

Analytical & Pharmaceutical Group Research Efforts University of Puerto Rico, Mayagüez Campus

Mission

The mission of the Analytical & Pharmaceutical group is: “Become a preferred provider of pharmaceutical scientists, Near Infrared and Raman spectroscopic methods to facilitate the development and implementation of PAT manufacturing”.

The mission of the Analytical and Pharmaceutical group is based on the fact that the pharmaceutical industry is vital to Puerto Rico’s economy. Over 40 pharmaceutical companies at more than 60 manufacturing sites are located within an area of 3,500 square miles. The pharmaceutical industry provides Puerto Rico over 30,000 direct jobs and more than 100,000 indirect jobs since a full range of suppliers of materials, services, and support professionals are available on the island. Together they provide more than 60% of the island’s exports, and generate over one billion dollars of new investment each year. In 2001, this manufacturing force provided 16 of the top 20 prescription drugs sold in the United States.

The mission reflects the group’s principal focus in developing young pharmaceutical scientists with a strong background in analytical chemistry and pharmaceuticals. Students are equally encouraged to learn about analytical chemistry and pharmaceuticals, and present in both pharmaceutical and chemical meetings. The research activities are important as a means to develop human resources in support of Puerto Rico’s pharmaceutical industry, and at the same time contribute to the development of new methods to analyze intact pharmaceutical materials. The group’s projects include innovative research efforts, and also a number of activities to encourage the transfer of knowledge and methods to pharmaceutical manufacturing sites.

The mission also reflects the importance of Process Analytical Technology. The Food and Drug Administration has recently encouraged pharmaceutical companies to move towards innovative manufacturing strategies. These strategies involve quality by design manufacturing where processes are monitored with timely measurements of critical quality parameters, and this information is used for process control. This movement has been called Process Analytical Technology (PAT). A PAT guidance has been issued and it states: “Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system. The health of our citizens (and animals in their care) depends on the availability of safe, effective, and affordable medicines.”¹ The availability of drugs cannot be taken for granted, as FDA’s list of drug shortages usually contains several products, and most drug shortages are related to manufacturing problems.² The mission reflects that the group is not totally focused on analytical chemistry and is dedicated to improving pharmaceutical manufacturing.

University of Puerto Rico – Mayagüez Campus

The Analytical & Pharmaceutical group is part of The University of Puerto Rico which has over 70,000 students and is composed of 11 campuses. The Mayagüez Campus has about 12,000 students, and is the only campus with Engineering and Agricultural programs, and as such attracts a large number of students that are very talented in science and mathematics. The campus currently has over 1000 graduate students in over twenty programs that offer master degrees and Ph.D. programs in Marine Science, Civil Engineering, Chemical Engineering, Computing Information Sciences and Engineering and Applied Chemistry. The Department of Chemistry has 42 students working towards a Ph.D. degree, 40 students in the M.S. in Chemistry program, and over 240 undergraduate students.

Group Composition

The research group is currently composed of 3 graduate students, and 8 undergraduate students. The 3 graduate students are progressing towards an M.S. in Chemistry, and the undergraduate students are from the Chemistry, Chemical Engineering, and Industrial Biotechnology programs.

The Analytical & Pharmaceutical Group is emphasizing undergraduate research efforts. Two recently approved research grants will provide excellent opportunities for talented students to continue towards a Ph.D. while performing research related to the pharmaceutical industry and developing as important future contributors to our pharmaceutical industry. However, it is necessary to reach talented students early in their undergraduate careers, and make them aware of the excellent opportunities in research related to pharmaceutical materials and processes. Thus, the Analytical and Pharmaceutical group now has 8 talented undergraduate students performing research.

Pharmaceutical Engineering

Our group is part of the Pharmaceutical Engineering program at UPR-Mayagüez that has recently earned two very prestigious grants in collaborations with Rutgers, Purdue, New Jersey Institute of Technology. The first grant obtained was an IGERT grant for competitive research and education in nanopharmaceutical product and process development. The second research grant is the prestigious Engineering Research Center award, the largest grant awarded by the National Science Foundation. The NSF Engineering Research Center (ERC) is being established with a \$15 million, five-year grant to enhance the quality and consistency of materials used in drug tablets, processed foods, agrichemicals and other composite organic products. Research will focus on the structure of component materials, including particle shapes and sizes and forces that bind them together. The center also will study how to use particle engineering to efficiently produce structured materials in large quantity in a consistent and cost-effective manner.

Current Research Projects

Physical Information to Understand Pharmaceutical Processes

The use of NIR spectroscopy to obtain physical information from pharmaceutical processes constitutes the principal research project in the group. The scientific literature repeatedly mentions that NIR spectra provide both physical and chemical information. However, most NIR applications have involved removing the majority of the physical information from spectra to obtain chemical information such as drug concentration.³

Near infrared spectroscopy can contribute to pharmaceutical manufacturing with applications to determine identity, polymorph and drug content.^{4,5} However, the use of NIR spectroscopy to provide both physical and chemical information offers the greatest promise to improve pharmaceutical manufacturing. The use of NIR spectroscopy for physical measurements has been very limited.⁶⁻⁸ Pharmaceutical manufacturing processes are often controlled by physical interactions between particles, even though Quality Control groups usually use chemical tests to evaluate these processes. The lack of physical understanding leads to many of the production problems observed in pharmaceutical manufacturing.

Determination of Drug Content in Solid Oral Dosage Forms

The second research priority is the use of NIR spectroscopy to determine drug content in tablets. Current analytical methods involve the use of High Performance Liquid Chromatography (HPLC) and extensive sample preparation to determine the drug content of tablets, where only 10 – 30 tablets are analyzed in a batch that may contain several million tablets.¹⁰ NIR spectroscopy is capable of obtaining spectra of tablets, and multivariate methods are then used to predict the drug content in tablets. The research group has now acquired extensive experience in the determination of drug content in pharmaceuticals blends and tablets.⁹⁻¹⁴

The group is currently working in the determination of drug content in tablets where the drug content is less than 1.0% (w/w). The determination of drug content is especially critical in potent drug formulations, where a 0.1 mg drug aggregate could represent a 100% overdose for a unit dose of 0.1 mg. However, the majority of published applications have been in tablets with over 20% (w/w). The determination of drug content in a formulation with 0.5 – 1.0% (w/w) drug content was recently described.¹⁰ In another recent study the detection limit for low drug content pharmaceutical mixtures was estimated as being 0.2 – 0.3% (w/w).¹³

The next challenge is the transfer of drug content procedures from academic labs to pharmaceutical companies. This challenge involves method development, maintenance of the calibration model, and incorporating the method within the company's Quality Control system. This will be a significant challenge, and one that we are preparing for.

Blending

The third research consists in using near infrared spectroscopy to monitor, understand, and eventually control pharmaceutical blending. This third area is important since blending processes

are part of the manufacture of solid oral dosage forms that constitute over 80% of the pharmaceutical products manufactured.

The evaluation of pharmaceutical blends has been a significant difficulty in manufacturing processes during the past 10 years, and companies have had many difficulties in sampling blends with sample thieves.^{13, 14} Stream sampling was proposed as an alternative and the drug content in the blends was determined with NIR spectroscopy.¹⁴ Current research efforts involve the use of a NIR spectrometer interfaced to a 16-quart V-Blender to obtain one spectrum during each revolution of the V-blender. Even though at least two researchers showed the feasibility of using NIR spectroscopy to monitor blending processes, the implementation of this technology in pharmaceutical manufacturing has been very limited.^{15, 16} The group is currently working with one local pharmaceutical company to implement in-line blend monitoring at their manufacturing site.

Lubrication of Pharmaceutical Blends

High volume pharmaceutical manufacturing requires the use of lubricants to facilitate tablet ejection from compressing machines. However, lubricants may also bring a number of undesired problems that have been widely documented in the pharmaceutical scientific literature. New analytical methods are needed to understand lubrication and provide process knowledge in support of FDA's Process Analytical Technology initiative. A new Raman spectroscopic method to detect magnesium stearate in powder blends and tablets has been developed.¹⁷ The group is also using near infrared spectroscopy to further understand the lubrication process.

Encouraging and stimulating the adoption of Process Analytical Technology

The group's support of the PAT initiative has involved two synergistic efforts. The first effort has been in performing research associated with the initiative. The second effort has involved encouraging the adoption of PAT in Puerto Rico, and encouraging the local manufacturing industry to be at the forefront of this important FDA initiative.¹⁸⁻²³ A PAT Discussion Group has been started with the participation of the principal pharmaceutical companies in the island, and the support of INDUNIV (Puerto Rico Industry University Government Research Consortium). This group meets every two months to facilitate the visualization and implementation of PAT in the island's pharmaceutical industry. In addition, several conferences have been organized to promote the adoption of PAT in Puerto Rico, and keep Puerto Rico at the forefront of pharmaceutical manufacturing.^{19, 20} This effort is progressing as evidenced in a recent conference two local pharmaceutical sites reported their progress in PAT applications.²⁴

Human Resources Contributions

A total of 12 students have completed their M.S. in Chemistry in our group since its beginning in 1999. A total of 5 of these students are currently working in Puerto Rico's pharmaceutical industry, 3 are in academic institutions, 1 in government, and 2 have continued studying towards a Ph.D. One of the undergraduate students will complete her Ph.D. in Analytical Chemistry at Purdue University in December of 2006.

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