic studies are reviewed by the Institutional Review Board, the Radioactive Drug research Committee, and the Radiation Safety Committee.



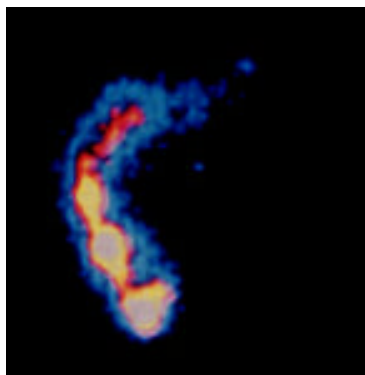
This frequently involves radiolabelling dosage forms using a neutron activation approach which was developed in Dr. Jay's lab and was the subject of the Ph.D. thesis of **Dr. Alan Parr** (now at GlaxoSmithKline). A small amount of a carefully chosen stable isotope (e.g. samarium-152) is incorporated into the dosage form during its manufacture. This allows preparation of dosage forms under industrial scale conditions without exposing the formulator to ionizing radiation. The finished dosage form is then exposed to a neutron flux.



The capture of neutrons by the stable isotope results in the formation of a radioactive isotope that will ultimately emit gamma rays that can be detected by the gamma camera. This procedure allows one to radiolabel dosage forms that cannot easily be labelled otherwise, e.g. polymer-coated controlled-release dosage forms.



Here is an example of a coated dosage form that was designed to release the active ingredient in the large intestines for the topical treatment of colitis. This time-lapse scintiphoto shows the intact tablet leaving the stomach and moving across the duodenum.

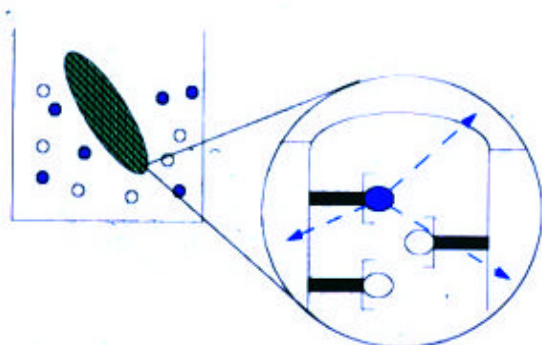


Four-to-five hours later, this dosage form has entered the ascending colon and has disintegrated releasing its contents demonstrating that the dosage form performed as it was designed to. The segments of the ascending colon can be seen clearly.

Gamma scintigraphy has been employed to study a variety of dosage forms and drug delivery systems including aerosols, ophthalmics, pharyngeal, etc. This imaging technique can also be used in *in vitro* applications (see foam fractionation section above). Much of this work was carried out in collaboration with **Dr. Robert M. Beihn** of Scintiprox, Inc.

2. Scintillation Proximity Assay.

Scintillation Proximity Assay



Radioimmunoassay is a competitive binding assay in which a radiolabelled antigen competes with an unlabelled antigen for a limited number of binding sites on antibodies. By binding these antibodies onto the pore surface of a membrane in which fluors have been entrapped within the membrane matrix, only those labelled antigens bound to the membrane are in close enough proximity to the fluors to induce scintillations. Thus, the step involving the separation of bound and unbound radio-antigen can be eliminated. This scintillation proximity approach has been applied to a one-step radioimmunoassay utilizing microporous polymeric membranes. The

results of this work were recognized by the Society of Nuclear Medicine by the presentation of the **Berson-Yalow Award**. This work was the Ph.D. thesis project of **Dr. Robert K Mansfield** who currently is employed by MDS Tricom in Tampa, FL.

Recent Publications

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C-H Hsu, Z Cui and M Jay. Nanoparticles engineered from microemulsion precursors for Coenzyme Q10 (CoQ10) delivery: preparation and characterization. AAPS Annual Meeting, Toronto, Canada. November 10-14, 2002. Submitted.

JC Weekley, RJ Mumper, and M Jay. Nanosuspensions as Aqueous Scintillation Cocktails. AAPS Annual Meeting, Toronto, Canada. November 10-14, 2002. Submitted.

C-H Hsu, G Ludwig, P M Bummer and M Jay. Solubility and in vitro Cytotoxicity of Ester Prodrugs of Nicotinic Acid for Pulmonary Liquid Ventilation. AAPS Annual Meeting, Toronto, Canada. November 10-14, 2002. Submitted

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