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OUTSOURCING NEWSLETTER

Captivating Pre-clinical Advancements

OVERVIEW:

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This newsletter will be distributed and out for publication each quarter. Each issue of this newsletter will contain one main topic of interest to its members. We hope all members will enjoy this issue and will continue to share this with their colleagues and other sectors. We would be glad to hear what you think about the newsletter and about your ideas for topics for forthcoming issues.
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American Association of Pharmaceutical Scientists

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Message from the AAPS Outsourcing Community Chair

Elizabeth Hoffner
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Dear Colleagues,

It is with great pleasure we present to your our second newsletter of 2021. We have endeavored to include articles and content of special interest to the Outsourcing Community as well as the general membership of AAPS.

Thanks also to those of you that attended and contributed to our “Outsourcing Best Practices” panel at the end of April. It was an upbeat and engaging event and well worth a listen online if you did not have a chance to join!

We continue our efforts to bring to you relevant and timely content and welcome your membership and feedback. Please let me know how we can serve you better.

With kind regards,
Beth

Application of Dissolution Testing for API Quality Characterization

By Samir Haddouchi

Dissolution testing is an extremely powerful tool to acquire knowledge about pharmaceutical products. Unfortunately, dissolution profiles are often used without a complete understanding of their meaning and are often considered only when the regulatory agencies require us to provide data for a submission or to demonstrate appropriate batch-to-batch consistency.

Alternatively, one can use the dissolution technique in order to learn more about the properties of the Active Pharmaceutical Ingredient, the composition of the formulation as well as the route of administration. The scientist should drive to adapt the testing conditions, keeping in mind the aim of the in vitro dissolution method (e.g., formulation development, IVIVC, or Quality Control).

The in vitro profiles can represent either the dissolution rate of the active ingredient or the release rate from the finished formulation. A more frequent use of API characterization tools such as intrinsic and apparent dissolution (Eur. Ph. §2.9.29 and 2.9.43, respectively) can be of great help in achieving such a goal.

The intrinsic dissolution relies on testing the dissolution rate from a known and controlled surface, from pure API, with a theoretically null porosity. This allows a comparison without consideration of the physical properties of the powder.

The apparent dissolution is using the flow through cell dissolution concept (known as USP4) which has been used for many years for testing different dosage forms such as tablets and capsules. It is also known as the method of choice for extended release and poorly soluble drugs. Nowadays the flow through cell technology is used widely for testing API with respect to its rate of dissolution.

Using the flow through a cell, one can easily compare the biopharmaceutical properties of different batches of a drug substance, taking into account their physical properties.

Here is an example of a case study: Acetaminophen.

- Acetaminophen powder
- Acetaminophen crystal grade
- Acetaminophen capsule grade
- Acetaminophen fine powder
- Acetaminophen micronized
- Acetaminophen microcaps

When measuring the physical properties of the various batches (surface area and the particle size), the following results were obtained:

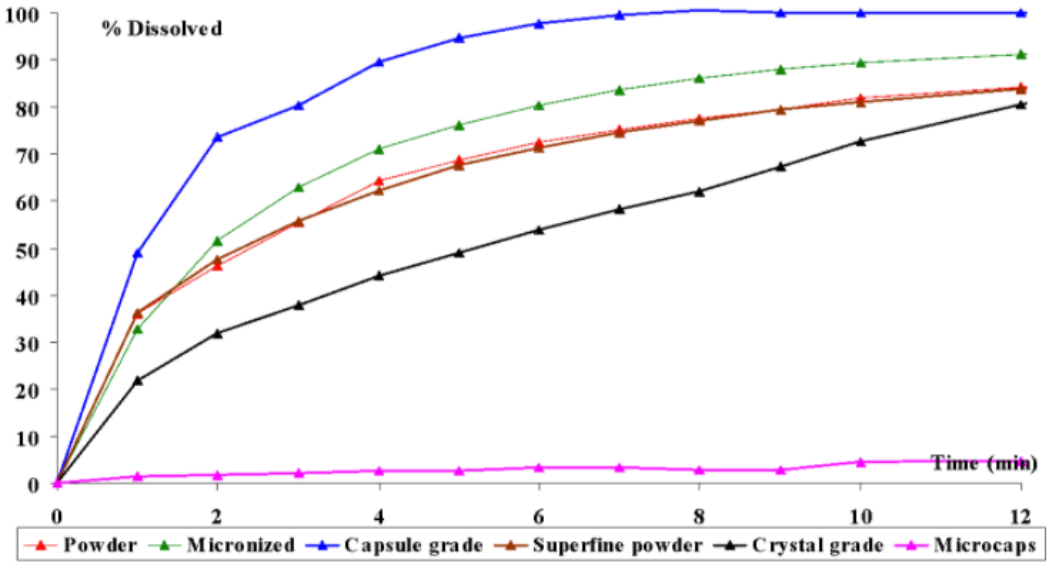
Product	Surface area (m^2/g)	Mean diameter (µm)
powder	0.16	88.45
capsule grade	0.53	394.4
crystal grade	0.33	58.86
fine powder	0.38	48.36
micronized	0.68	34.82
microcaps	---	419.8

All batches were tested using Intrinsic Dissolution Rate, with an amount of 100 mg per replicate, with a pH 5.8 aqueous buffer and 3 determinations per batch. The results obtained were very similar:

Product	K (h-1)
powder	1.8
capsule grade	1.7
crystal grade	1.8
fine powder	1.8
micronized	1.8
microcaps	---

Indeed, for Acetaminophen, there was no difference expected with regards to solid-state (polymorphism, hydrates, etc…). Thus, intrinsic dissolution rate was expected to be similar, despite the difference of physical properties.

The same batches were tested using Apparent Dissolution Rate being done with the Flow-through Cell dissolution system (USP4), using cells for powder, in a closed system, with the same pH 5.8 aqueous buffer, with a flow rate of 16 mL/min and 100 mg per replicate. The results obtained show the different curves below.



Conclusion

The results above demonstrate that it is possible to characterize the biopharmaceutical properties of active pharmaceutical ingredients.

Having such knowledge allows for example to investigate the root cause of bio-inequivalence and to proceed with a more systematic approach for drug product optimization.

Both intrinsic and apparent dissolution testing bring different information about the API tested but, overall, it is of importance to proceed with such API characterization.

Such knowledge may obviously guide the development of a new formulation but can also be very valuable during the life cycle of any product, when considering post approval changes such as new sources/ suppliers of raw material and its possible impact on the performance of the drug product.

Samir Haddouchi
Managing Director
SPS Pharma Services

Prior to joining SPS Pharma Services in 2005, Samir spent more than 10 years in the pharmaceutical industry.

As a chemist, he started working on the analytical development of agrochemical compounds at Sandoz Agro in the region of Basel (Switzerland).

During the Novartis merger, he moved to Orléans (France) in 1998 to join the analytical group in the technical development department where he became responsible for dissolution.
In 2005, he resigned from Novartis to create SPS Pharma Services in Clermont Ferrand which is the first and only CRO specialized in Dissolution and Release Testing.
Since then, Samir manages SPS facility and is in charge of projects management.

In April 2013, SPS Pharma Services moved to a new larger facility in Orleans (France) in order to ensure better efficiency and provide a broader range of services to its clients, including cGMP routine testing.

The facility has been successfully inspected by US FDA and is registered as Pharmaceutical Establishment for both US and Europe.

Fields of interest and expertise: analytical development (LC), in vitro dissolution and release testing (all techniques from USP1 to USP7), in vitro-in vivo correlations (IVIVC), formulation development, laboratory automation.

Samir is regularly invited as speaker in international conferences as well as expert for various organizations (scientific societies and Health Authorities).
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Intraoperative radar using fluorescence-guided surgery

By Aishwarya Bapat

Surgical management of disease is an integral part of health care. Achieving surgical goals allows for optimal disease treatment while preserving form and physiological function, depending primarily on visualization [1]. Recently, surgeons have started to use fluorescent light for surgical navigation to improve intraoperative identification and to guide resections of lesions [2,3]. The first use of fluorescence imaging in surgery was done in 1948 using intravenously administered fluorescein to visualize intracranial neoplasms during neurosurgery4. Imaging techniques such as X-ray, Computed tomography (CT) , Ultrasound (US), and Magnetic resonance imaging (MRI) are mainly used for surgical planning or interim assessment because they do not provide real time intraoperative guidance [3]. Fluorescence guided imaging provides deeper anatomical information and real time intraoperative feedback to aid in removal of diseased tissue.

Being able to see structures which need resection, and which need to be preserved is a profound unmet clinical need in surgery. This stems from the fact that visible light cannot

penetrate into blood and tissue due to high photon attenuation from absorbance and scatter [5]. Technology using near-infrared (NIR) fluorescent light within the NIR window of 700 to 900 nm lacks the ionizing radiation thus making it safe to use for both patient and caregiver [6]. It offers advantages such as low background and absorption of biomolecules, as well as favorable tissue absorbance and scattering. One major limitation of NIR fluorescence imaging is the lack of clinically available high performance targeting agents which can be attributed to the high developmental cost and complex regulatory requirements [5]. NIR fluorescent contrast agents specific for different targets have been developed including agents for vascular mapping and tissue perfusion, angiograms of the eye, cancer, ureter and urinary calcification, nerves and intervertebral disks, diseases of brain, gastrointestinal tract, skin, inflammation etc [5,7].

Most fluorescent agents that highlight non-diseased tissue take advantage of structural characteristics or prevalent binding sites and illuminate an entire structure or tissue type [1]. Contrast agents applicable to NIR fluorescence imaging fall into two categories namely visible and NIR [8]. Some of the key parameters for NIR fluorophores are excitation, emission, extinction coefficient, quantum yield, solubility, photostability, pharmacokinetics, toxicity, particle size, charge, and charge distribution properties [5,9]. Currently, the only FDA approved agents are Indocyanine green (ICG), δ-Aminolevulinic acid (5-ALA), and Methylene blue (MB). Other novel fluorophores reported in the process of clinical translation are IRDye800, cyanine derivatives, and quantum dots [8]. Other delivery systems that are being investigated as imaging agents include polymer dots, carbon dots, antibody-drug conjugates, nanoparticles etc. each having its own unique characteristics [10]. Apart from these agents, smart probes are being developed which targets specific tissue or biochemical process [1]. Some of the targeting strategies used for NIR fluorophores include enhanced permeability and retention effect, targeted NIR fluorophores, pH-activable NIR fluorophores, and tissue specific NIR fluorophores etc [9].

Several NIR image guided systems are commercially available or evaluated in clinical settings. A typical fluorescence imaging system consists of a spectrally resolved light source which excites a fluorophore within a turbid medium [5]. The agent is administered to visualize the organ or tissue of interest with sufficient sensitivity and contrast [3]. A typical fluorescent IGS instrument has three fundamental components: an excitation source, a collection source, and a display unit. The excitation sources excite the fluorophore at a working distance from the surgical field and emits a light that does not overlap with the emission wavelength of the fluorophore.

Common excitation sources include light-emitting diodes, laser diodes, and/or filtered broadband lamps [8]. Each of the sources has its own advantages and disadvantages and the choice for one should be decided after careful consideration [5]. The collection source then relays the NIR signal from the excited fluorophore to the camera for interpretation. The FIGS hardware must be able to filter out and minimize background light to achieve a high level of sensitivity [8]. An adjustable field of view is mandatory for surgical imaging and can be accomplished using either zoom or fixed magnification lensing [5]. Display monitors are used to integrate the NIR and surgical field images to provide real time feedback to the surgeons during surgery [8]. The *Novadaq SPY* system is an US FDA approved intraoperative NIR fluorescent imaging system. Some of the other systems available for experimental use are Fluoptics Fluobeam, and *FLARE* imaging system etc [11]. Increasing sensitivity to low contrast agent concentrations, quantification of fluorophore concentration, and adapting to multi-fluorophore imaging capabilities are some of the most important considerations for

fluorescent image-guided surgery instrument development.

The timeline for clinical translation of a new imaging system or contrast agent includes pre-clinical validation, manufacturing under cGMP, clinical trials to support regulatory approval, marketing, and post-marketing surveillance. To fulfill regulatory requirements, many current clinical trials are centralized around investigating safety and efficacy of the fluorescent IGS agents [12]. Some of the key clinical parameters include optimal visualization by maximizing signal to background ratio to maximize contrast, chosen target, type of contrast agent, route of administration, and the imaging goal.

In summary, fluorescence imaging has the potential to support surgical procedures and the feasibility to improve clinical outcomes and patient management. Some of the unmet needs requiring attention are improved characteristics for pharmacokinetics and specificity as well as sophisticated image analysis softwares [3]. Fluorescence imaging is a high innovation research field and has transformative potential and any real time improvement in the intraoperative visual differentiation between different tissue types would represent a significant advance [1,5,13]. Integration of fluorescence imaging with other non-invasive imaging approaches can empower precision of cancer surgery. Some of the potential future applications for FIGS to address the vast variety of clinically unmet needs include multimodal imaging to increase accuracy of diagnosis and photodynamic therapy for theranostic purposes [8].

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Barriers to targeted renal delivery and strategies to overcome them

By Chinmay M. Jogdeo & David Oupický

The kidneys are an important organ of the human body responsible for getting rid of waste products, toxins, and drugs through the urine. The kidneys also play a vital role in maintaining the fluid balance of the body. Additionally, the kidneys have multiple endocrine roles. They secrete hormones of the renin-angiotensin system and are involved in the production of calcitriol, erythropoietin, and prostaglandins. Apart from this, they also play a role in the activation of vitamin D and the metabolism of insulin. Overall, the physiological roles of the kidneys extend far beyond their excretory function. Hence, renal pathologies have a devastating effect on the human body [1]. Acute kidney injury (AKI) and chronic kidney disease (CKD) are among the most common kidney diseases. According to the Centers for Disease Control and Prevention, each year, about 15% of American adults, or 37 million people, are expected to have CKD, and 18% of all hospitalized patients have AKI worldwide [2, 3]

Although the incidence of kidney diseases is high, effective treatments have remained limited. Effective pharmacological therapies for these diseases do not exist as current medication only slows disease progression. Ultimately, many patients experience kidney failure, with dialysis and kidney transplantation as the only treatment options. With the world experiencing a global pandemic, patients needing maintenance dialysis were disproportionately affected. A recent study indicated a very high mortality rate of 20% among maintenance dialysis patients with COVID-19 [4]. Thus, better treatments are needed. The inability of therapeutic interventions to reach adequate concentrations in the kidney is a major hurdle in developing better therapies. This limitation could be overcome by kidney-targeted nanomedicine and nanoparticle-based drug delivery strategies. Efforts have been directed in this direction; however, no such approach has reached the clinic yet [5].

The barriers to kidney-targeted therapies are multifaceted and begin from blood circulation, entry into the kidney, and reaching the target sites within the kidney [6]. The kidney has a million filtration units called nephrons. Each nephron consists of a glomerulus with a tuft of microcapillaries responsible for the charge and size-selective filtration of the blood. The glomerular filtration barrier (GFB) of the glomerulus comprises the glomerular endothelial cells, the glomerular basement membrane, and the podocytes. This unique three-layered structure has a net negative charge and a series of pores of varied sizes, which introduces charge and size restrictions that delivery systems must circumvent to escape blood circulation through the kidney [7].

Broadly, nanomaterials with a hydrodynamic diameter of less than 10 nm and molecular weight less than 30-50 kDa readily undergo glomerular filtration. However, shape plays a significant role in influencing this cutoff. Recent research has unveiled that nanomaterials with a high length to width aspect ratio may easily pass through the GFB, given their diameter is smaller than the size cutoff. This holds true even if their molecular weight is greater than the cutoff for glomerular filtration. This was demonstrated by Ruggiero et al. using 300 nm long single-walled carbon nanotubes [8].

Since the GFB is negatively charged, electrostatic forces also affect filtration, and cationic materials pass through the GFB more efficiently. However, the liver, spleen, and lungs are major obstacles in the intravenous delivery of such cationic systems. The blood circulation time is an important parameter that affects the efficiency of most systemically administered drugs. Before reaching the kidneys, the nanoparticles encounter blood cells, platelets, proteins, and macrophages which can affect their biodistribution [6]. To overcome these limitations, several passive and active delivery approaches based on prodrugs, antibody-drug conjugates, polymeric drugs, low molecular weight protein and peptide-drug conjugates, and RNA interference-based systems have been investigated in the treatment of kidney diseases.

Research into kidney-targeted delivery systems started in the 1990s, and in 1994 Actinomycin D loaded poly (isobutyl cyanoacrylate) nanoparticles that accumulated in rat mesangial cells were first described as a targeted delivery system for glomerular mesangial cells [9]. Since then, a number of passive and actively targeted delivery systems have been developed.

Based on the paradoxical glomerular filtration and tubular accumulation of long single walled carbon nanotubes described by Ruggiero, Alidori et al. successfully used ammonium functionalized carbon nanotubes to simultaneously deliver siRNAs against Mep1b and Trp53 for the treatment of AKI [10]. Disregarding the perceived size restrictions of the GFB, Williams et al. synthesized mesoscale PLGA-PEG nanoparticles (about 400 nm in size), which surprisingly accumulated in the kidneys via the basolateral side driven by the pressure drop in the nephrons and the large absorptive pressure of the peritubular capillaries [11]. Drugs attached to polyvinylpyrrolidone-co-dimethyl maleic anhydride [poly (VP-co-DMMAn)] nanoparticles showed about 80% accumulation in the kidneys 24 h after intravenous administration [12, 13]. More recently, Jiang et al. described the preferential renal accumulation and uptake of triangular, rectangular, and tubular DNA origami nanostructures and the reno-protective properties of rectangular nanostructures against AKI [14].

Targeting ligands further advanced the development of renal-targeted delivery systems, especially systems targeting the renal tubules. Researchers have taken advantage of the abundance of unique receptors and transporters on the renal tubular cells. The CD44, folate, and megalin-cubulin receptors on the tubular cells are three of the most widely used targets. Low molecular weight chitosan, a natural ligand for the megalin receptor, is one of the most popular polymers used to target the kidney [15-17]. Since the basic structural unit of chitosan is glucosamine, Lin et al. Synthesized 2-deoxy-2-aminodiglucose conjugated prednisolone for targeting the kidneys [18]. Recently, our lab utilized the CXCR4 chemokine receptor, which is overexpressed in AKI kidneys to deliver siRNA against p53 to injured proximal tubule cells. Low molecular weight proteins (LMWP) have also been extensively studied to deliver drugs to the proximal tubular cells. Lysozyme, which almost freely passes through the GFB, is the most widely researched LMWP [19, 20].

Similarly, protein fragments, including fragments of albumin, have also been used [21]. Apart from LMWPs, peptides have been used to target the kidneys. Geng et al. conjugated Captopril to the G3-C12 peptide and reported 2.7 times increase in kidney accumulation compared to Captopril alone [22]. KTP is a kidney-targeted peptide composed of seven amino acids (MCLPVAS). Wang et al. utilized KTP to modify rhein-loaded nanoparticles, which showed excellent kidney-targeted distribution in mice with streptozocin-induced diabetic nephropathy [23]. Similarly, (KKEEE)3K is another peptide that can be specifically taken in by the proximal tubular cell by megalin receptors [24, 25].

The renal tubules play an important role in the reabsorption of solutes from the urine, mediated by a number of receptors and transporters. Hence, a majority of the kidney-targeted systems have achieved tubular targeting. However, the glomerulus is the first part of the nephron that encounters any potential toxic substances and is often affected prior to tubular injury. Hence, developing delivery systems targeting the glomerulus is equally important. Ásgeirsdóttir et al. utilized liposomes conjugated with anti-E-selectin antibodies to deliver dexamethasone to the glomerular endothelial cells of mice with anti-glomerular basement membrane glomerulonephritis. A 3.6 times higher accumulation of targeted liposomes compared to non-targeted liposomes was seen [26]. Lupus nephritis (LN) is one of the most detrimental complications of systemic lupus erythematosus. LN is initiated by the deposition of an abnormal immune complex in the glomeruli and the subsequent activation of immune effector cells, which leads to renal tissue damage. If not managed effectively, LN can eventually result in kidney failure. Jia et al. developed a micelle forming dexamethasone prodrug which primarily accumulated in the kidneys of mice with LN. Compared to free dexamethasone, the prodrug demonstrated no toxicity and was more efficacious in attenuating LN progression than the free drug in a 5-month long study [27, 28].

Targeted delivery systems have the potential to overcome barriers and achieve localized, selective delivery of therapeutic agents to the kidneys, thus reducing the dose and associated side effects. Although significant advances have been achieved in the lab, translation to the clinic is still a distant dream. Developing better, reproducible animal models and understanding the anatomical and physiological differences between healthy and diseased kidneys will help bridge this gap between the lab and the clinic. Moreover, shedding light on the complex relation between the shape, size, charge, and other physical properties of the delivery systems and the kidneys will greatly boost the design of better, translatable delivery systems.

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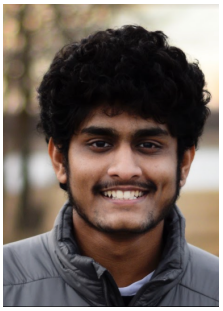

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Spotlight on..

Anahita Keyhani Ph.D

Dr. Keyhani joined Altasciences in May 2015, and has over 20 years of CRO experience in regulated bioanalysis for preclinical and clinical development. As Senior Director, Scientific Operations, Mass Spectrometry, Dr. Keyhani leads a team of over 40 scientists dedicated to method development and regulated bioanalysis. Prior to joining Altasciences, her professional career was spent mainly within the bioanalytical group at Charles River Laboratories. She also worked at Merck in Montreal as a Senior Scientist in Pharmaceutical Research and Development and, during her Masters, participated in research and development projects in the development of pediatric and adult nutritional products at Abbott's Ross Product division. In addition to her role as a scientific and client relationship manager; she actively trains, coaches and mentors scientists from cross-functional departments throughout Altasciences.

Dr. Keyhani received her Bachelor of Science and Master of Science degrees from Ohio State University, with a PhD from McGill University.
Dr. Keyhani has authored or co-authored over 15 peer-reviewed publications. She has presented numerous posters and presentations in the bioanalytical domain with focus on bringing innovative workflows into the framework of regulated bioanalysis

Why and how did you choose your sector in the beginning of your career path?

In 1991, I completed my MSc at Ohio State University, and due to my husband's employment moved to Montreal, Quebec. The broad strokes of my life plan included a PhD in science, a family, and a career. Before the wonders of the internet and information at the click of a button, I simply showed up at a Professor's door to chat and discuss their research focus, and asked if they were interested in taking on a graduate student. I was accepted at McGill University in the Department of Food Science and Agricultural Chemistry, to work on the Maillard Reaction with Dr. Yaylayan. The topic interested me, and as my PhD supervisor was starting his academic career and developing a research program, it was a great opportunity to work on novel research. In September of 1992, I started my PhD on a stimulating and rewarding research topic. Two things became evident by 1994: I was not interested in an academic career and industry careers in Montreal for PhD-level flavor chemists were practically nonexistent. Leaving Montreal for career aspirations was not a viable option, so I evaluated my technical skill set to determine what was transferable to industry opportunities in Montreal.

I became aware of Contract Research Organizations (CROs) and secured a position as a CRO laboratory scientist. My graduate work involved gas chromatography-mass spectrometry, and at the time CROs were investing in the quantitation of analytes in biological matrices using liquid chromatography-mass spectrometry (LC-MS).

As an entry-level Scientist, I was assigned bioanalytical method development, validation, and sample analysis projects. As 1997 represented the early days of bioanalytical outsourcing, significant effort was needed to develop SOPs, workflows and logistics. Fortunately, the expertise I had acquired in food science and nutrition were translatable and of significant value in setting up bioanalysis workflows. So rather than choosing a career path based strictly on my studied discipline, a combination of professional and personal considerations led to a fruitful endeavor into the world of bioanalysis, which has continued to this day.

To what degree do you think mentorship has benefitted your career?

The concept of "mentorship" was not in *Vogue* early in my career and the interactive professional tools that we have now certainly were not available. At the time, when opportunities arose, I would discuss my challenges with individuals in my professional and personal network, and learn from their experience and knowledge. Times have changed, and now mentorship and knowledge-sharing is the norm. In transitioning from my previous role as a scientist responsible for LC-MS bioanalysis projects and program management, to my current leadership role managing people and departments, mentorship and training, internal and external to Altasciences, has proved beneficial.

Now that you have advanced within your career, what do you enjoy about being a mentor?

Passing on knowledge to the next generation of blossoming staff provides the opportunity to clarify and embed the lessons I've learnt within myself. Providing guidance, training and support to help people determine the best career path forward is one of the most rewarding aspects of my job. I often work with new staff to develop an understanding that in addition to the science; protocols (Study Plans), validation plans, laboratory phase plans, method and general SOPs, and regulatory guidance documents provide the framework and road map for generating quality data. How best to approach a new bioanalytical program, write standard operating documents, hire the right staff, negotiate timelines, communicate with clients and work with different personalities all while maintaining a positive influence for change came with time and practice. There is so much knowledge to share.

Several women have formally requested me to be their mentor. One of the challenges they all have in common, regardless of industry or expertise, is how to communicate and advocate for themselves and their teams within organizational silos and hierarchies. This can be a tremendous challenge for female leaders, especially if they are new immigrants to Canada and the USA. These women are all highly accomplished, technically and scientifically. Their challenge is greater since there is the added navigation of work place cultural differences and accepted communication styles. I always enjoy sharing the lessons I have learned over the years, and hopefully facilitating their journey.

Having your career being developed within the CRO sector of pharmaceuticals, how has the involvement of CRO changed in the process of drug development, from the beginning of your career to now? How do you see the involvement of CRO in pharmaceuticals in the future?

My CRO career began in 1997, and has developed and evolved synchronously with the transformation and ascent of the CRO industry, particularly for bioanalysis. Twenty years ago, CRO bioanalytical laboratories supported sample analysis for bioequivalence studies, and, at times, analysis of bioanalytical samples supporting Phase III studies.

At that time, the majority of the pharmaceutical industry's bioanalytical samples for drug development were analyzed in their own laboratory facilities. The innovator companies had the personnel and infrastructure to manage the bioanalysis for all phases of drug development (discovery, GLP, regulated bioanalysis), and maintained complete oversight and ownership of the bioanalytical method development, validation and sample analysis as their drug candidates progressed.

The acquisition of life science start-ups by established pharma companies to rejuvenate their R&D pipeline, the development of biotherapeutics, and the technology revolution intersected in the early 2000s, and transformed the dynamics of bioanalysis. The smaller companies had already implemented outsourcing strategies to have CROs support bioanalysis, and rather than move the laboratory work in-house when acquiring the small companies, pharmaceutical firms left the work with the CRO labs. Over time, the financial and operational benefits of this model became apparent, and the era of lab procurement groups and outsourcing began in earnest.

The momentum in the development of biotherapeutics, and regulatory guidance for immunogenicity, increased the demand for laboratory bandwidth to support bioanalytical analysis in preclinical and clinical studies. At the same time, the information technology revolution facilitated real-time communication and logistics between multiple stakeholders. This contributed to a sense of comfort and willingness to outsource laboratory analysis to CROs. Precision manufacturing (reduced lot-to-lot variability for consumables), instrumentation advancements (automation, increased sensitivity, specificity, multiplexing), and simplified software interfaces permitted bioanalysis to be managed within the CRO model. Well-trained staff supervised by subject matter experts perform the sample management, routine bench work, data processing, and QC review. In addition, the types of samples generated in each clinical and nonclinical study increased as more analytes, metabolites, biomarkers, ADAs etc. could be measured, to enrich the scientific dossier.

The paradigm shift of the past two decades has significantly benefitted CRO bioanalytical laboratories and has elevated career opportunities and progression for employees. CRO laboratories have transformed into centers of scientific, regulatory, and logistical expertise, and provide the opportunity for impactful career opportunities in drug development.

What soft skills and techniques are essential in the CRO environment for management of bioanalytical validations and sample analysis?

First and foremost, bioanalysis requires a method aligned with the scope of the study and intended use of the data. Successful bioanalytical scientists need to develop a wide range of both hard (technical and measurable) and soft (people and personality) skills. Bioanalytical scientists can build trust and empathy with the project sponsor/client by proactive communication, coupled with an ability to demonstrate that the project/program needs are well understood (scientifically and operationally), and that the laboratory execution and management of the study are well controlled.

Beyond the science, data, and reporting, the day-to-day includes communicating and influencing stakeholders (internal and external), managing technical staff, setting and adjusting deadlines, prioritizing tasks, motivating staff, and planning and monitoring workflow. Interfacing between a client or stakeholder's expectations and the reality of what data can actually be delivered, and when, requires negotiation and communication abilities.

Critical ingredients for success include the flexibility and resourcefulness to make the necessary adjustments with a solution-oriented mentality in the face of unexpected issues, such as emergent science and logistical hurdles.

What advice would you give to young professionals starting out?

Always work to excel at the job at hand and find opportunities to learn and contribute to your new workplace, and build awareness of your place in the work ecosystem. Your initial career opportunity is just a stepping stone on a path that you probably have not contemplated, or imagined. Every position provides the opportunity to develop new or complementary skills. Critically review your organizations' internal and external websites, since this will provide significant insights on their core business, messaging and values. Look for an organization with exceptional leadership and management, and if there is something you are interested to know more about, set up a time to meet with colleagues in person or virtually. I have never turned down such a request and am always happy to help.

Be aware that your key contributions and personal attributes will be noticed, and often rewarded with opportunities. For example, be punctual, dependable, provide quality work, and avoid unnecessary confrontation. Make the effort to connect with people at all levels of the organization. Regardless of your intentions, how you are perceived by your colleagues, subordinates, company management, and even friends, could have a significant impact on your future career prospects. Every opportunity I have had in my professional career has been due to individuals in my network advocating for me when I was not present. Social media platforms and the ease of reaching out to people have created an environment where it is easy for prospective employers and colleagues to learn much about you. Be aware that this holistic picture of you exists, and ensure that it presents your skills, abilities, and personality in the best possible light.

AAPS Student Chapter:

University of Maryland Eastern Shore

By: Himali Gujarati, Chair and Patrice Jackson-Ayotunde Ph.D, Faulty Advisor

The University of Maryland Eastern Shore AAPS Student Chapter was established in 2017 and is composed of Ph.D. Pharmaceutical Science graduate students and Postdocs. The primary goal of the chapter is to enhance scientific knowledge through seminars/workshops and professional development through networking opportunities. AAPS has provided us such opportunities and to explore the field of pharmaceutical science even further. AAPS's student chapter resources have a lot to offer, from inviting a guest speaker, organizing industrial visits to connecting with fellow student chapters. Annually, our student chapter conducts "Outreach Month'' in April. The goal of our outreach month is to spread words about our student chapter. We visit and interact with local high school, community colleges, and universities students. We plan several activities and each member plays a significant role. Every year our students make visits to Salisbury University and Wicomico Community college and have an interactive session with presentation and communicating with interested students and faculties. The events were continued as virtual sessions in the year of 2020 due to the pandemic.

To support student networking, mentorship, and career development opportunities, we made an industrial tour to Cadista Pharmaceutical Inc in 2018. Our students had an opportunity to gain first-hand experience of industrial operation and to communicate with the employees.To further explore the industrial field, we recently invited 3 guest speakers from industry to share their research and career journey. We hosted a virtual interactive session where students were able to ask career related queries.

Our panel had speakers from various fields of Pharmaceutical Sciences, Dr. Arthur Ciociola, VP and global Head regulatory affairs, Ophthalmology, Novartis, and Dr. Palem Asso. Director of drug safety quality management, Exelixis, was part of our panel. The chapter plans to continue such events in the future.

Our monthly meetings consist of planning and discussion for the coming months, where we all come together along with our faculty advisor Dr. Patrice Jackson-Ayotunde who guides us with our planning. Twice a month we have AAPS club lunches and dinner. To bring together all the members, we have held blowing nights, movie nights with snacks, and trips. Such activities help members to communicate better and build a stronger team. Another social activity where students are encouraged to participate is food can drive before Christmas holidays.

Year 2020-2021 was a slow one due to pandemic and COVID restrictions, but our members worked hard to bring new ideas each time and keep progressing. The year was full of fun activities done virtually or by following COVID guidelines. We hope to grow by each consecutive year and help our students to grow professionally and personally. In the future, we plan to collaborate with various other regional AAPS student chapters.

Better understanding the Organic Anion Transporters

By Julie Nguyen

Transporters have gained attention in the field of pharmacology as they are expressed throughout our bodies and play important roles in the absorption, distribution, and excretion of endogenous and exogenous substances including drugs. Organic anion transporters (OATs) are known to interact with a wide variety of negatively charged drugs and can impact their clinical safety and efficacy profiles. Unfortunately, little is known about OAT-drug interactions as they are difficult to discern on a molecular level in the absence of any solved crystal structures for OATs. Therefore, in a previous study, *in silico* homology models of hOAT1 and hOAT3 were generated based on the solved crystal structure for *Piriformospora indica* phosphate transporter (PiPT) [1]. The models were docked with their respective prototypical substrates, amino acid contacts involved in substrate recognition predicted, and single point mutations generated [1]. Following mutagenesis, singly mutated hOAT1 and hOAT3 transporters were subject to accumulation and saturation studies to determine their role in substrate binding and subsequent translocation [1]. The findings from this previous study indicated singly mutated constructs did not result in altered binding affinity (Km) [1]. However, the question remained whether these predicted amino acid contacts would significantly alter affinity when present in various double and triple combinations.

For my project, multiple combination hOAT1 and hOAT3 mutants were generated and functional accumulation screens were conducted to determine the impact on overall transport activity [2].

Mutants that retained transport activity were then further assessed by kinetic assays to determine any changes in Km [2]. Functional accumulation screens showed none of the hOAT1 multiple mutants retained para-aminohippurate (PAH) transport activity [2]. In contrast, the generated hOAT3 multiple mutants retained estrone sulfate (ES) transport activity [2]. Subsequently, kinetic analysis revealed that hOAT3 multiple mutants did not exhibit statistically significant changes in estimated Km values as compared to hOAT3 wild-type [2].

This study provides further insight as to the importance of these predicted critical amino acid residues in substrate binding interactions. Further characterizing these molecular interactions will allow for improved manipulation of drug substrate pharmacokinetics as well as prediction of drug-drug interactions, both of which can be utilized in drug design and development.

References:

1. Jay C. 3-D Homology Modeling of Organic Anion Transporters (OATS): Defining the Biochemical Basis for OAT-Substrate Interactions. 2019.
2. Nguyen J. Human Organic Anion Transporters 1 and 3: Structural Elements Impacting Transporter-Substrate Binding Interactions. 2021.

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Tips to have an attractive LinkedIn profile

- Use your LinkedIn summary to tell a story about yourself.
- Know your target audience and use the right keywords.
- Try to avoid use of empty buzzwords.
- List relevant skills.
- Choose a professional looking profile picture.
- Have a catchy headline.
- Try to get endorsements from others in your field of interest.
- List any certifications, licenses, Projects, Volunteer Experiences, Accomplishments you have and languages you know.
- Add links for any previous work you have done (such as publications, patents, etc.)
- Make sure your LinkedIn profile and resume match.
- Seek out relevant and recent recommendations.
- Start posting that you think are interesting and relevant.
- Join various LinkedIn Groups.
- Use the LinkedIn Alumni tool to connect with the alumni of your school/college.
- Do not forget to give honest recommendations/endorsements to people who deserve it.
- Use LinkedIn as a platform to share your thoughts and comments on topics that matter to you!

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