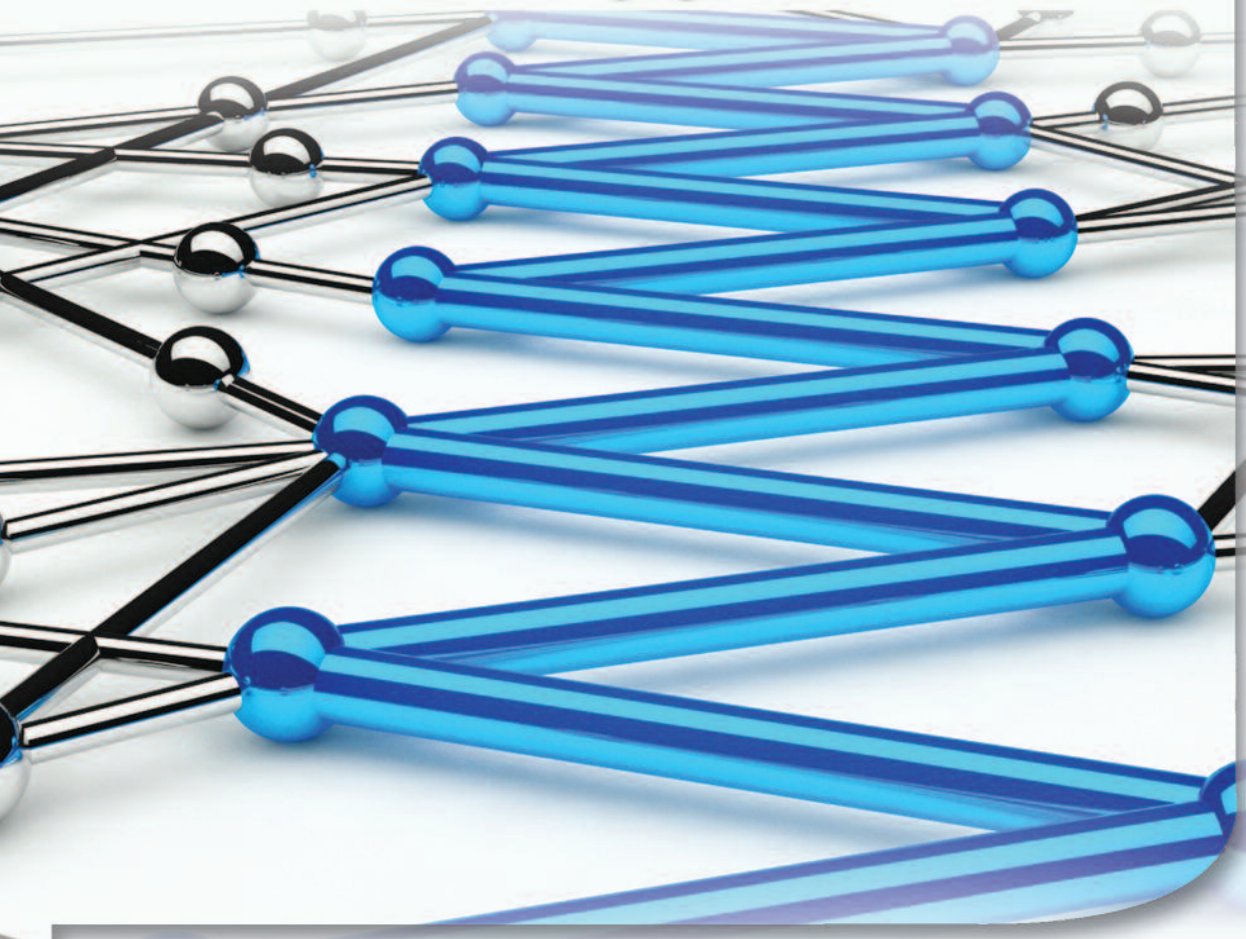
Drug Development® & Delivery

January/February 2017 Vol 17 No 1 www.drug-dev.com

Next-Generation Medical Applications



The science & business of drug development in specialty pharma, biotechnology, and drug delivery

Kevin Nelson, PhD
Enabling Controlled Pharmaceutical & Biologic Delivery for Next-Generation Medical Applications

Cindy H. Dubin
Analytical Testing: Market Drivers, Growing Demand & Client Needs

Patrick Walsh
Avista Pharma Solutions: Experience, Responsiveness & Expanded Capacity Driving Growth

IN THIS ISSUE

INTERVIEW WITH **VIRAL GENE, INC.'S** PRESIDENT & GENERAL COUNSEL CHRIS KIM

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References: 1. White House Office of Press Secretary. Fact sheet: Obama administration announces additional actions to address the prescription opioid abuse and heroin epidemic. White House website. https://www.whitehouse.gov/the-press-office/2016/03/29/fact-sheet-obama-administration-announces-additional-actions-address. Accessed December 20, 2016. **2.** Centers for Disease Control and Prevention. Understanding the epidemic. CDC website. https://www.cdc.gov/drugoverdose/epidemic/. Accessed December 20, 2016.

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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
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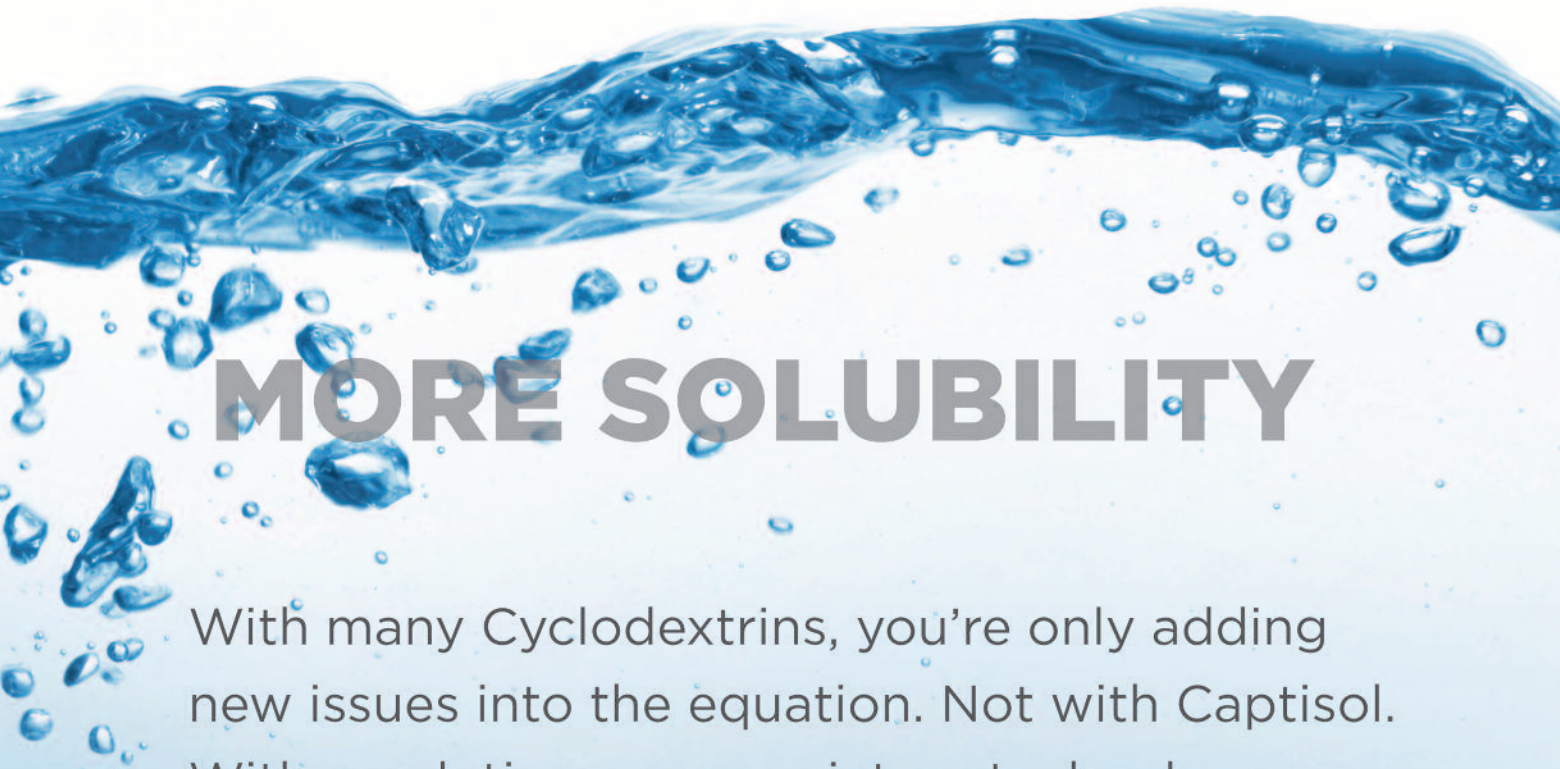
MORE TECHNOLOGY.



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p.48

Table of Contents

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Next-Generation Medical Applications

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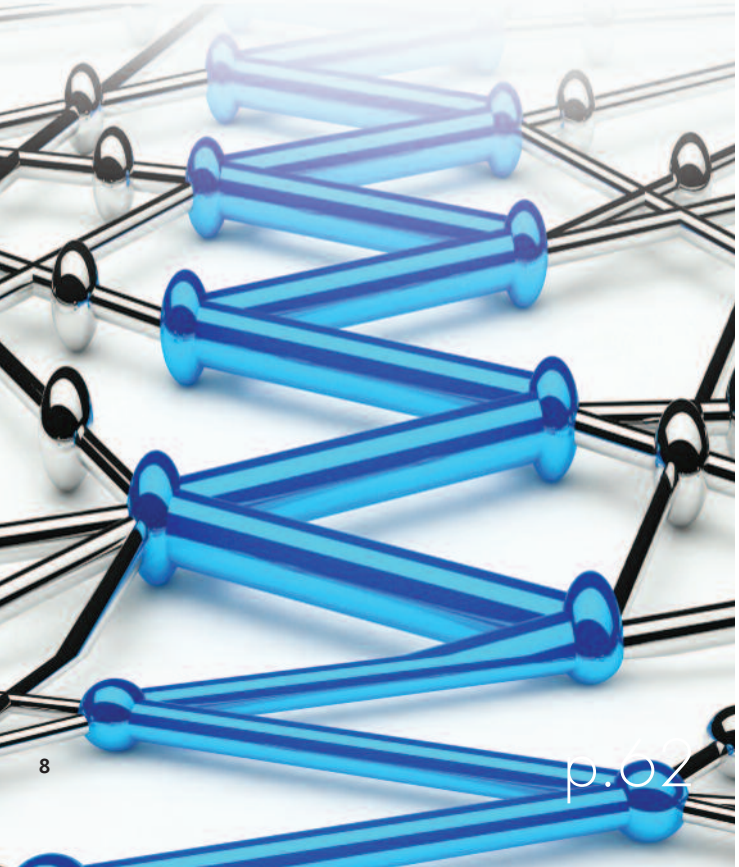

p.02

Table of Contents

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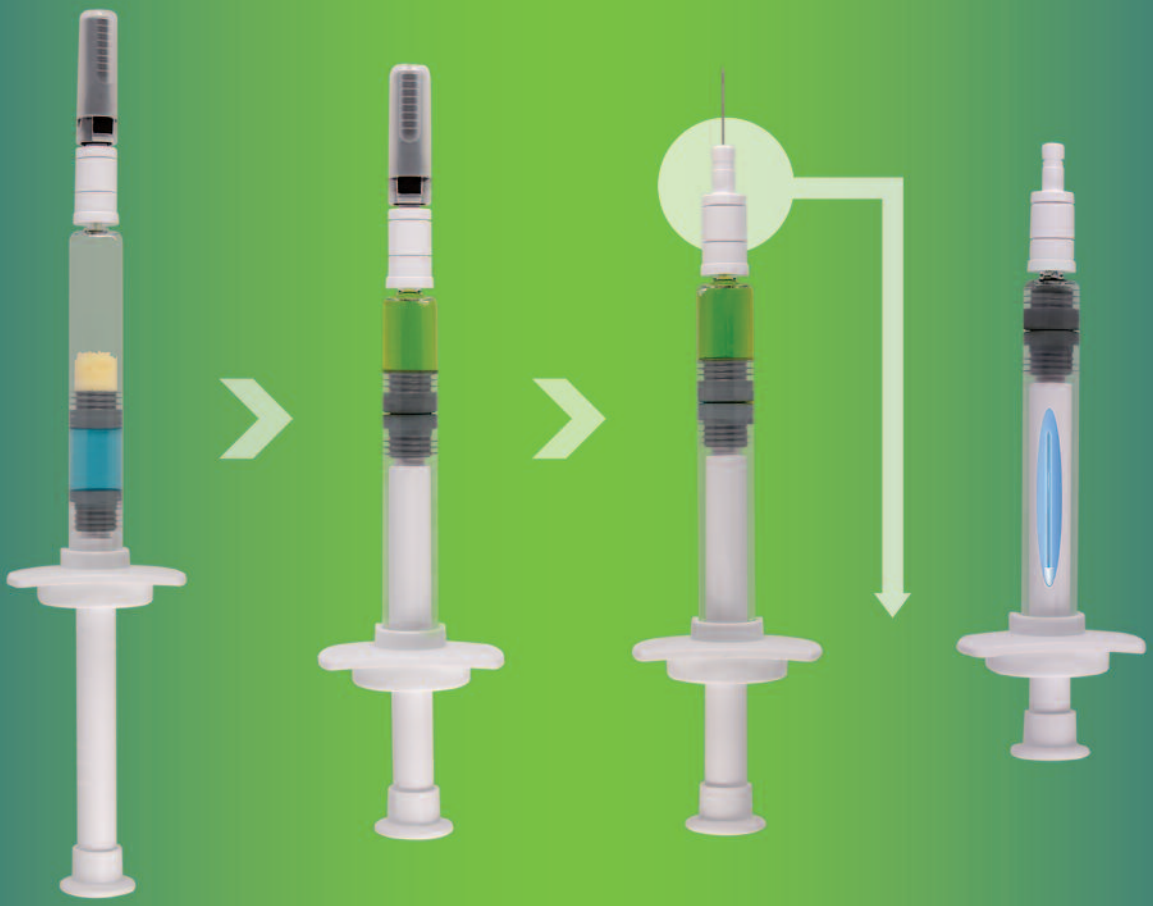

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C3J Therapeutics Unveils Development of Two New Product Formulations

C3J Therapeutics, Inc. recently announced the development of two new formulations of its lead candidate, C16G2, a novel peptide-based drug for the prevention of dental caries.

In Phase II trials conducted in 2016, the company demonstrated that a novel dental varnish formulation containing C16G2 achieved significant reductions of Streptococcus mutans, which is recognized as the major causative agent of dental caries. A single varnish application outperformed multiple tooth gel applications delivered by custom dental tray or by brushing. The varnish formulation of C16G2 is a product candidate for in-office treatment similar to fluoride varnishes commonly applied by dentists or hygienists, and is therefore potentially well-suited for the in-office treatment of high risk, caries prone populations.

Given the efficacy demonstrated to date of this professionally applied product, and recognizing the need for an additional convenient at-home dosing method, C3J Therapeutics has also developed an innovative tooth strip product for delivery of the drug to the tooth surface biofilm. The company has successfully manufactured room temperature stable tooth strips in preparation for the upcoming Phase II clinical trials.

"The clinical results obtained to date demonstrate that tooth surface contact and drug concentration are both key to effective therapy," said Todd Patrick, President and CEO of C3J Therapeutics. "The trials evaluating the varnish show that this formulation delivers superior microbiology results compared to other applications. We believe that just a few doses of the drug will have the potential to re-engineer the oral microbiome, thereby providing long-term protection. Additionally, we feel the tooth strip formulation has the potential to become a convenient, at-home application for multiple treatments. The excellent safety profile greatly enhances the therapeutic window of this investigational product."

C3J Therapeutics anticipates initiating clinical trials in the first quarter of 2017 to explore the efficacy of both tooth strips and varnish in commercially relevant treatment paradigms. These studies include evaluation of the varnish applied at a frequency appropriate for populations with high disease burden, and the varnish in combination with tooth strips. The combination of varnish plus tooth strips enables an in-office professional varnish treatment to be followed with self-application of tooth strips at home. Results from the Phase II studies are expected by the third quarter of 2017, and preliminary data will be presented at the International Conference on Anti-Caries Remineralizing Agents (ICNARA) taking place in Napa Valley, CA, from April 30-May 2, 2017.

C3J Therapeutics is a clinical-stage biotechnology company focused on improving human health through the development and commercialization of targeted, pathogen-specific antimicrobials (STAMPs) that treat and prevent human diseases caused by microbial dysbiosis. The proprietary STAMP platform technology has potential applications to a variety of bacterial infections, and disorders, particularly related to the human microbiome.

Catalent to Develop Softgel Capsules for JOT's Leading Orphan Disease Candidates

Catalent Pharma Solutions recently announcedit is to evaluate Jupiter Orphan Therapeutics, Inc.'s novel formulation of resveratrol, JOTROL, for delivery using Catalent's R.P. Scherer softgel technology. Under the agreement, Catalent will assess different softgel delivery technologies for JOTROL to determine the optimum oral dosage form, before going on to manufacture doses for human PK studies and Phase II clinical studies.

JOTROL, which is being developed to remedy resveratrol's poor bioavailability and dose-limiting gastrointestinal side effects, is being studied in multiple pre-clinical and clinical trial programs in progress for the treatment of rare diseases linked to single gene deficiencies. These include Friedreich's Ataxia and Mucopolysaccharide (MPS) diseases, as well as partner programs for treatments in pancreatic cancer, Machado-Joseph, and Alzheimer's disease.

Under the arrangement, Catalent will assess both conventional softgel and Catalent's proprietary OptiShell gelatin-free technology, which allows for higher fill temperatures and pH, and therefore can accommodate semi-solid and highly viscous formulations, and a wider range of excipients designed to improve bioavailability and stability.

"Developing better treatments that improve patient experience and lead to better real-world outcomes is vital for drug innovators' success," said Dr. Aris Gennadios, Catalent's President of Softgel Technologies. "Catalent is dedicated to using our breadth of formulation technology expertise and experience across thousands of innovative molecules to improve patient acceptance and adherence."

Christer Rosén, Chairman, CEO and Founder of JOT, added "We selected Catalent as our development partner for our JOTROL therapies because of their breadth of experience in formulation and softgel technology, coupled with their wide range of complementary capabilities."

Catalent will conduct its work on JOTROL from its primary, 453,000-sq-ft, North American softgel development and manufacturing center-of-excellence in St. Petersburg, FL, where the company offers formulation development and manufacturing of prescription and OTC softgels, and has an annual capacity of more than 18 billion capsules a year.

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics, and consumer health products. With over 80 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance, and ensuring reliable clinical and commercial product supply.

Jupiter Orphan Therapeutics, Inc. (JOT) is a clinical-stage specialty pharmaceutical company developing therapies for rare diseases linked to single gene deficiencies. JOT, a Delaware Corporation with its principal office located in Jupiter, FL, was founded in the summer of 2015. In its short period of operations, JOT has assembled a very strong management and scientific team as well as defined five pipeline products, which of one is already in Phase II. JOT has developed a unique formula, JOTROL, for the well-known natural product resveratrol that has many observed pharmacologic effects. Resveratrol is a dietary polyphenol found in grapes, red wine, berries and nuts.

Protalix BioTherapeutics Announces Positive Interim Results

Protalix BioTherapeutics, Inc. recently announced positive interim results from the company's Phase II clinical trial of alidornase alfa for the treatment of Cystic Fibrosis (CF) for the first 13 CF patients enrolled in the study. Fifteen patients have been enrolled in, and are expected to complete, the study. Alidornase alfa is a plant cell-expressed, chemically modified recombinant DNase enzyme resistant to inhibition by actin, which the company has specifically designed to enhance the enzyme's efficacy in CF patients.

The Phase II trial is a 28-day switch-over study to evaluate the safety and efficacy of alidornase alfa in CF patients previously treated with Pulmozyme. Participation in the trial is preceded by a 2-week washout period from Pulmozyme before treatment with alidornase alfa via inhalation.

The initial primary efficacy result shows that alidornase alfa improves lung function as demonstrated by a mean absolute increase in the percent predicted forced expiratory volume in one second (ppFEV1) of 4.1 points from baseline. A commercially available small molecule CFTR modulator for the treatment of CF has reported a mean absolute increase in ppFEV1 of 2.5 from baseline in its registration clinical study. This score was achieved while 74% of the patients participating in the trial of the CFTR modulator were also treated with Pulmozyme on top of the modulator. While this marketed CFTR addresses a certain mutation applicable to less than 50% of CF patients, alidornase alfa is being developed to treat all CF patients.

Sputa available DNA samples were analyzed for approximately half of the patients. A mean reduction of approximately 60% in DNA content from baseline was observed, and a mean reduction of approximately 90% from baseline was observed for sputa visco-elasticity. This data provides further supportive evidence of improved lung function after treatment with alidornase alfa, as demonstrated by the increase in ppFEV1. No serious adverse events were reported, and all adverse events that occurred during the study were mild and transient in nature.

"We are enthusiastic about the data generated in this trial as we were able to see meaningful improvements in efficacy in a way that have not been reported for a long time in the challenging CF space. We are looking forward to reporting full results from the study before the end of the first quarter of 2017," said Moshe Manor, Protalix's President and Chief Executive Officer.

"The preliminary efficacy results of alidornase alfa are very encouraging, even when compared to past trials of approved drugs for the treatment of CF. Although the study was performed on a small number of patients, the data is very encouraging because it shows clinically meaningful results," added Professor Eitan Kerem, Chairman of Pediatrics, Head of The Cystic Fibrosis Center, Hadassah University Hospital. "I look forward to following the results of upcoming trials of alidornase alfa. If the data continues to be as positive, clearly alidornase alfa will be a key treatment for all CF patients."

Protalix is a biopharmaceutical company focused on the development and commercialization of recombinant therapeutic proteins expressed through its proprietary plant cell-based expression system, ProCellEx. Protalix's unique expression system presents a proprietary method for developing recombinant proteins in a cost-effective, industrial-scale manner. Protalix's first product manufactured by ProCellEx, taliglucerase alfa, was approved for marketing by the US FDA in May 2012 and, subsequently, by the regulatory authorities of other countries.Protalix has licensed to Pfizer Inc. the worldwide development and commercialization rights for taliglucerase alfa, excluding Brazil, where Protalix retains full rights. Protalix's development pipeline includes the following product candidates: PRX-102, a modified version of the recombinant human alpha-GAL-A protein for the treatment of Fabry disease; PRX-106, an orally delivered anti-inflammatory treatment; PRX-110, a chemically modified DNase I for the treatment of Cystic Fibrosis; and others. For more information, visit www.protalix.com.

MyoKardia Announces Advancement to Next Phase of Global Collaboration With Sanofi

MyoKardia, Inc. recently announced that Sanofi has notified the company it has elected to continue the global cardiomyopathy research collaboration formed in August 2014.

The terms of the research agreement provided Sanofi the option of either concluding the collaboration at year-end 2016 or extending the agreement. Per Sanofi's decision to advance the collaboration, MyoKardia is now eligible for a $45-million milestone payment payable by January 31, 2017.

"MyoKardia and Sanofi share a passion for science and a commitment to patients. The continuation of this research collaboration provides valuable support for further innovation and development of critically important therapies for patients with serious cardiovascular diseases," said Tassos Gianakakos, Chief Executive Officer.

The research and development agreement is one of the most significant commitments to heritable cardiomyopathies, and encompasses three MyoKardia programs. Two of these programs are focused on hypertrophic cardiomyopathy (HCM), and one targets dilated cardiomyopathy (DCM).

In September, MyoKardia outlined its expected path to registration for its lead product candidate MYK-461 in the initial indication of symptomatic, obstructive HCM, for which the company was granted Orphan Drug Designation by the US FDA. MyoKardia is studying MYK-461 in the Phase II PIONEER-HCM trial.

MyoKardia received a separate $25-million milestone payment from Sanofi in November 2016 for the filing of an Investigational New Drug (IND) application with the FDA for its MYK-491 program in DCM. MyoKardia intends to initiate a Phase I study of MYK-491 in healthy volunteers in the first half of 2017. In the United States, MyoKardia maintains commercial rights to MYK-461 and HCM-2 as well as co-promotion rights for MYK-491.

MyoKardia is a clinical-stage biopharmaceutical company pioneering a precision medicine approach to discover, develop, and commercialize targeted therapies for the treatment of serious and rare cardiovascular diseases. MyoKardia's initial focus is on the treatment of heritable cardiomyopathies, a group of rare, genetically driven forms of heart failure that result from biomechanical defects in cardiac muscle contraction. MyoKardia has used its precision medicine platform to generate a pipeline of therapeutic programs for the chronic treatment of the two most prevalent forms of heritable cardiomyopathy — hypertrophic cardiomyopathy, or HCM, and dilated cardiomyopathy, or DCM. MyoKardia's most advanced product candidate, MYK-461, is an orally administered small molecule designed to reduce excessive cardiac muscle contractility leading to HCM and has been evaluated in three Phase I clinical trials. MyoKardia is now studying MYK-461 in the Phase II PIONEER-HCM trial in symptomatic, obstructive HCM (oHCM), a subset of HCM. In April 2016, the US FDA granted MYK-461 Orphan Drug Designation for the treatment of symptomatic oHCM. MYK-491, the second clinical candidate generated by MyoKardia's product engine, is designed to increase the overall force of the heart's contraction in DCM patients by increasing cardiac contractility. MyoKardia intends to initiate a Phase I study of MYK-491 in healthy volunteers in the first half of 2017.

RedHill Biopharma Announces Exclusive US Co-Promotion Agreement With Concordia

RedHill Biopharma Ltd. recently announced the signing of an exclusive co-promotion agreement with a subsidiary of Concordia International Corp., an international specialty pharmaceutical company focused on generic and legacy pharmaceutical products and orphan drugs, granting RedHill certain US promotion rights for Donnatal, a prescription oral drug used with other drugs in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis (inflammation of the small bowel).

Under the terms of the agreement, RedHill will be responsible for certain promotional activities related to Donnatal. Concordia will continue to be responsible for the manufacturing and supply of Donnatal in all territories. Donnatal accounted for 7.7% of Concordia's consolidated revenues in the first half of 2016. RedHill and Concordia will share the revenues generated from the promotion of Donnatal by RedHill based on an agreed upon split between them. The initial term of the co-promotion agreement with Concordia is for 3 years. RedHill expects to initiate gradual promotion of Donnatal in the coming months.

"We are pleased to partner with Concordia for the US promotion of Donnatal, a trusted brand among physicians for symptoms of IBS and acute enterocolitis. With a core US commercial team in place, we plan to initiate promotional activities in the US in the coming months with a specialty gastrointestinal sales force. RedHill's strategic transition into a revenue-generating, gastrointestinal-focused, specialty pharmaceutical company with commercial presence in the US, is planned to support potential future commercialization of our Phase III-stage potential blockbusters BEKINDA for gastroenteritis and other GI indications, RHB-105 for H. pylori infection and RHB-104 for Crohn's disease, if approved by FDA," said Dror Ben-Asher, Chief Executive Officer of RedHill.

"This agreement is a cost-effective approach to promoting Donnatal in a manner consistent with our long-term strategic focus on operational excellence," added Allan Oberman, Chief Executive Officer of Concordia. "RedHill's commercial team is highly motivated and has previous experience in gastroenterology sales. We look forward to partnering with them to market Donnatal to more key prescribers who we believe can help raise the product's profile and potentially allow us to reach more patients in the US."

Irritable bowel syndrome (IBS) is a chronic multifactorial disorder characterized by recurrent abdominal pain or discomfort associated with altered bowel function. IBS negatively impacts patients' quality of life and can affect patients physically, emotionally, socially, and economically. IBS is one of the most common gastrointestinal disorders. It is estimated that at least 30 million Americans suffer from IBS. The US potential market for IBS treatments is estimated to exceed $2.3 billion by 2020. Studies estimate that IBS affects 10% to 15% of US adults, with about twice as many women as men and most often occurs in people younger than age 45.

Domain Therapeutics Grants Alkermes Non-Exclusive License for Technology

Domain Therapeutics recently announced the signing of a licensing agreement for its GPCR BioSens-All technology with Alkermes, a biopharmaceutical company that focuses on developing medicines for the treatment of central nervous system diseases. As per the agreement, Alkermes is entitled to use BioSens-All as part of its drug discovery efforts. No financial details have been disclosed.

"We are very pleased to grant the first of a limited series of non-exclusive licenses for our BioSens-All technology. It is a further validation of the power of this technology that is designed to increase the success rate of drug discovery," said Pascal Neuville, Chief Executive Officer of Domain Therapeutics. "With additional validation from our ongoing relationships with several pharmaceutical partners, we believe that BioSens-All is a key platform for improved candidate identification and reduced early stage attrition."

"We are pleased to have worked with Domain Therapeutics in licensing the BioSens-All technology," said Mark Namchuk, SVP Research, Pharmaceutical and Non-Clinical Development at Alkermes. "With both screening and characterization applications, we believe this technology will be a valuable tool in our discovery efforts."

Contrary to what was previously believed, GPCRs, one of the largest and most successful classes of therapeutic targets, do not function as toggle switches that turn on or off a single cellular signaling pathway, but rather as complex biological hubs that engage multiple cellular signaling events. This paradigm shift, known as ligand-biased signaling or functional selectivity, opens promising avenues for the identification and development of better drugs; selectively activating pathways relevant to the desired therapeutic response while avoiding others responsible for undesirable effects.

The ability to understand GPCR functional selectivity obviously impacts the drug screening and profiling strategies needed to identify optimal drug candidates with correctly biased profiles. BioSens-All can monitor several dozen signaling pathways, in living cells, in parallel assays and in a homogeneous format. This allows the link to be made between specific signaling signatures of drug candidates and their biological effects. The BioSens-All technology generates and analyzes comprehensive signaling data on GPCR drug candidates, potentially accelerating the discovery and development of biased drugs.

The GPCR biosensor technology was originally developed by a team of researchers led by Prof. Michel Bouvier from the Institute for Research in Immunology and Cancer (IRIC) at the Université de Montréal, including Prof. Graciela Pineyro at the Ste-Justine Hospital research center, Dr. Christian Le Gouill at the Université de Montréal, Prof. Terry Hebert and Prof. Stéphane Laporte at McGill University, and Prof. Richard Leduc at Sherbrooke University. Domain Therapeutics acquired exclusive commercialization rights to the technology through two licensing agreements signed in 2013 and 2016.

G protein-coupled receptors (GPCRs) belong to the family of membrane receptors and constitute one of the main classes of therapeutic targets for many indications of the central nervous system, metabolic disorders, and cardiovascular, respiratory, urinary, or gastrointestinal diseases, and more recently, cancer. The binding of a hormone or a specific ligand to a receptor's binding site activates one or several pathways for intracellular signaling, which enables the cell to provide an adapted response to the change in its environment. The many drugs that target GPCRs represent about 30% of all treatments on the market, but only address 15% of GPCRs. Industry scientists in the sector are now researching treatments that work on the remaining 85% of GPCRs, treatments better adapted to patients' physiology and with fewer risks of side effects. The molecules in question are called allosteric modulators and biased ligands. BioSens-All technology allows the understanding of signaling pathways activated by each candidate molecule, thus predicting its pharmacological profile. This approach makes it possible at a very early stage to choose the molecules that have the potential of being active without presenting side effects or inducing tolerance to treatment.

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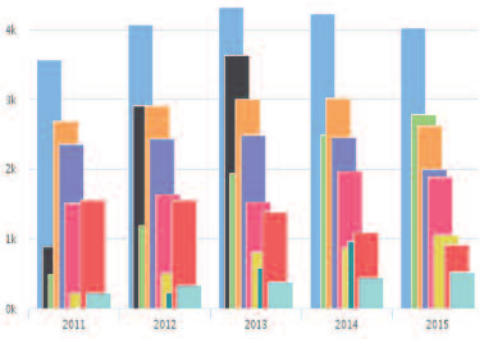

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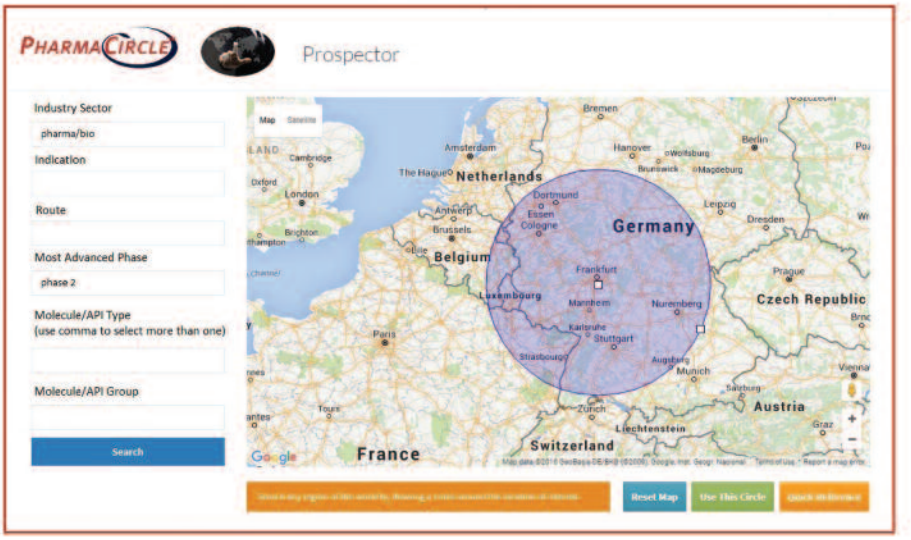

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Prospector - Business Prospecting Application	✓	✓
Spyglass - Watch List Application	✓	✓
Drug Delivery Technology Analyzer		✓
Patent Exclusivity Trackers		✓
Paragraph IV Filings & Case Tracker		✓
API Source/Manufacturer Locator		✓
Drug Label Comparison Tools		✓
Timescape - Development Timeline Application		✓
Reconnaissance - Competitive Landscape Analysis		✓
Merge Simulator - Acquistion & Merger Simulation		✓
Management Details & Contact Information		✓

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Advanced Delivery Devices

Disruptive Delivery Technology Partnerships Are Key to Pharmaceutical Life Cycle Management

By: Michael D. Hooven, MSME

It's a challenging time for pharmaceutical executives. Facing the dual imperatives of delivering innovative therapies that address unmet patient needs while delivering profitable growth, they are performing a balancing act between two often conflicting objectives - fostering innovation and containing costs. The industry is responding by embracing disruptive technology that can concurrently help on both fronts and also speed time to market for pharmaceutical products and services. According to a Deloitte 2016 industry report, some of this transformation will take the form of more technology deals as the integration of technology and pharma gains traction and accelerates. A key concept in the report: drugs will remain important but will represent a diminishing share of what comes together to deliver an overall outcome.[1]

Consequently, a well-balanced biopharmaceutical product portfolio now includes a pathway for continual product innovation, such as incorporating a new delivery component. This is expected to lead to a lower-risk product development strategy and greater overall success in the marketplace.

INNOVATION PROPELS PRODUCT LEADERSHIP

Companies including Roche/Genentech and Novartis provide examples of how such product leadership is achieved. The two companies' success centers on innovation in developing treatments for specific customer groups. Some of their most successful products of the previous 10 years include first-in-class therapies, such as Avastin (bevacizumab), Rituxan (rituximab), Herceptin (trastuzumab), and Gleevec (imatinib). These products have far higher average projected sales than follow-on products. But to maintain this leadership, they also turned their focus to increased patient convenience, with continual support of the customer base and innovative new treatment paradigms to improve the patient experience.

Many other companies are striving for leadership positions for their multiple high-value product franchises. Nowhere is innovation to enhance the patient experience more critical than with the rapidly growing number of high- volume, viscous biologics that now comprise over 50% of products in pharmaceutical development. For these drugs, delivery has been a challenge. But advanced delivery technology specifically developed to replace hospital-based delivery of large-dose drugs is providing new options for creating tomorrow's patient-friendly blockbusters.

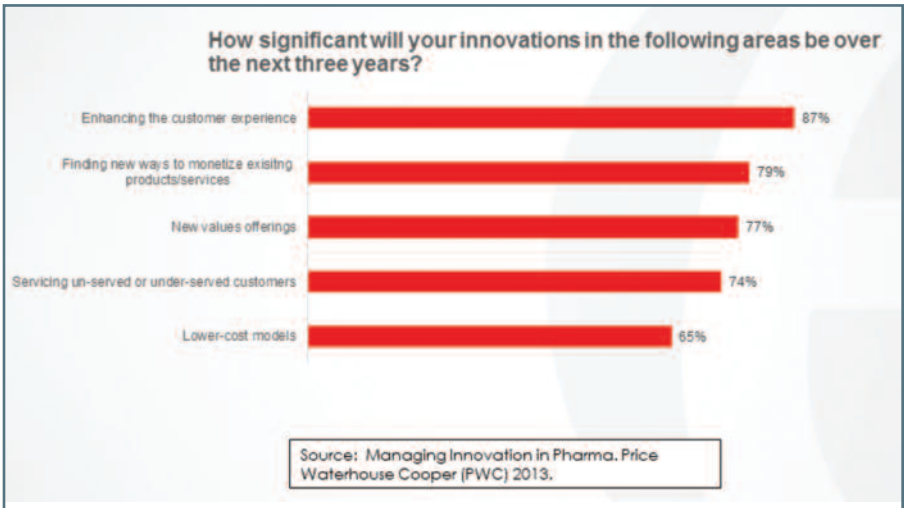
NEW DELIVERY SYSTEMS CAN IMPROVE BIOLOGICS' BIOAVAILABILITY, ENABLE SUBCUTANEOUS INJECTION

Although progress has been made in the manufacturing of biologics, particularly in the past few years, progress in the development of delivery systems able to improve the bioavailability of biologics has remained rather limited – until now.

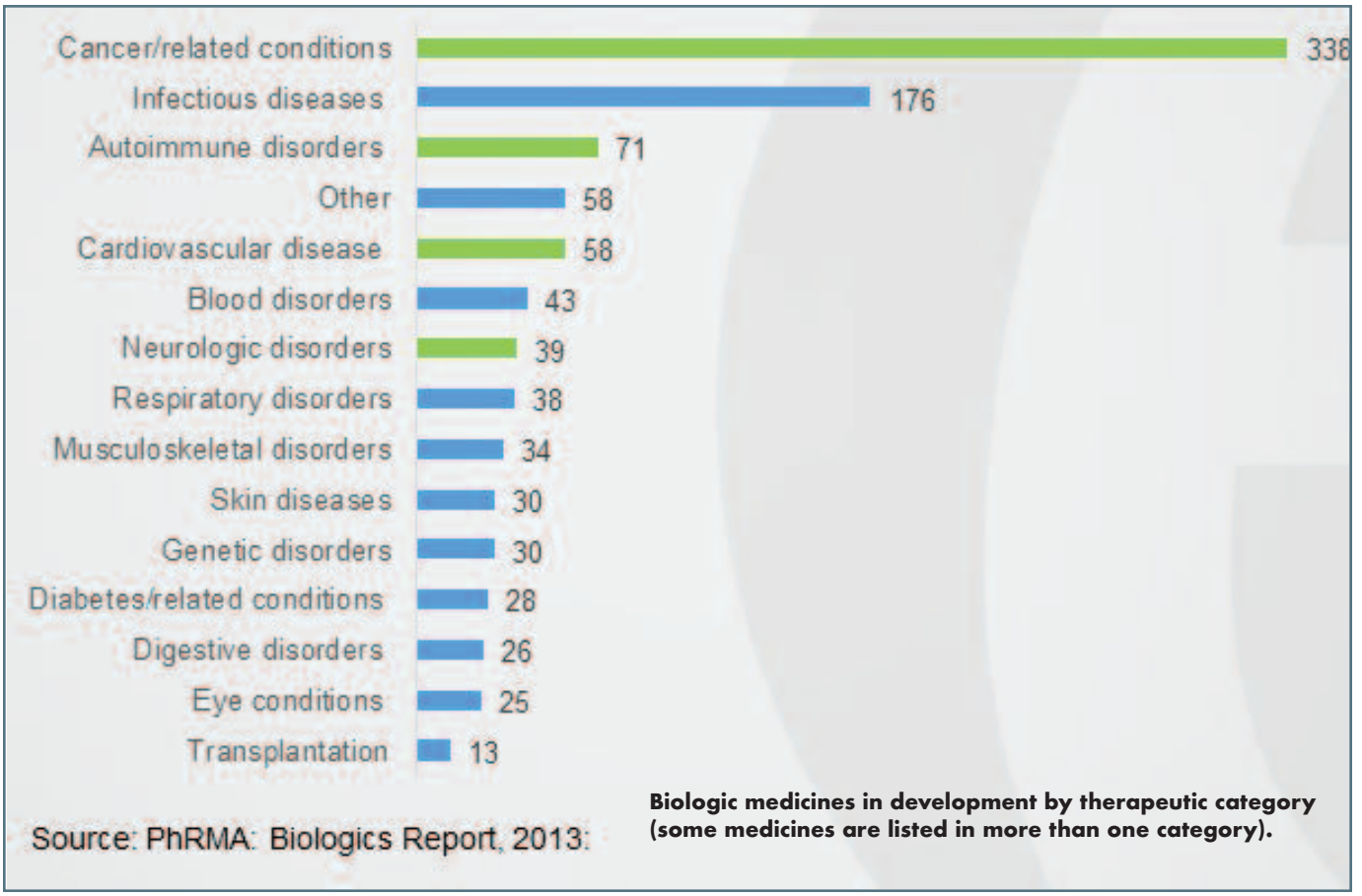
Subcutaneous delivery is generally the preferred way to administer an injectable therapeutic. However, subcutaneous injections have been limited in the amount of drug substance that can be delivered. There are several reasons for this. One of the main concerns in formulation development is the exponential relationship between the concentrations of biologics and viscosity of the formulation. The highly viscous formulations often required to ensure a desired concentration cannot be readily injected.[2,3] Generally, the volume of a bolus subcutaneous injection has been limited to no more than 1 to 2 ml. Now advanced delivery technology from Enable Injections can comfortably deliver up to 50 ml subcutaneously with a small wearable device.

For proteins, issues of viscosity, solubility, and protein aggregation are major obstacles, especially with small-gauge needles that patients prefer. For large protein biologics, such as monoclonal antibodies, companies must overcome volume and bioavailability constraints before subcutaneous injections can mirror intravenous-like dosing regimens. Monoclonal antibodies (mAbs) often have high-dose requirements, so they must be formulated at very high concentrations. At low concentrations, an antibody solution's viscosity increases moderately as a function of protein concentration. But at the high concentrations of some molecules (>100 mg/mL), viscosity increases exponentially.

In addition, concentration to the necessary level in the final product may not be possible for all products because in many



Pharma executives are focusing on enhancing the customer experience.



Biologic medicines in development by therapeutic category (some medicines are listed in more than one category).

cases, upstream purification and manufacturing processes may be the limiting factor in achieving maximum concentration for the final drug product, more so than delivery and fill/finish processes. Finally, drug-product properties, such as pH and osmolality, along with the use of certain excipients, may also limit the most appropriate drug-product concentration. These properties may need to be kept within certain ranges to prevent patient discomfort and injection site reaction.

Several ways to circumvent these volume limitations, including increasing the concentration of the active ingredient in the formulation, are being pursued. While such a change in the administered volume of a drug product offers the ability to deliver a larger dose, this approach can have disadvantages. There are limitations to how rapidly any volume of drug can be injected subcutaneously. The optimal injection time varies greatly by individual drug product. The medical literature regarding the relationship between injection volume and speed is limited. However, it is well known that neither the subcutaneous space — nor patients — can necessarily tolerate rapid injection of larger and larger dose volumes. Tissue disruption and site reaction may occur.

If the injection is rapid and the volume is too large, there is also potential for the product to leak back from the injection site, reducing the bioavailability relative to the total dose. Lastly, the patient may not be able to easily tolerate the rapid injection of a large volume, which could reduce compliance with the therapy. As such, a larger volume of product may require a larger device for self-delivery, and, potentially, a longer injection time.

Understanding subcutaneous tissue pressure is critical for the design of injection devices acceptable to the user. A recent study found that increased pressure and mechanical strain in the subcutaneous space is more directly related to increasing flow rate than to volume.[4] Therefore, it is imperative to ensure the user is not inconvenienced during a potentially lengthy administration of therapy.

A potential new solution to large-volume injection challenges is the development and use of systems that administer the dose into the subcutaneous space more slowly. Such systems can expand the possibilities for self-injection.[5,6] Due to the need for longer duration of injection, the device or system may need to be temporarily worn on the body at an appropriate injection site, such as the abdomen. Hence, the current industry interest in large-volume wearable injectors (on-body delivery devices).

The rise of viscous biologic drugs, the desired cost-saving shift toward patient self-injection and the emergence of safer, simpler, and more convenient devices are all contributing to the expansion of a new subcutaneous delivery mechanism for the rapidly growing number of large volume, viscous drugs.

ADDRESSING COSTS: ENABLE EASY PATIENT SELF-ADMINISTRATION OF BIG BIOLOGICS AT HOME

On-body delivery systems (OBDS) can be leveraged by a pharmaceutical company to accommodate disparate patient, prescriber, and payer preferences with the potential to improve compliance, build or protect market share, and lower overall health system costs.

The newest, most advanced of these high-volume injectors can move patient treatment from the hospital to the home, reducing costs while at the same time providing the innovator drug company with increased return on investment, and patients with a potentially more favorable treatment option for adherence to chronic and/or maintenance therapies. A time-and-motion study undertaken in eight countries reported significant time-savings for both healthcare professionals and patients through use of subcutaneous rituximab versus intravenous (IV) rituximab. The findings suggest potential for reduced waiting times, greater appointment availability, and improved efficiency of oncology units

"On-body delivery systems (OBDS) can be leveraged by a pharmaceutical company to accommodate disparate patient, prescriber, and payer preferences with the potential to improve compliance, build or protect market share, and lower overall health system costs. The newest, most advanced of these high-volume injectors can move patient treatment from the hospital to the home, reducing costs while at the same time providing the innovator drug company with increased return on investment, and patients with a potentially more favorable treatment option for adherence to chronic and/or maintenance therapies."

with the subcutaneous formulation. Subcutaneous injections can also be administered by the patient employing the user-friendly new delivery technology. Such injections are not generally painful and carry a reduced risk of infection and other complications.

Compared with IV drugs, the majority of participants considered subcutaneous drugs clinically safer and more cost-effective, resulting in higher patient satisfaction.[7]

DISRUPTIVE DELIVERY TECHNOLOGY THAT MERITS RAPID ADOPTION

Wearable injectors are designed to address the challenges of complexity, patient compliance, and cost associated with large-volume subcutaneous injections. The most advanced of these make self-injection safe, easy, comfortable, and convenient for patients – yet cost-effective for the pharmaceutical industry and payers. They bring to market a novel way to cut costs while adding overall value to the healthcare system, resolving drug formulation and delivery challenges by:

- Delivering more volume subcutaneously
- Delivering more viscous, high-concentration proteins subcutaneously
- Offering product differentiation in a competitive market
- Adjusting flow rate to reduce discomfort
- Enabling a simpler, faster method of product preparation
- Utilizing standard vials or syringes to minimize drug stability issues often encountered in new container closure development
- Automatically warming the drug as the injector is filled, thereby removing the typical wait time to use the device for a refrigerated medication
- For lyophilized drugs, completely automating mixing and reconstitution – removing any patient variability from the mixing process
- Using the smallest needle size possible to improve patient comfort
- Designing small wearables with a low profile that can be discreetly worn on the body for

Innovative, patient-focused large-volume drug delivery technology from Enable Injections, preferred by patient panels, automates warming and lyophilization, and makes development of stable, bioavailable, clinically-relevant formulations easier, faster, and less costly.

greater freedom and mobility

- Incorporating simple data-capture technology to aid in monitoring patient compliance and adherence to therapy

It is of course important to select the right device to deliver the right drug with the right viscosity and the right dose volume over the right period of time. Factors to consider include injection frequency, dose volume, drug viscosity, delivery rate, and duration. Pain, portability, and convenience are also important factors to take into account, which can drive preference rates amongst target patient populations as well as compliance.

With devices becoming increasingly integral to clinical development, regulatory approval, and lifecycle management, pharmaceutical companies should consider newly available drug delivery technology that can differentiate their products and help perform the balancing act between fostering innovation and containing costs. Incorporated data collection capability ensures the effectiveness of the drug delivery innovation by quantifying performance and acceptance of the device as well as optimal dose and flow rate. Such information provides confidence for future development of larger volume biologics for in-home subcutaneous injection. Data will also quickly demonstrate acceptability and likely product uptake, optimizing budgets.

Innovation pays off. A Price Waterhouse Cooper survey of pharmaceutical executives in 13 countries exhorts the industry to innovate beyond just finding new drug candidates – by creative partnering, for example. The PWC study found that returns on effective innovation are "huge." There was a clear correlation between innovation and growth. The top 20% of innovators anticipated three times as much growth as the bottom 20% in the next 5 years, and a clear majority of pharma C-suite respondents (86%) said innovation is important to their business.[8]

A large overall pharmaceutical pipeline reported by GBI Research demonstrates that a steady stream of incremental and breakthrough innovation is likely for the foreseeable future for various disease states. With the drugs alone becoming less important, partnering with a disruptive delivery technology could be the key to leadership positioning. Even if it does nothing else, such a partnership will certainly be an option that propels profitable growth by pleasing patients, a winning combination.

REFERENCES

1. 2016 Global Life Sciences Outlook. Deloitte.
2. Collins M. Here's What's Important About Alder Biopharmaceuticals Inc (NASDAQ:ALDR)'s Latest Release. Market Exclusive, July 26, 2016.
3. Burgess BE. Optimizing drug delivery for modern biologics. BioPharm Intl. 2012;25(5):30-32.
4. Rule S. Subcutaneous vs intravenous rituximab in patients with non-Hodgkin lymphoma: a time and motion study in the United Kingdom. J Med Econ. 2014;17(7):459-468.
5. Palm T, Sahin E, Gandi R, et al. The importance of the concentration-temperature-viscosity relationship for the development of biologics. BioProcess Int. March 10, 2015.
6. Škalko-Basnet N. Biologics: the role of delivery systems in improved therapy. Biologics. 2014;8:107-114.
7. Doughty D, Clawson CZ, Lambert W, et al. Understanding subcutaneous tissue pressure for engineering injection devices for large-volume protein delivery. J Pharmaceutical Sciences 2016:105:2105-2113.
8. Managing Innovation in Pharma. Price Waterhouse Cooper (PWC), 2013.

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BIOGRAPHY

Michael D. Hooven is President and CEO, Enable Injections, Inc. He has over 30 years of experience in the medical device industry in a broad variety of business, technical, and clinical areas. He is the Founder of five medical device companies and holds over 100 issued and pending US patents. Mr. Hooven is the Founder and a Director of AtriCure, Inc. (NASDAQ:ATRC), where he previously held positions as the Chairman and CEO. He is also Founder and Chairman of Enable Medical, a surgical device manufacturer that was acquired by AtriCure in August of 2005. Prior to Enable Medical, he was Director of Product Development at Ethicon Endo-Surgery from 1988 to 1994, where he had responsibility for all in-house product development and supervised a staff of 200 engineers. He held Engineering positions in pacemaker and lead development at Siemens/Pacesetter from 1986 to 1988 and at Cordis Corporation in neurosurgical products from 1981 to 1986. In addition, he is Director and past Chairman of BioOhio, a state-funded organization to accelerate life-science startups in Ohio. He earned his BSc in Physics and a MSME in Mechanical Engineering from the University of Michigan.

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FORMULATION DEVELOPMENT

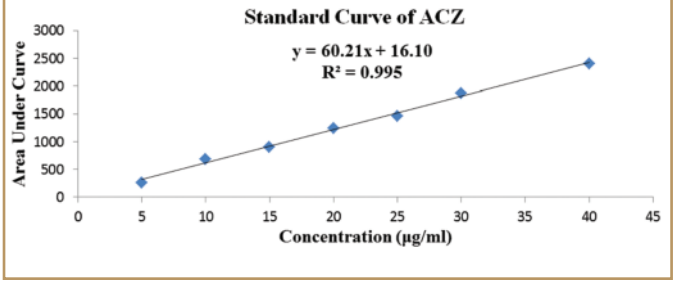
Optimizing the Spray-Drying Parameters for a Formulation of Nanoparticles-In-Microparticles System (NiMS) of Acetazolamide

By: Parijat Pandey, MPharm, and Harish Dureja, PhD

ABSTRACT

In the current research, a spray-dried nanoparticles-in-microparticles system (NiMS) of Acetazolamide (ACZ) was formulated. The objective behind the research was to examine the consequence of spray-drying parameters that are inlet temperature and feed rpm on the entrapment efficiency, loading capacity, percentage yield, and particle size on formulating NiMS of ACZ. The prepared NiMS were evaluated for entrapment efficiency, loading capacity, percentage yield, and particle size, and it was found that PP-5 (formulated using an inlet temperature of 160°C and feed rpm 30) has a maximum entrapment efficiency 17.94% (w/w), loading capacity 33.2% (w/w), percentage yield 25.8% (w/w), and smallest particle size of 763 nm out of all the five formulations (PP-1 to PP-5). The DSC analysis of PP-5 suggested that the entrapment of the nano and microparticles and spray-drying generate a noticeable crystallinity of ACZ and confers a nearly amorphous state to this drug. Infrared analysis of PP-5 showed no interaction between drug and polymer during the formulation process. The SEM of PP-5 found that the particles are of irregular shape, typically in the range of 2.5 to 3.5 µm. Therefore, NiMS of ACZ have been successfully formulated and it was observed there was an effect of inlet temperature and feed rpm of the spray dryer on the entrapment efficiency, loading capacity, percentage yield and particle size. Thus it can be concluded this study can be beneficial for the formulation of NiMS of ACZ by spray drying.

FIGURE 1



INTRODUCTION

In recent years, significant consideration has been focused on the expansion of novel drug delivery systems (NDDS). The reasons behind the development of NDDS include drug delivery to the site of action without any significant immunogenicity reactions, biological inactivation, or the potential side effect to the critical tissues, such as liver, lungs, bone marrow, kidney, etc. The main goal in developing NDDS is to advance the therapeutic efficacy and safety of existing drugs by altering the biodistribution pattern of the drugs, reducing the amount and frequency of dosing.[1] NiMS are the systems that reduce drug dosage frequency and increase patient com-

TABLE 1

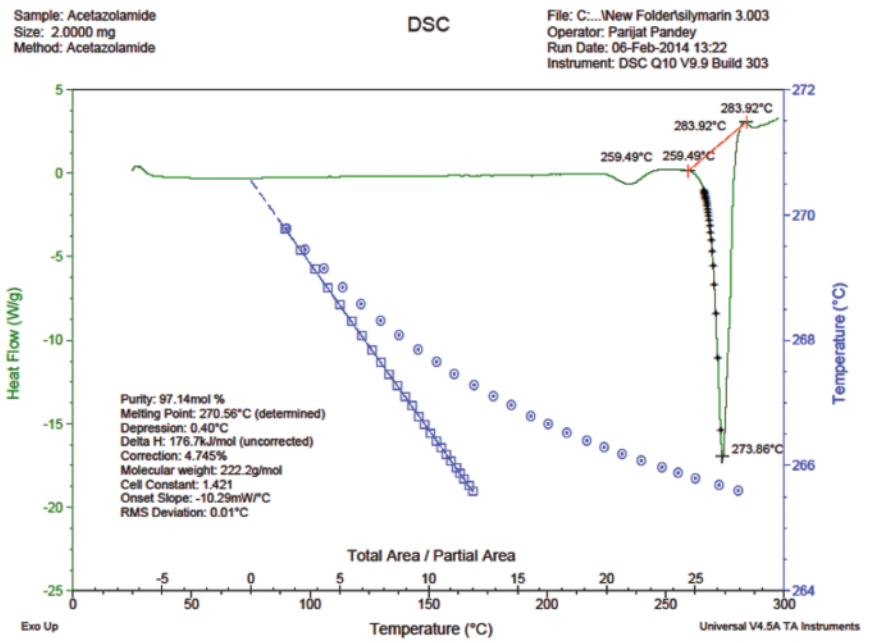
S. No.	Parameters	PP-1	PP-2	PP-3	PP-4	PP-5
1.	Inlet temperature	100°C	100°C	160°C	50°C	160°C
2.	Feed rpm	50	30	80	30	30
3.	Chitosan	70 ml	100 ml	70 ml	70 ml	100 ml
4.	NaTPP	32 ml	50 ml	32 ml	32 ml	50 ml

Different formulation data of NiMS (PP-1 to PP-5)

pliance.[2] The most important purpose in designing NiMS is to control particle size, surface properties, and make pharmacologically active agents release to achieve site-specific drug action at the dosage regimen and therapeutically optimal rate.[3] Chitosan has excellent potential in designing nanoparticulate drug delivery, the ability to control drug release, and is biocompatible with living tissue. Chitosan is a natural carbohydrate polymer and prepared by the partial N-deacetylation of chitin. Chitosan-based NiMS have advantages, mainly for the design of novel nanoparticulate drug delivery systems, due to their desirable properties such as biodegradability, bio- and mucoadhesivity, biocompatibility, and hydrophilic character that facilitate the poorly absorbable drugs administration across the various epithelial barriers, such as intestinal, nasal, and corneal mucosa.[4] Acetazolamide (ACZ) is a carbonic anhydrase inhibitor. In the eye, carbonic anhydrase inhibition decreases the flow of sodium, bicarbonate, and water into the posterior chamber. Suppression of this reaction in the ciliary process reduces the aqueous humour production by almost total enzyme inhibition. Thus, the intraocular pressure in both normal and glaucomatous eyes is reduced.[5]

Spray drying is a technique described as the feed conversion into a dry particulate form by subjecting the feed into a hot drying medium from a fluid state. Liquids of various types, such as slurries, emulsions, and dispersions, can be converted into solid particles with preferred size, porosity, shape, density, and distribution.[6] There are various spray-drying benefits, which include control of size and shape and porosity and density, a rapid and simple process that produces free flowing particles, scalability and reproducibility, cost

FIGURE 2



DSC Analysis of ACZ

effectiveness, and enhanced dissolution rate of drugs.[7] The spray-drying process effectiveness is exaggerated by different factors, such as inlet temperature, outlet temperature, flow rate, and feed concentration and rate.[8] Therefore, it is desirable to evaluate the various effects of spray-dried parameters on the ACZ-loaded NiMS. In the present study, the goal was to formulate NiMS of ACZ by spray drying, and the objective behind the study was to investigate the effect of spray-drying parameters, i.e., inlet temperature and feed rpm on the percentage yield, entrapment efficiency, loading capacity, and particle size.

MATERIALS

Chitosan (95% deacetylated), having a molecular weight of 40 to 80 kDa, was purchased from Fluka Chemika, Switzerland. Sodium tripolyphosphate (NaTPP) and glacial acetic acid were purchased from Central Drug House, New Delhi. ACZ

TABLE 2

Parameter	Conditions
Mobile phase	A mixture of 60 volumes of 0.33% percent w/v solution of tetrabutylammonium hydrogen sulphate and 40 volumes of acetonitrile
Detection wavelength	234 nm
Flow rate	1.0 ml/min
Column	Column 25 cm x 4.6 mm made up of stainless steel, packed with octadecylsilane bonded to porous silica (3 µm)
Detector	Variable Wavelength Detector (VWD)
Apparatus	Agilent Technologies, 1200, Germany
Retention time	1.5 to 2.0 min
Linearity range	5 to 40 µg/ml

HPLC parameters for analysis of ACZ

was obtained from Kaizen Pharmaceuticals, Chandigarh. Tetrabutylammonium hydrogen sulphate was obtained from Spectrochem Pvt. Ltd, Mumbai. Acetonitrile (HPLC grade) was purchased from Rankem, New Delhi.

METHODS

Preparation of ACZ-Loaded NiMS

In the current research, NiMS were prepared using the ionic gelation method.[9] In this method, chitosan (0.5% w/v) was dissolved in 0.3% v/v glacial acetic acid. 500 mg of the ACZ was dissolved in it. The solution of sodium tripolyphosphate (NaTPP) (0.2% w/v) was prepared in distilled water. The NaTPP solution (32 to 50 ml) was added to the chitosan solution (70 to 100 ml) dropwise stirring continuously. The suspension was spray dried (JISL, Navi Mumbai) at a feed rate (30, 50, and 80 rpm) and at specified temperature (50°C, 100°C, and 160°C) to get the free flowing powder. The aspirator blower capacity was 118 Nm^3/hr, and the nozzle size was 0.7 mm with auto de-blocking device. To study the effect of various formulation variables, NiMS were prepared as shown in Table 1.

In the current research, using Agilent Technologies 1200 series, Germany [Quaternary pump, a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm), UV detector dual wavelength]. HPLC analysis was performed utilizing the parameter as shown in Table 2.[10]

Initially, the column was washed with a mixture of acetonitrile and methanol with varying flow rate for half an hour and decreasing ratio of methanol. After that, the column was saturated with 1.0 ml/min of flow rate for 30 mins and mobile phase. After that, the standard drug dilution samples (5 µl) were injected and run for 10 min. The drug retention time was found between 1.5 to 2.0 min. In Table 3, HPLC of standard solution of ACZ is shown, and the calibration curve was prepared as shown in Figure 1.

TABLE 3

Drug Concentration (µg/ml)	Area Under Curve	Statistics
5	265.5	**Slope = 60.218**
10	693.7	**Intercept = 16.052**
15	903.8	**Correlation coefficient = 0.9952**
20	1240.4	
25	1458.8	
30	1870.2	
40	2411.7	

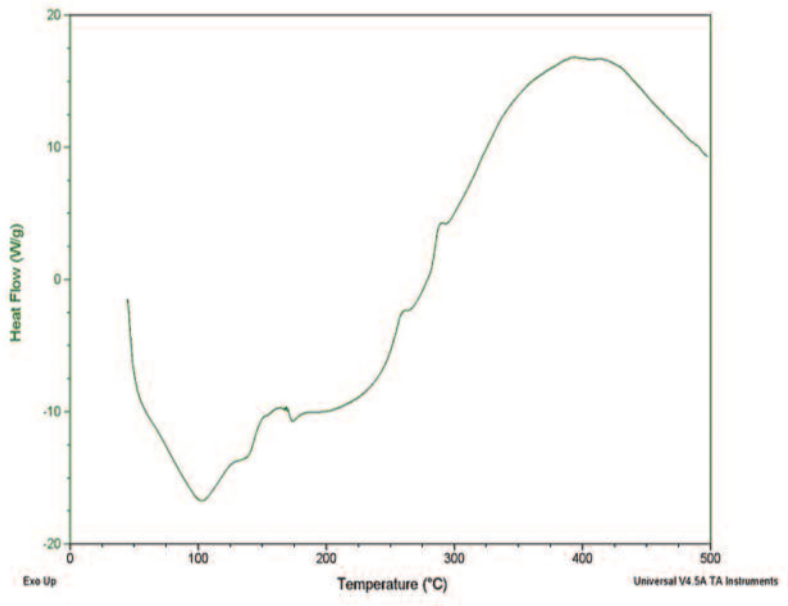
HPLC of standard solution of ACZ

TABLE 4

Batch No.	Percentage Yield (%)	Entrapment Efficiency (%)	Loading Capacity (%)	Mean Particle Size	
				(Z-average)	Peak-1
PP-1	14.54±0.07	4.15±0.03	15.02±0.06	1639.7±4.32	319.20±.2.91
PP-2	17.55±0.06	12.68±0.02	24.54±0.04	1613.9±7.87	440.60±5.64
PP-3	10.65±0.05	1.05±0.05	14.69±0.02	1908.1±5.12	429.30±4.68
PP–4	12.02±0.06	1.18±0.03	14.98±0.02	3642.03±7.16	162.92±0.97
PP-5	25.80±0.02	17.94±0.01	33.10±0.01	768.66±5.13	524.90±5.15

Characterization of NiMS (PP-1 to PP-5)

FIGURE 3



DSC Analysis of PP-5

CHARACTERIZATION OF NIMS

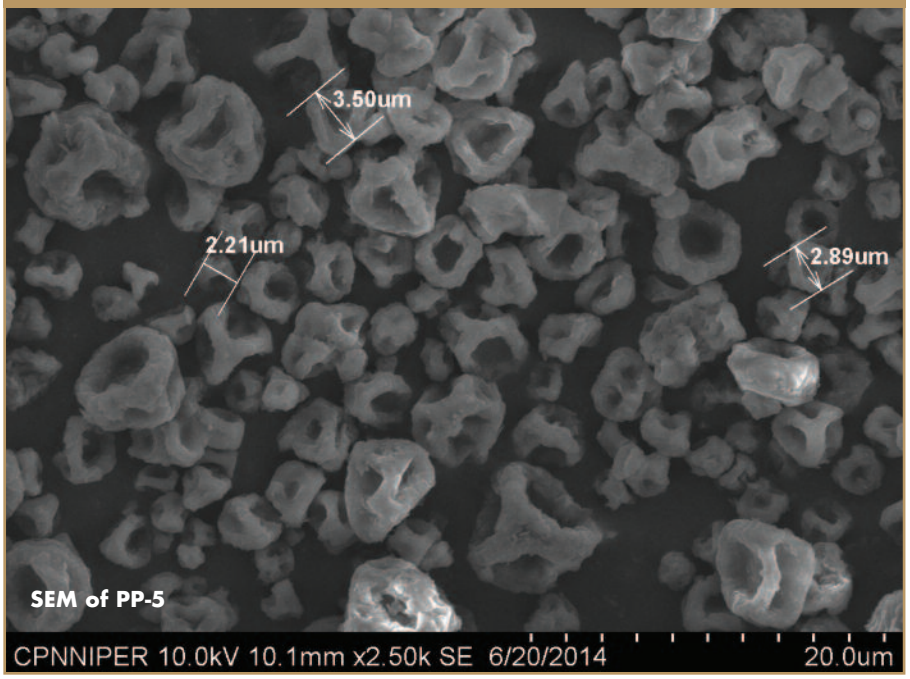
Particle Size Analysis

For analysis of particle size, using Zetasizer Instrument (Beckman Coulter Desla Nano, USA) equipped with the hydro-dispersing unit by dissolving 2 mg of sample in 5 ml of distilled water, the dilution of sample was analyzed. In a polystyrene cuvette in hydro-dispensing unit, the dilution of sample was filled, and the scan was carried out at 64 runs per sample. At the end of scan, the average diameter of all the 64 runs were taken out and recorded as Z-average.

Percentage Yield, Entrapment Efficiency & Loading Capacity

The ACZ percentage yield, entrapment efficiency, and loading capacity were determined directly using NiMS. The analyses of HPLC were carried out using a system (Agilent Technologies 1200 series, Germany) that consisted of a column 25 cm x 4.6 mm made up of stainless steel packed with octadecylsilane bonded to porous silica (3 µm). The mobile phase was a mixture of 60 volumes of a 0.33 % w/v solution of tetrabutylammonium hydrogen sulphate and 40 volumes of acetonitrile. The wavelength was set at 234 nm, and the flow rate was 1.0 mL/ min.[10] The percentage yield, entrapment efficiency, and drug loading were calculated (Equations 1, 2, & 3).[11]

FIGURE 4



Differential Scanning Calorimetry (DSC) Analysis

DSC was carried out on DSC Q10 (Waters Corporation, USA) using indium as standard to calibrate the instrument. In sealed pans of aluminum, samples were heated at a rate of 10°C/min under nitrogen atmosphere (60 ml/min) and temperature range from 30°C to 300°C, with empty pan as reference.

Fourier Transform Infrared (FTIR) Spectrophotometry

FT-IR is a technique of obtaining infrared spectra using an interferometer by first collecting an interferogram of a sample signal, and then obtaining the spectrum performing a Fourirer transform on the interferogram. Fourier transform IR spectra were recorded on FT-IR (Alpha, Bruker, Germany). Over the range of 500 to 3500 cm^{-1}, the spectra were recorded.

Scanning Electron Microscopy (SEM)

The NiMS were mounted on metal stubs using double-sided tape and using Sputter gold coater and visualized under scanning electron microscope. The particles were coated with gold to a thickness of about 450 Å.[12] The surface appearance and morphology of spray-dried PP-5 was observed via SEM (Hitachi S 3400 N, Japan).

EQUATIONS 1,2&3

$$\text{eqn (1) Percentage yield (\%)} = \frac{\text{Total NiMS weight}}{\text{Total solid weight}} \times 100$$

$$\text{eqn (2) Entrapment Efficiency (\%)} = \frac{\text{Mass of drug in NiMS}}{\text{Mass of drug used in formulation}} \times 100$$

$$\text{eqn (3) Loading Capacity (\%)} = \frac{\text{Mass of drug in NiMS}}{\text{Mass of NiMS recovered}} \times 100$$

RESULTS & DISCUSSION

In the current research, the spray-drying technique was used for the conversion of suspensions into solid particles (nanoparticles/microparticles) and no additional drying adjuvant was needed. TPP is an anion that can form cross-linkage involving ionic interactions between the TPP

TABLE 5

Types of Peak	Peaks of Pure Drug	Peaks of PP-5
C=O Stretching (amides)	1675 cm^{-1}	1679 cm^{-1}
N-H Stretching (amides)	3171 cm^{-1}	3162 cm^{-1}
N-H Bending (amides)	1543 cm^{-1}	1547 cm^{-1}
N-H Stretching (Sulphonamides)	1361 cm^{-1}	3158 cm^{-1}
S=O Antisymmetric Stretching (Sulphonamides)	1172 cm^{-1}	1368 cm^{-1}

Comparison of peaks of pure drug and PP-5

molecules (negatively charged) and amino group (positively charged) of chitosan. The opalescence indicated the development of particles with a size range of nanoparticles to microparticles with the incorporation of ion TPP to chitosan solution.[13] In spray drying, there are various factors that affect the formulated product, such as inlet temperature, outlet temperature, feed rpm, feed concentration, aspirator rate, nozzle size, etc. Out of these factors, inlet temperature and feed rpm of spray dryer were selected to evaluate, and the analysis of percentage yield, entrapment efficiency, loading capacity, and particle size of all five formulations were carried out and are tabulated in Table 4. It has been observed that the PP-5 formulations have the highest percentage yield (25.8%) with highest entrapment efficiency (17.94%), highest loading capacity (33.2%), and with a smallest particle size of 763 nm.

Particle Size Analysis

By means of laser diffractometry, using Zetasizer instrument (Beckman Coulter Desla Nano, USA) equipped with a hydrodispersing unit, particle sizing experiments were carried out. The particles size analysis of each batch (PP-1 to PP-5) have been tabulated in Table 4.

Percentage Yield, Entrapment Efficiency & Loading Capacity

When we compared the results of percentage yield, entrapment efficiency, and loading capacity of PP-1 and PP-2, which have the same inlet temperature, PP-1 showed the better result as compared to the PP-2, due to the PP-2 having the lower feed rate so that the solution gets efficient time to get converted into solid particles. While the entrapment efficiency, loading capacity, percentage yield of two formulations (PP-3 and PP-4) were lowest because the prepared solution was not completely converted into the solid particles due to the higher feed rate and lower temperature, respectively. The best results showed by the PP-5 with respect of having highest percentage yield, entrapment efficiency, and loading capacity due to the higher inlet temperature and lower feed rpm of spray dryer. The results of percentage yield, entrapment efficiency, and drug loading of all five batches (PP-1 to PP-5) are tabulated in Table 4.

Differential Scanning Calorimetry (DSC) Analysis

The ACZ was confirmed by DSC analysis, and there was a sharp peak at 273.86°C almost corresponding to its melting point (260.52°C) (Figure 2). During NiMS formation, the loss of endothermic peak of PP-5 (Figure 3) showed that the drug may have been dispersed in the amorphous form in the polymer matrix.[11,14] The entire amalgamation of the drug in the NiMS formulation indicates the molecular dispersion of the drug is within the system. By spray drying, the peak of drug disappeared in NiMS, indicating the drug was molecularly dispersed in the medium of chitosan as a solid solution. These outcomes suggest the spray-drying process produces a marked decline in crystallinity of ACZ and confer to this drug a nearly amorphous state.[11]

Fourier Transform Infrared (FTIR) Spectrophotometry

The spectra were recorded for pure drug (ACZ) and ACZ-loaded PP-5 and the comparison of peaks of pure drug and PP-5 are tabulated in Table 5. There was no major variation in the FTIR spectra of pure ACZ and PP-5. No significant shifting of functional peaks, no overlapping of characteristic peaks, and also no appearance of new peaks were observed upon comparison of obtained spectra with reference spectra. The results suggest drug stability during the entrapment process. The FTIR data suggested that molecular interactions that could alter the chemical structure of the drug did not occur. Therefore, no chemical interface between the functional group of drug and polymer exist.[14]

Scanning Electron Microscopy (SEM)

Figure 4 shows the SEM of the PP-5 of spray-dried powder. It was found that the particles were of irregular shapes, typically in the range of 2.5 to 3.5 µm. The irregular particles may be attributed to the fact that during the spray-drying process, high pump rates result in a large volume of spraying solution to be dried, but heated air might not transform liquid droplets into solid droplets, immediately leading to the formation of bigger irregular-shape particles that are not completely dried and tend to form aggregates.[15]

CONCLUSION

Spray drying has been successfully applied to prepare ACZ-loaded NiMS. The effect of spray-drying parameters that are inlet temperature and feed rpm of the spray dryer were evaluated on the percentage yield, entrapment efficiency, loading capacity, and particle size of ACZ-loaded NiMS. The PP-5 was regarded as the best batch because it has the highest entrapment efficiency (17.94%), loading capacity (33.2%), and percentage yield (25.8%) with the smallest particle size (763 nm). The current research supports the approach to prepare redispersible ACZ-loaded NiMS in a powdered form by using the spray-drying technique and also marked the effect of spray-drying parameters on the formulation of ACZ-loaded NiMS. From the research, it has been concluded that the formulation with higher inlet temperature and lower feed rpm resulted in maximum percentage yield along with entrapment efficiency, loading capacity, and smallest particle size. ◆

REFERENCES

1. Bhowmik D, Chiranjib R, Jayakar RM. Role of nanotechnology in novel drug delivery system. J Pharm Sci Tech. 2009;1(1):20-35.
2. Pandey P, Dureja H. Nanoparticles-in-microparticles systems (NiMS) a an overview. J Innovative Biol. 2014;1(4):195-199.
3. Lee YS, Johnson PJ, Robbsins PT, Bridson RH. Production of nanoparticles-in-microparticles by a double emulsion method. a comprehensive study. Eur J Pharm Biopharm. 2013;83:168-173.
4. Patil MS, Bhoskar M. Optimization and evaluation of spray-dried chitosan nanoparticles containing doxorubicin. Int J Curr Pharm Res. 2014;6(2):7-15.
5. Leaf DE, Goldfarb, DS. Mechanism of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. J Appl Physiol. 2007;102:1313-1322.
6. Sollohub K, Cai K. Spray drying technique: II. current applications in pharmaceutical technology. J Pharm Sci. 2009;99(2):587-597.
7. Kaushik D, Dureja H. Recent patents and patented technology platforms for pharmaceutical taste masking. Recent Pat Drug Deliv Formul. 2014;8(1):37-45.
8. Kaushik D, Dureja H. Taste masking of bitter pharmaceuticals by spray- drying technique. J Chem Pharm Res. 2015;7(4):950-956.
9. Pandey P, Dureja H. Spray-dried nanoparticles-in-microparticles system (NiMS) of acetazolamide using central composite design. Nanotech Nanosci Asia. 2016;6(in press).
10. Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare. The Indian Pharmacopoeia Commission, Ghaziabad. 2014;985-990.
11. Elzoghby AO, Samy, WM, Elgindy NA. Novel spray-dried genipin- crosslinked casein nanoparticles for prolonged release of a alfuzosin hydrochloride. Pharm Res. 2012;30:512-522.
12. Kommanaboyina B, Rhodes, CT. Trends in stability testing with emphasis on stability during distribution and storage. Drug Dev Ind Pharm. 1999;25(7):857-868.
13. Li FQ, Yan C, Bi J, Lv WL, Ji RR, Chen X, Su JC, Hu JH. A novel spray-dried nanoparticles-in-microparticles system for formulating scopolamine hydrobromide into orally disintegrating tablets. Int J Nanomed. 2011;6:897-904.
14. Pirooznia N, Hasannia S, Lotfi AS, Ghanei M. Encapsulation of Alpha-1 antitrypsin in PLGA nanoparticles: In vitro characterization as an effective aerosol formulation in pulmonary diseases. J Nano Biotech. 2012;10(20):1-15.
15. Wan LSC, Heng PWS, Chia CGH. Preparation of coated particles using a spray-drying process with an aqueous system. Int J Pharm. 1991;77:183-191.

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BIOGRAPHIES

Dr. Harish Dureja earned his Master's degree from Punjabi University, Patiala, and his Doctorate (Gold-Medal) from M.D. University, Rohtak. He is presently working as Associate Professor in the Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak (India). He has 16 years of experience in teaching and Research. He has written 10 invited book chapters/monographs in various books published by international publishers. He is author of more than 115 publications in various national and international journals of repute. He has been awarded two research projects for research on anti-cancer drug delivery by the AICTE and UGC. His current research interests include in silico ADME modelling, nanoparticulate drug delivery, and pharmaceutical regulatory affairs.

Mr. Parijat Pandey earned his Master's degree in Industrial Pharmacy and is presently pursuing his PhD as Research Scholar (JRF) in the Department of Pharmaceutical Sciences, M.D. University, Rohtak. He has published 8 manuscripts in various international and national journals and is a life member of IPGA.

CNS DELIVERY

Bypassing the BBB: Drug Delivery From the Olfactory Mucosa to the CNS

By: T.R. Shantha, MD, PhD, FACA

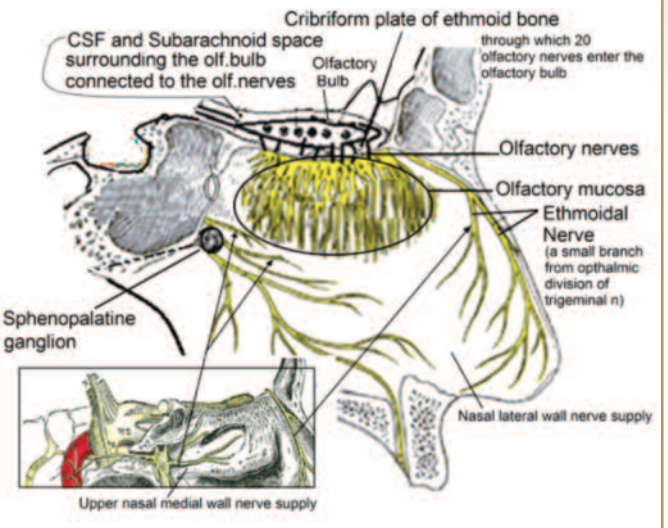
INTRODUCTION

As therapeutic agents have evolved to treat central nervous system (CNS) afflictions, the blood brain barrier (BBB) has prevented the use of many of these drugs for treating neurodegenerative diseases, such as Alzheimer's, Parkinson's, tumors, and other CNS diseases.[1-17] The BBB blocks entry of many traditional and newly discovered drugs inside the brain that can protect neurons; promote nerve repair; and cure, curtail, and treat many untreatable CNS diseases. This problem is partly resolved by the use of the intranasal olfactory mucosa to deliver therapeutic agents to the CNS bypassing through the BBB. This simple, rapid delivery route is ideal over any other micro-anatomical structure and site due to the unique connections and transportation routes between the nasal olfactory mucosa, 20 olfactory nerves, olfactory bulb, subarachnoid space cerebro spinal fluid (CSF), and CNS (Figures 1-6).[13,17-24] The following will explore and explain how therapeutic and non-therapeutic agents, such as brain-eating amoeba,[24] meningococcus, and rabies virus,[20,23,24] and such can reach the brain, bypassing through the formidable BBB based on the unique micro-anatomic and physiologic characteristics of the nasal olfactory mucosal route and its CNS connections[18] that allow transportation directly into the CNS. These findings are based on decades of our own as well others' studies.[3-11,16,18-22]

ANATOMICAL & HISTOLOGICAL ASPECTS

The olfactory mucosa is situated within the recesses of the skull under the cribriform plate of the ethmoid bone that forms the roof of the nose, situated 7 cm from the nostril, being positioned partly on the nasal septum and partly on the superior turbinate

FIGURE 1



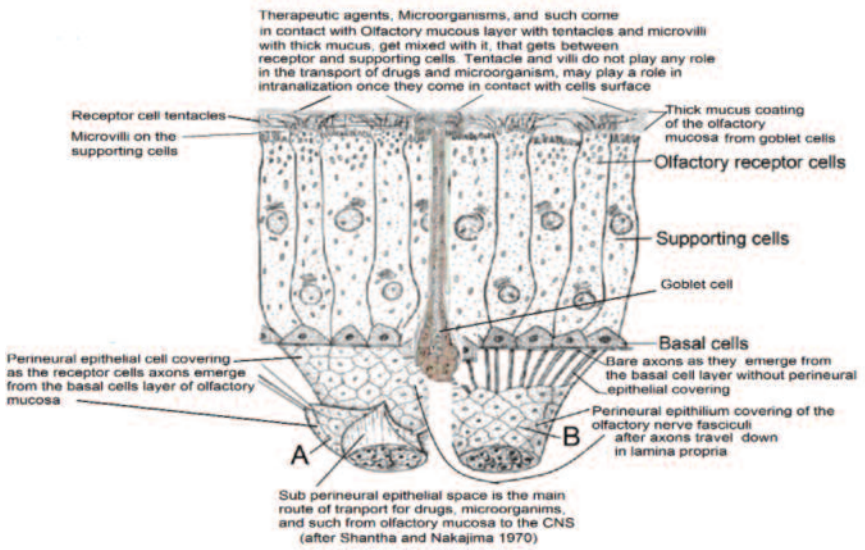
Shows the olfactory mucosa and other nerve structures on the walls of the nasal cavity. Note the olfactory mucosa (circled) is the solitary structure that is directly exposed to therapeutic agents, microorganisms, and amoeba that are transported rapidly to the CNS by 20 olfactory nerves from the olfactory mucosa to the olfactory bulb from where they are transported to the CNS, bypassing the BBB (Modified from Gray's Anatomy).

(Figures 1-4).[11,17,18] It is not easily accessible in humans;[17] hence, therapeutic agents need to be delivered to this narrow passage to treat CNS afflictions as described further (Figure 1). The olfactory mucosa is made up of a mucus layer situated on the top of the receptors cells, supporting cells between the receptor cell, basal cells below the receptor and supporting cells, and goblet cells extending from the lamina propria opening on the olfactory mucosa supplying the mucosal coating to the olfactory mucosa (Figures 2-5). The lamina propria, below the receptor and basal cells, has 20 olfactory nerve bundles with BV (ethmoidal) and lymphatics (deep cervical) surrounded by connective tissue, which

form the epineural and perineural connective tissue around the 20 olfactory nerve trunks that are connected to olfactory bulb leptomeninges and dura.

There are 10 to 23 cilia from each receptor cell (extension of dendrites from receptor cells) and microvilli of the sustentacular cells embedded in a thick viscous layer of mucus secreted from goblet cells from the lamina propria that do not allow them to move and may also not participate in the transport of olfactory mucosa-delivered therapeutic agents. Based on our studies, there is a possibility that CSF surrounding the olfactory bulb seeps from the olfactory nerve fasciculi between these cells and emerging axons, supplying the neurotrophic factors, and at the same time, keeping the olfactory mucosa wet (Figures 1-4). A collection of axons form the olfactory nerves (olfactory nerves trunks or fasciculi) surrounded by perineural epithelial cells,[18-20] not by Schwann cells,[2,18] creating sub-perineural epithelial and inter-axonal spaces around each nerve fasciculus (Figures 5 & 6), which act as a highway and byway to the subarachnoid space around the olfactory bulb and brain. Our study for decades has shown that this perineural epithelial covering is a direct extension of pia-arachnoid mater extension from the olfactory bulb akin to the leptomeninges that cover the entire peripheral nervous system derived from the rest of the CNS (including sensory and motor end organs, perisynatpic cells of the motor endplate).[19,20]

FIGURE 2



Shows the olfactory mucosa and olfactory nerves and their perineural epithelial covering forming the sub-perineural epithelial space that transports therapeutic agents and such to the CNS bypassing BBB. Note some axon bundles are not covered by the perineural epithelial cells as shown in section B, as they emerge from the basal cells for a short distance and then get grouped and sheathed by perineural epithelial cells, which allows the CSF and therapeutic agents to leak to the lamina propria and then get picked up by the lymphatic system (from Shantha and Nakajima 1970).

MODE OF SPREAD & FINAL DESTINATION OF THERAPEUTIC AGENTS DELIVERED TO OLFACTORY MUCOSA

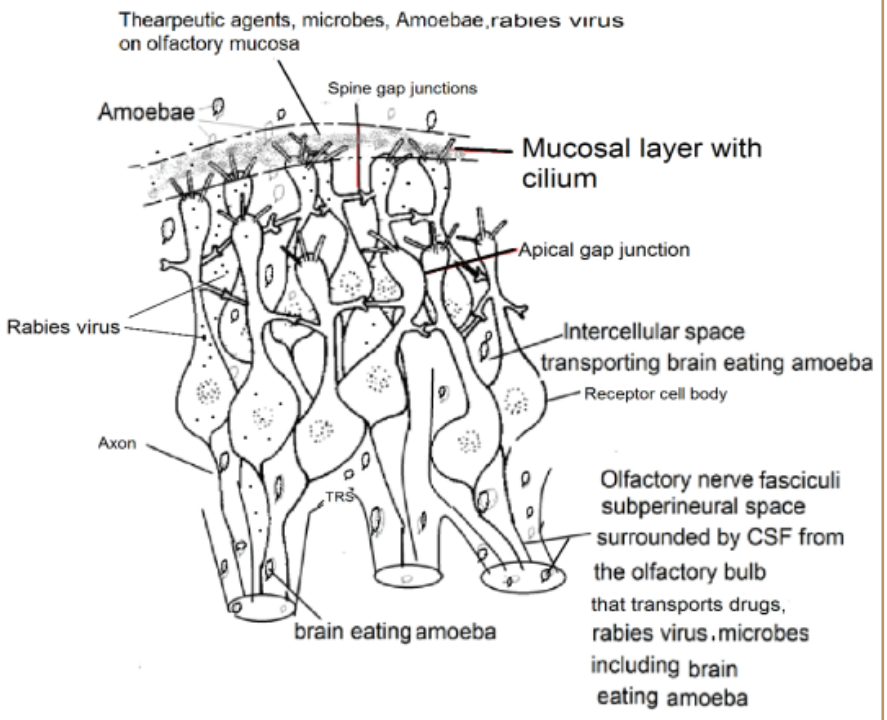
Without going into micro-anatomical detail, the following are the routes taken by therapeutic agents deposited on the olfactory mucosa through intra-neuronal and extra-neural pathways to various centers of the CNS bypassing the BBB based on decades of our own and others' studies:

1. A majority of therapeutic agents deposited on the olfactory mucosa are transported between the supporting cells, receptor cells, and dying receptor cells in the olfactory mucosa (Figures 2-4). At any given time, about 10% of the receptor cells are dying, creating a space (Figure 3) for transport of therapeutic agents and microorganisms to the sub-perineural epithelial space around the 20 olfactory nerves (Figures 1-5). Therapeutic agents (including microbes) deposited on the olfactory mucosa spread between receptor and supporting cells, reaching the lamina propria. Due to paucity of perineural epithelial cells covering around some of the emerging axon bundles (Figure 2), some of it enters the BV and deep cervical lymph nodes through lymphatics from the lamina propria.[28]

2. From the intercellular route of the olfactory mucosa, most therapeutic agents are transported to sub-perineural epithelial and inter-axonal spaces of the 20 olfactory nerves (Figures 2, 3, 5 & 6). The therapeutic agents spread around the olfactory bulb's subarachnoid space CSF (Figures 1 & 4) through the olfactory nerves entering through the cribriform plate of the ethmoid bone.

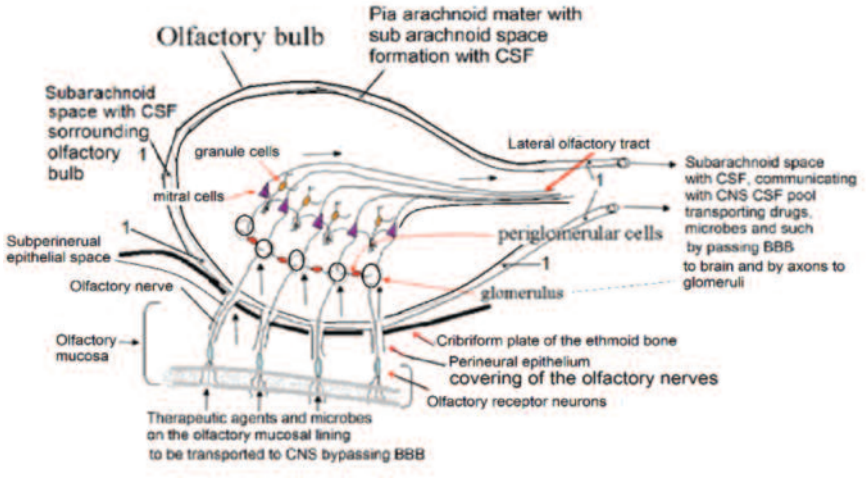
3. From the olfactory bulb subarachnoid space CSF (Figures 1, 4 & 5), therapeutic agents and microbes are transported to the CSF in the subarachnoid space, specifically to the suprachiasmatic and interpeduncular CSF cisterns (Figure 5) then to neuropile through the CNS Virchow-Robin space and blood vessels' paravascular routes.

FIGURE 3



Shows the spaces and connections between the olfactory mucosal receptors cells that allow the therapeutic agents, microorganisms, viruses, and brain-eating amoeba transported to the CNS through the olfactory nerves to the olfactory bulb and CSF through these intercellular spaces (Diagram modified from Graziadei 1971).[28]

FIGURE 4



Shows the olfactory mucosa, olfactory nerves, olfactory bulb with axonal connection at the glomeruli, CSF in sub-perineural epithelial space, the subarachnoid space of the olfactory bulb, olfactory pathway transporting the therapeutic agents, microorganisms, and such to the CNS, bypassing the BBB.

4. From this subarachnoid space and CSF cisterns, therapeutic agents spread to the temporal lobe, hypothalamus, thalamus, amygdala, entorhinal cortex, hippocampus, prefrontal cortex, and such (Figure 4 & 5). This is why we believe therapeutic agents to treat Parkinson's, Alzheimer's, and other neurodegenerative diseases can utilize insulin and other adjuvant therapeutic agents[13,6,17] using these main transportation routes bypassing the BBB (Figure 3 & 5).

5. From the CSF pool around the olfactory bulb and brain, therapeutic agents spread to the subarachnoid space around the spinal cord due to CSF circulation and are distributed to the neuropile and neurons of the spinal cord through the Virchow-Robin space[22] and parascular glymphatic routes.

6. Therapeutic agents from CSF delivered through olfactory nerves spread to the brain structures and neuropile through the CSF and subarachnoid space, the Virchow-Robin space, paravascular routes, and glymphatics deep into the brain and spinal cord to the site of pathology for healing.

7. Therapeutic agents and microbes from Virchow-Robin spaces[22] around the CNS and peripheral NS penetrating blood vessels from the subarachnoid space are transported through the paravascular space formed around all the blood vessels of the brain and astroglial cells' end-feet encasing these blood vessels (named the glymphatic space/channel/transportation routes). It is one of the most important transportation routes regarding how thera-

peutic agents from the olfactory mucosa to CSF reach deep brain neuronal structures in the treatment of CNS diseases, including Parkinson's and Alzheimer's diseases, evading and dodging the BBB. Brain metabolites also take the same exit routes to systemic circulation.[27]

8. Intra-axonal (transcellular-axoplasmic) spread results when therapeutic agents deposited in the olfactory mucosa are endocytosed by dendritic olfactory receptor cells, then to axoplasm of receptor cells and then into axons, olfactory nerves, olfactory bulb, glomeruli, then through the olfactory tracts axons to mitral and tufted cells, then to olfactory tubercle, amygdala, the prepyriform cortex, the anterior olfactory, nucleus, and the entorhinal cortex as well as to the hippocampus, hypothalamus, and thalamus (Figures 4 & 5). This is a very slow spread except for neurotrophic viruses, such as rabies.[20,23]

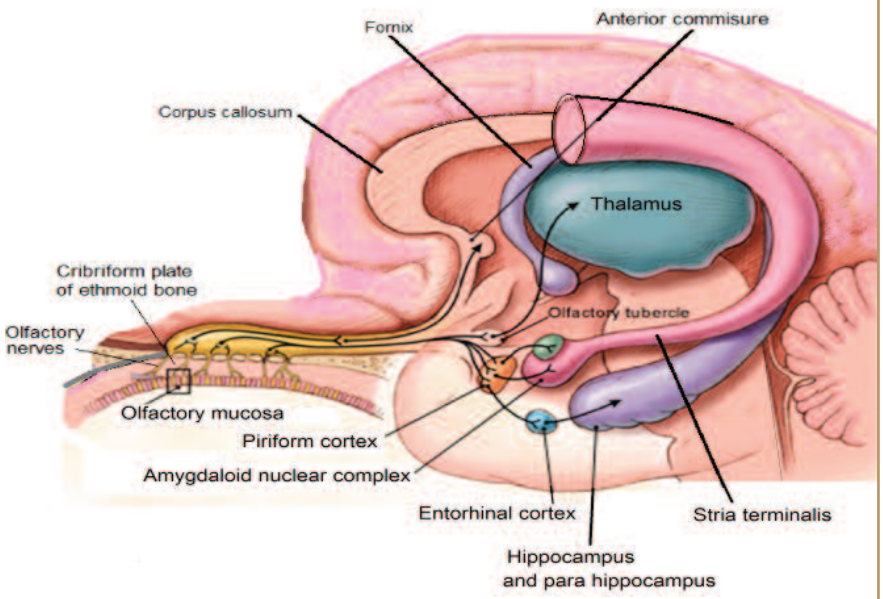
9. Therapeutic agents absorbed from the blood vessels of the olfactory and nasal mucosa reach the choroid plexus, then therapeutic agents permeate to the ventricle, central canal of the spinal cord, then to CSF and then to neuropile close to the ependymal lining from systemic absorption through the respiratory and nasal mucosa. Spreading through this route is minimal at best.

10. The olfactory mucosa is surrounded by valveless Batson plexus of veins[25] that may uptake very small amounts of therapeutic agents from the lamina propria on turbinates and ethmoidal air sinus walls and transport them to the cavernous sinus, other venous sinuses, and to CSF in the subarachnoid space to be transported to neuropile as previously described

11. The blood vessels (probably Batson plexus) and nerve root filaments on the medial walls of the ethmoid air sinus adjoining the olfactory mucosal lamina propria may transport minute quantities of therapeutic agents to CSF and then to the CNS.

12. Regarding delivery to the olfactory, lymphatics play no role in transport of therapeutic agents to the CNS. They only pick up the therapeutic agents and particulate matter leaked through the olfactory nerves at the lamina propria under the basal cells from the olfactory mucosa (Figures 2 & 4) and transport them to the deep cervical lymphatic system.[18,26]

FIGURE 5



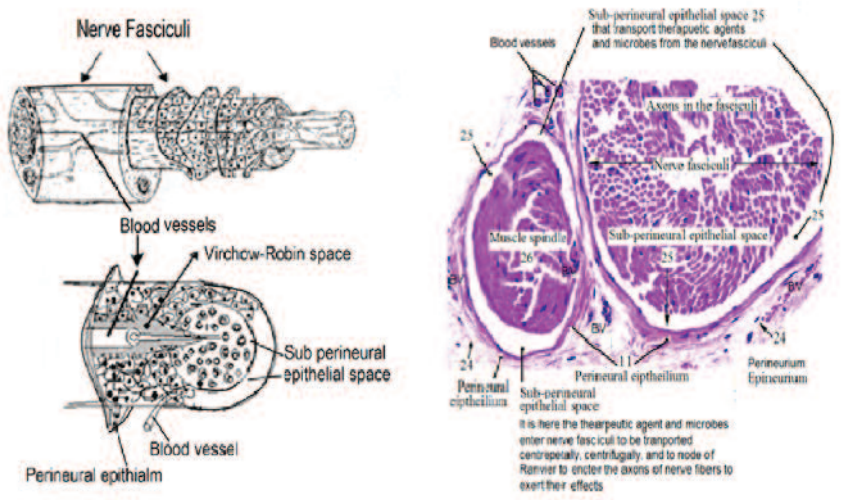
Shows the route of transport of therapeutic agents, bacteria, viruses, and brain-eating amoeba from the olfactory mucosa to various memory centers (labeled) and other areas of the brain, bypassing the BBB through sub-perineural epithelial and inter-axonal spaces to CSF content around the olfactory bulb and subarachnoid space as well as through the axoplasmic spread of the olfactory nerve axons to the olfactory bulb and connected brain centers.

OLFACTORY MUCOSAL TRANSPORT OF NON-THERAPEUTICS

Evidence of sub-perineural epithelial spread (Figures 1-7) of therapeutic agents through the olfactory nerves from the olfactory mucosa is further substantiated by the "brain-eating amoeba"[24] and meningococci, transported through the olfactory nerve sub-perineural epithelial and inter-axonal space, not through trans-axoplasmic transport, which is the route for rabies virus,[20,23] and maybe other neurotrophic viruses.

Figures 1-6 are self-explanatory and detail the structure and the possible route of transport of therapeutic agents and microbes from the olfactory mucosa to the CNS as previously described.

FIGURE 6



The left image shows the Virchow-Robin space and the covering of the trigeminal nerve fasciculi that transports therapeutic agents to the sub-perineural epithelial and inter-axonal spaces space around after intranasal administration and also to the node of Ranvier to axoplasm. The right image shows the cross section of the trigeminal nerve fasciculi with perineural epithelial covering, creating a potential sub-perineural epithelial and inter-axonal space where therapeutic agents and rabies virus and such enter to be transported by axons and the CSF to the CNS, bypassing the BBB. Compared to olfactory mucosa, not enough therapeutic agent is transported through the trigeminal complex by passing the BBB to affect the outcome of CNS diseases.

TRIGEMINAL NERVE BRANCH AS A ROUTE FOR TRANSPORT

Our studies showed that the only branches exposed in the olfactory mucosal region are the anterior ethmoidal nerve, a branch of ophthalmic division of the trigeminal nerve, and a small fasciculus branch from the sphenopalatine ganglion, not the entire trigeminal complex as reported and publicized.[1,2,10] These small nerve fasciculi are covered with various connective tissue layers (epineural and perineural connective tissue) and multiple layers of perineural epithelial cells with sub-perineural epithelial and inter-axonal potential spaces that communicate with subarachnoid space CSF of the CNS and spinal cord (Figure 6) that has the potential to transport therapeutic agents to the CNS CSF.[18-21] It is a slow route, and minimal to exert direct effect to cure or curtail CNS diseases. On the other hand, the trigeminal nerve complex plays a major role in the transport of rabies virus to the brain from the facial bites.[20,23]

CONCLUSIONS

We conclude that the olfactory mucosa, olfactory epithelium, olfactory nerves, sub-perineural epithelial and inter-axonal spaces, olfactory bulb, olfactory bulb surrounding CSF, olfactory and suprachiasmatic tract along with suprachiasmatic cisterns and inter-peduncular cisterns, Virchow-Robin space, and glymphatic transport and clearance pathway, are the main necessary highways for the direct transport of therapeutic agents, microorganisms, viruses, and amoeba to the CNS, bypassing the BBB. There is a constant seepage with retrograde and downward flow of CSF from the olfactory bulb surrounding CSF to the lamina propria, lamina propria lymphatic, BV, and olfactory mucosa itself, and vice versa. Intranasal olfactory mucosal administration of therapeutic agents for the treatment of neurodegenerative and many CNS diseases overcomes the limitations due to the BBB, and provides an effective direct delivery method for a selective group of therapeutic agents to treat the brain regions that are pathologically affected with Alzheimer's and Parkinson's disease as well as other CNS diseases. ◆

REFERENCES

1. Thorne RG, Frey WH. Delivery of neurotrophic factors to the central nervous system. Clin Pharmacokinet. 2001;40:907-946.
2. Illum L. Transport of drugs from the nasal cavity to the CNS. Eur J Pharm Sci. 2000;11:1-18.
3. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target. 1998;5:415-441.
4. Thorne RG, Emory CR, Ala TA, Frey WH. Quantitative analysis of the olfactory pathway for drug delivery to the brain. Brain Res. 1995;692:278-282.
5. Sakane T, et.al. Transport of cephalexin to the cerebrospinal fluid directly from the nasal cavity. J Pharm Pharmacol. 1991;43(6):449-451.
6. Talegaonkar S, Mishra PR. Intranasal delivery - An approach to bypass the blood brain barrier. Indian J Pharmacol. 2004;36(3):140-147.
7. Majgainya S, Soni S, Bhat P. Novel approach for nose-to-brain drug delivery bypassing blood brain barrier by pressurized olfactory delivery device. J App Pharm.

2015;7(3):148-163.
8. Parvathi M. Intranasal drug delivery to brain: An overview. Int. J Res Pharmacy Chem. IJRPC 2012;2(3):889-895.
9. De Lorenzo, AJD. The olfactory neuron and the blood–brain barrier. Sci. 1970;70:466-467.
10. Frey WH. Bypassing the blood-brain barrier to deliver therapeutic agents to the brain and spinal cord. Drug Deliv Tech. 2002;2:46-49.
11. Gopinath PG, Gopinath G, Kumar TCA. Target site of intranasally sprayed substances and their transport across the nasal mucosa: a new insight into the intranasal route of drug delivery. Curr Ther Res. 1978;23,596-607.
12. Dahlin M, Bergman U, Jansson B, Bjork E, Brittebo E. Transfer of dopamine in the olfactory pathway following nasal administration in mice. Pharm Res. 2000;17:737-742.
13. Craft S, et al. Intranasal insulin therapy for Alzheimer's disease and amnestic mild cognitive impairment. Arch Neurol. Published online September 12, 2011:1-13.
14. Reger MA, Watson GS, Frey WH II, et al. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging. 2006;27:451-458.
15. Teen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease: is this type 3 diabetes? Alzheimers Dis. 2005;7:63-80.
16. de la Monte SM, Wands JR. Treatment of Alzheimer's disease in the US;7,833,513 B2.
17. Shantha TR. Alzheimer's disease treatment with multiple therapeutic agents delivered to the olfactory region through a special delivery catheter and iontophoresis. US20120323214, US20140012182, US20150080785, WO/2015/013252A1, and WO/2009/149317A3.
18. Shantha TR, Nakajima Y. Histological and histochemical studies on the rhesus monkey (Macaca Mulatta) olfactory mucosa. Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia. Z. Zellforsch. 1970;103:291-319.
19. Shantha TR, Bourne GH. Perineural epithelium; structure and function of nervous tissues. Academic Press. 1969;1:379-458.
20. Shantha TR. Presented at Hanoi: Rabies Cure: Nasal and Oral Route of Transmission of Rabies Virus and Possible Treatment to Cure Rabies. Rabies in Asia conference in Hanoi (RIACON). September 10, 2009. US Patent Application Publication Number: 201110020279 Al. Jan. 27, 2011.
21. Shantha TR, Bourne. GH. The perineural epithelium: and significance. J Nature. 1963;4893:577-579
22. Shantha TR. Peri-vascular (Virchow-Robin) space in the peripheral nerves and its role in spread of local anesthetics. ASRA Congress at Tampa. Regional Anesthesia. March-April;1992.
23. Baer G, Shantha TR, Bourne GH. The pathogenesis of street rabies virus in rats. Bulletin World Health Org. 1965;33:783-794.
24. Baig AM. Pathogenesis of amoebic encephalitis: are the amoebae being credited to an "inside job" done by the host immune response? Acta Trop. 2015;148:72-66.
25. Batson OV. The function of the vertebral veins and their role in the spread of metastases. Ann Surg. 1940:112:138-149.
26. Jackson RT, Tigges J, Arnold W. Subarachnoid space of the CNS, nasal mucosa and lymphatic system. Arch. Otolaryngol. 1979;105:180-184.
27. Nedergaard M. Garbage truck of the brain. Science. 2013;340(6140):1529-1530.
28. Graziadei PPC. Topological relations between olfactory neurons. Zeitschrift für Zellforschung und Mikroskopische Anatomie. 1971;118(4):449-466.

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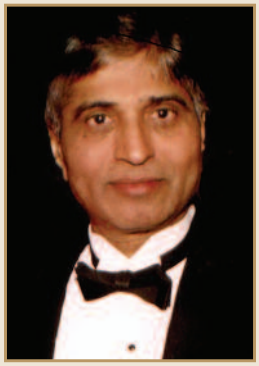
BIOGRAPHY



T.R. Shantha, MD, has been a member of the faculty of Emory University School of Medicine, Medical College of Georgia, Grady Memorial Hospital, Georgia Baptist Hospital, Columbus Medical Center, and is presently a visiting professor at JJM Medical College. He has published more than 100 research articles since 1962 in peer-reviewed reputable journals, including Nature (7 papers), Science, NEJM, J Urology, Anesthesia, Anatomy, Exp. Eye Research, American J of Physiology, etc. He discovered Terbutalene as a treatment for Priapism, which is now used all over the world as the first line of treatment in emergency rooms and by urologists. He has won numerous awards for his academic contributions, including AMA and AAPI distinguished physician awards. He was one of the nominees for the Nobel Prize in Physiology and Medicine in 2007 for his and Dr. Bourne's research work on the membranes of the nervous system discovered at Emory University. His work is quoted in many medical textbooks and research literature. He has more than 56 patent applications, many published and issued. He is presently working on the treatment of Alzheimer's and Parkinson's disease, sleep apnea, and other CNS diseases.

ORALLY DISINTEGRATING TABLETS

Patient-Centric Dose Design, Developments in Orally Disintegrating Tablets

By: Leon Grother, MS, and Mathias Bayru, MS, MBA

INTRODUCTION

The orally disintegrating tablet, or ODT, offers an easy-to-take alternative form to consumers of over-the-counter (OTC) treatments who perhaps do not have access to water, and patients of prescribed drugs who cannot, or will not, swallow standard oral dosage forms, such as tablets and capsules. It is not only patients at either end of the age spectrum – the very old and the very young – who suffer from an inability to swallow, or dysphagia, either, with a recent study indicating that 70% of younger people aged 16-34 who were surveyed reporting that they had difficulties swallowing tablets and capsules.[1] Pre-existing conditions may affect compliance too, and those with mental health issues may not want to take their medications, instead, secreting the tablets in their mouth before disposing of them later, or saving them for misuse or even self-harm in the form of an overdose. It can be easier to give a medication to a child using an ODT and of course, in the animal health arena, it can be a significant challenge to get pets or livestock to swallow tablets.

While liquid formulations can provide successful dosing options in some cases, the ODT can work in all of these situations. ODTs are designed to disperse quickly within the oral cavity, removing the need to swallow a solid tablet or capsule. When a drug is absorbed within the mouth, it enters the bloodstream directly, thus avoiding the first-pass metabolism by the liver, where side-effect-causing metabolites may be formed. It also gives a rapid onset of action, which may be advantageous before or during acute episodes of conditions such as migraine or psychiatric events.

A number of technologies are available to create ODTs. These include Catalent's Zydis® ODTs, which are made via freeze-drying technology, and others, such as loosely compressed tablets. Loosely compressed tablets typically take 15-20 seconds to disperse in the mouth, with a chalky, gritty mouthfeel, unlike Zydis tablets, which will normally disperse in less than 3 seconds with a smooth mouthfeel.

Zydis technology has been used to formulate a number of commercial products, particularly those for which a fast onset of action is beneficial. Recently, higher doses of up to 200 mg have been launched, and peptide and protein products formulated in this way are also available.

The structure of a Zydis tablet is key to its rapid dispersal properties, as the tablets are highly porous. This is achieved via a matrix of fish or bovine gelatin, or by using one of several non-gelatin polymers, plus structure-forming mannitol, which also aids in the solubilizing of the tablet. As well as the drug active, other ingredients, such as sweeteners, colors, flavorings, and acidity modifiers, are often incorporated to increase palatability.

The ingredients are all dissolved or suspended in water, accurately dosed into blister trays, and then frozen in liquid nitrogen freeze tunnels before being placed in freeze dryers. There, the water sublimes, leaving behind the porous matrix structure of the ODT, often referred to as a wafer. Figure 1 is an electron micrograph image of the matrix. The choice of packaging materials is important, and each blister strip is sealed using specially designed, multi-layer foils that are resistant to moisture ingress. Various options are available to optimize and tailor the patient's experience of taking a medication that includes Zydis technology,

for example, blister strips can be customized with multiple combinations of perforations, thumb-peel tabs to allow for easy opening, and printing options too, including helpful directions, regimen information or product branding. After "lidding" the blister strips may be packed into outer cartons.

A significant amount of analytical work is required when developing a new ODT. X-ray diffraction is used to determine the crystalline state of the API and relevant excipients; whether it is crystalline or amorphous will have a bearing on the structural integrity of the final dosage forms. Differential scanning calorimetry is used to determine the melting point and other thermal events. This assists in calculating the necessary times for freeze-drying, while ensuring that the frozen product does not melt during the drying process.

Another technique, dynamic vapor sorption, is used to determine the moisture sorption and desorption profiles. This is important, as a freeze-dried formulation can be sensitive to highly humid environments and can shrink and lose its rapid disintegration characteristics. This helps inform the choice of packaging and formulation characteristics, allowing the products to be marketed in all geographic regions, including those where high humidity is common.

A MORE PALATABLE OPTION

As an ODT is designed to reside in the mouth for only a number of seconds; it cannot avoid the taste buds. If the taste of the active ingredient, or the sensation it generates on the tongue, is not too unpleasant, the simple strategy of including flavor ingredients and sweeteners in the formulation can be sufficient to make it acceptable to patients. For many other APIs, this is not the case. Many taste unpleasant, or can produce burning, numbing, or tingling sensations. If a patient-friendly ODT is to be created, then more creative formulation methods will have to be applied.

One way this can be achieved is via the Zydis Ultra formulation. The taste-masking is provided by the presence of a coating around particles of the API, which can be as small as 100 µm in size. This is less than half the size of the smallest particles that can be coated using more traditional coating processes. Smaller particles make for a better mouthfeel in an ODT; larger particles give a gritty sensation as the tablets disintegrate.

In place of a fluidized bed coating method, in the Zydis Ultra process, API particles are mixed with micronized polymer agglomerates in a vessel that has an acoustic vibrator. When the vibrator is activated, the contents begin to accelerate rapidly, and the polymer is deposited around the API. The vibration and collisions within the mixer result in a continuous polymer layer being formed. It is this layer that confers the desired taste-masking prop-

FIGURE 1

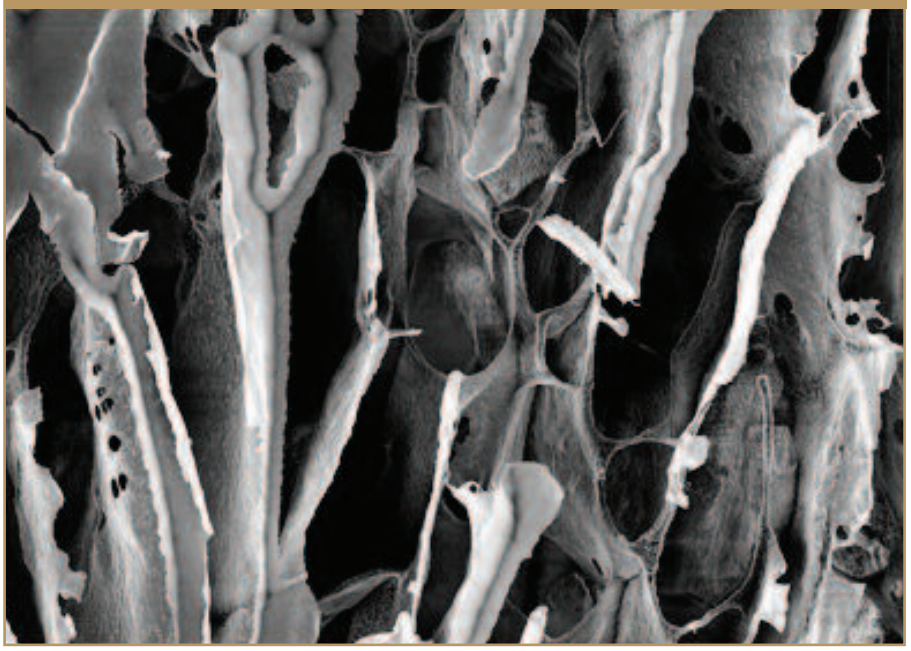


FIGURE 2

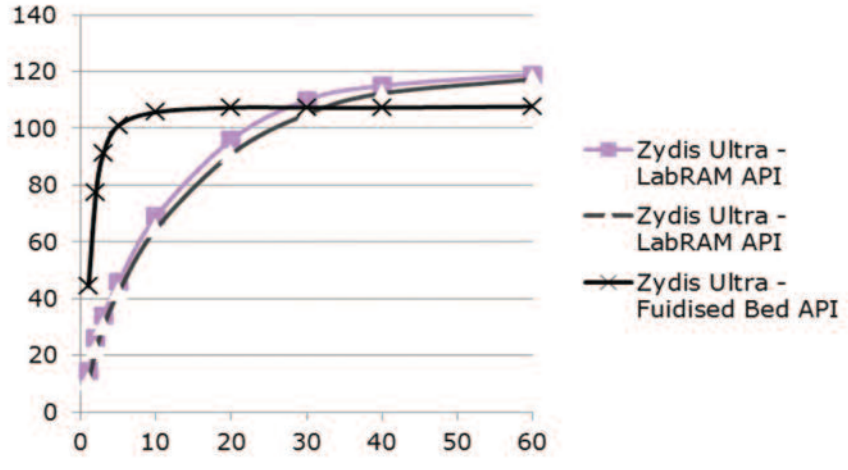
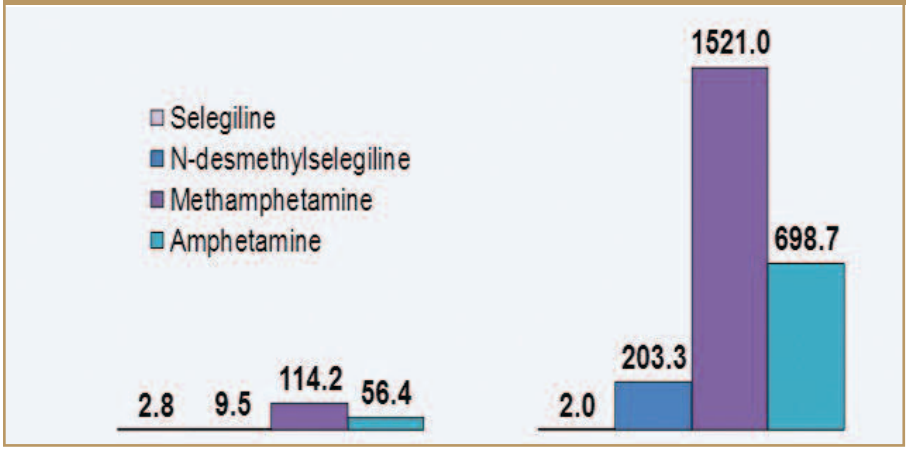


FIGURE 3



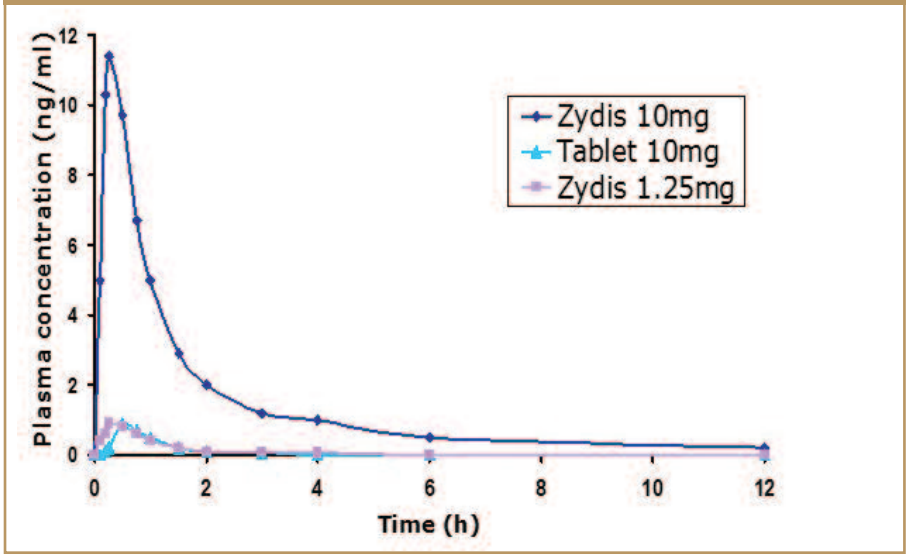
erties. No solvent is needed for this coating process.

In contrast to a traditional coating, the coated API inside is released slowly, a phenomenon that indicates that taste-masking has been achieved, while still meeting the US Pharmacopeial convention (USP) criteria for immediate release. The API still has 70%-85% potency w/w compared to uncoated particles. The difference between the release profiles of the two can be seen in Figure 2.

A common alternative technique for taste-masking is the incorporation of cyclodextrin excipients. Cyclodextrins are sugar-based, ring-shaped macromolecules with holes in the middle that can trap smaller molecules inside if they are the right size. If the cyclodextrin has the appropriate size of hole, the API will become trapped, which prevents it from touching the taste receptors on the tongue.

As an example, a beta-cyclodextrin ODT formulation was created of the very bitter tasting antihistamine, cetirizine. More than three-quarters of a test group claimed its taste profile was acceptable and that the reformulated product incorporating Zydis technology was more pleasant tasting than the standard formulation.

FIGURE 4



ODTS OF THE FUTURE

Recent developments have made it possible to formulate a number of different types of medicine as ODTs that at first sight, one might think would not be compatible with this type of oral dosage form. For example, ODTs can be made from very lipophilic APIs, by way of using an oily emulsion in place of the aqueous solution or suspension that is normally the starting point for an ODT formulation.

Although no products made in this way are yet marketed, tablets have been formulated using a mass fraction of 15% olive oil-in-water emulsion. This has allowed ODTs containing 15 mg of the oil to be created, and an oil-soluble API could be dissolved in this before the tablet is formed. This has been proven with ibuprofen, which, if formulated as an ODT, could offer significant advantage to consumers in speed of onset.

Another innovative possibility is the prospect of formulating a two-layer ODT that would allow two different ingredients to be incorporated within each dose. This could be particularly beneficial if those ingredients were otherwise incompatible, whether it were two different APIs or an API and an excipient, for example, vitamins B and C; and the artificial sweetener, aspartame, which is unstable above pH 6.5 and so is incompatible with many basic excipients and APIs, such as calcium carbonate.

The prospect of formulating biologics as ODTs offers even more promise for the dose form. Biologics usually have to be dosed via injection or infusion, because the complex structures can rarely withstand the highly acidic enzyme-containing environment in the gastrointestinal tract. If they can be delivered through the mucous mem-

"Recent developments have made it possible to formulate a number of different types of medicine as ODTs that at first sight, one might think would not be compatible with this type of oral dosage form. For example, ODTs can be made from very lipophilic APIs, by way of using an oily emulsion in place of the aqueous solution or suspension that is normally the starting point for an ODT formulation. Although no products made in this way are yet marketed, tablets have been formulated using a mass fraction of 15% olive oil-in-water emulsion. This has allowed ODTs containing 15 mg of the oil to be created, and an oil-soluble API could be dissolved in this before the tablet is formed. This has been proven with ibuprofen, which, if formulated as an ODT, could offer significant advantage to consumers in speed of onset."

branes in the mouth, they could enter the bloodstream undamaged as the acidity of saliva is normally close to neutral, and none of the protease enzymes that digest proteins are present.

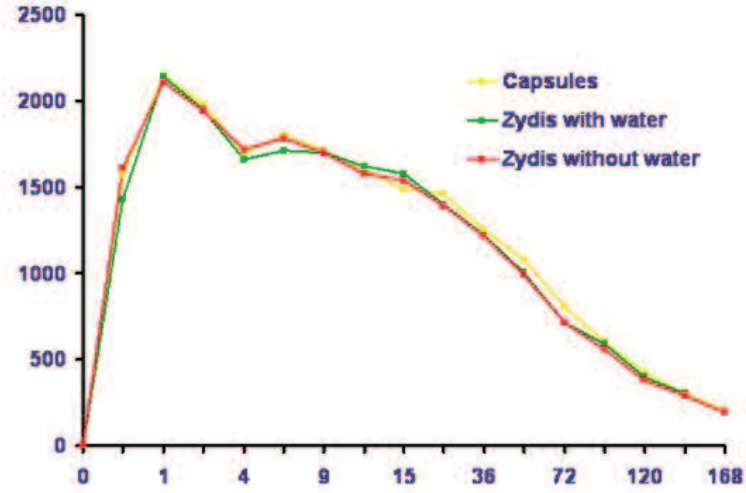
There are regional variations in the thickness of the epithelium that can be exploited; the sublingual epithelium is typically 100-200 µm, while the buccal membrane is thicker, at 500-800 µm. Absorption enhancers and bioadhesives can be included in the ODT formulation to promote absorption. Catalent's Zydis Bio technology was developed as a way of achieving oral delivery of biologics.

There are various other advantages, such as room-temperature stability, whereby cold chain distribution will not be required. This is particularly important for biologic products, such as vaccines, that are destined for developing countries, where access to refrigeration cannot be relied upon, and in pandemic situations, where speed of distribution is key to success.

The peptide drug calcitonin has been successfully formulated in this way, and vaccine ODTs could be particularly important in the future. By avoiding the need for injection, there would be none of the pain, and potential for injection site reactions, that can engender reluctance to immunization among patients and parents. The mucosal response that can occur is a further benefit in immunizations against infections, such as human papillomavirus, influenza, and pneumonia.

Preclinical studies in mice have shown the potential of an ODT influenza vaccine. The loss of bodyweight is indicative of disease severity, and those mice infected with influenza but who were unvaccinated lost significant amounts of weight. In contrast, those who were given the oral vaccine showed no significant loss in bodyweight, even after they were challenged with the influenza virus.

FIGURE 5



Regardless of the type of API that is being delivered, the fact that ODTs offer a route to pre-gastric absorption instead of parenteral delivery can offer some significant benefits to patients. Not only does it offer the potential for a faster onset of action, but by removing that first-pass metabolism of the liver, side-effect profiles can be greatly improved.

The ability to deliver pre-gastrically depends very much on the molecular weight, lipophilicity, and required dose level of the API. Some APIs, even if these properties are favorable, are still not suitable for pre-gastric absorption. But where it is feasible, if the ODT is designed correctly, then it is possible to ensure that the active will be absorbed buccally or sublingually, without being swallowed.

As an example, the monoamine oxidase B drug selegeline, used in Parkinson's disease and depression, may cause patients to suffer side-effects. These result from some of the active metabolites generated by liver enzymes, including methamphetamine. Therefore, if the drug enters the bloodstream directly, these metabolites are not formed and the side-effects they cause cannot occur.

The graph shown in Figure 3 shows the comparison of metabolites formed in a standard 10-mg selegeline tablet, and a 1.25-mg ODT formulation of the same active. Figure 4 shows that the lower-dose ODT produces the same area under curve (AUC) as a conventionally formulated selegeline tablet. And, importantly, the two are bioequivalent. As can be seen in the graph in Figure 5, the AUC for the ODT, taken both with and without water, is essentially the same as a standard 10-mg formulation.

ODTs have become a standard dosage form for a number of medicines, where the fast onset of action or ease of dosing are important. They offer significant advantages to both patients and consumers of OTC medications, and although their advantage over conventional tablets is perhaps more obvious when thinking of the young and old, there are many people outside of these groups who have difficulty swallowing tablets and capsules and would welcome an ODT alternative dose form. Recent developments in ODT technology have widened the range of actives that can be formulated and product types that are possible. In particular, the promise of formulating biologics and ODT vaccines that do not require a healthcare worker to administer them, as with many that are injected, or that do not require cold storage and transit, often to the less accessible parts of the world where so many vaccines are required, is hugely exciting. ◆

REFERENCE

1. In a study commissioned by Hermes Pharma and conducted by Spiegel Institut Mannheim based on 2,000 individuals in Germany and North America (www.epmmagazine.com accessed Sep.23, 2016).

To view this issue and all back issues online, please visit www.drug-dev.com.

BIOGRAPHIES

Leon Grother is Principal Scientist at Catalent Pharma Solutions in Swindon, UK. He earned his BSc in Pharmaceutical Science from the University of Greenwich, London and his Masters in Industrial Pharmaceutical Science from the University of Manchester, UK. He has worked within R&D for more than 15 years, primarily on Catalent's Zydis® ODT technology formulation and process development. During this time, he has gained expertise in freeze-drying and is a named inventor on several patents related to formulation of lyophilized dosage forms.

Mathias Bayru is Catalent Pharma Solutions' Group Product Manager for Drug Delivery Solutions. He is responsible for driving the global marketing strategy for the oral drug delivery solutions business unit, including patient-centric Solutions, Zydis® ODT technology, FlexDose solutions for stick pack, and OptiDose CR for optimal and modified controlled release. Mr. Bayru has more than 12 years of experience in the pharmaceutical industry, and prior to joining Catalent's marketing team, held roles as Marketing Manager for several CDMOs and Senior Scientist for Big Pharma companies. His market knowledge and expertise spans the launch and development of solid and sterile dosage forms, OTCs, and medical devices. Mr. Bayru earned his Master's degree in Pharmacology and his MBA from Montpellier University.

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Drug Development
EXECUTIVE

Viral Gene: Protein-Targeting Cancer Vaccine Could Boost Survival Rates

Chris Kim
President & General Counsel
Viral Gene, Inc.

Dr. Scott Waldman
Professor & Chair
Sidney Kimmel Medical College's Department of Pharmacology & Experimental Therapeutics, Thomas Jefferson University

Harry A. Arena, MBA
President & CEO
Targeted Diagnostics & Therapeutics, Inc.

Colorectal cancer kills more than 49,000 Americans each year and is the second-leading cause of cancer deaths in the US. Dr. Scott Waldman, Professor and Chair of Sidney Kimmel Medical College's Department of Pharmacology & Experimental Therapeutics at Thomas Jefferson University, Dr. Adam Snook, and a team from Thomas Jefferson University's Departments of Microbiology and Immunology, Dermatology and Cutaneous Biology, and Medical Oncology, have pioneered a vaccine to stop the spread of cancers originating in the gastrointestinal tract, including cancers of the colon, rectum, pancreas, stomach, and esophagus.

Targeted Diagnostics & Therapeutics, Inc. (TDT), a biotechnology company headquartered in Exton, PA, obtained the worldwide exclusive rights to this technology in 1994. After 15 years of research, and numerous preclinical lab and animal studies to evaluate biological activity and safety, Dr. Waldman filed an Investigational New Drug Application that was approved by the FDA in 2013. A successful Phase I clinical trial (completed in 2015) tested stage I and II colon cancer patients to determine the vaccine's safety, tolerability, and immunological efficacy.

Viral Gene Inc. was established by Chris Kim, President and General Counsel, to obtain funding for, and conduct, a 2017 Phase II trial. Viral Gene was granted worldwide exclusive license and marketing rights for this vaccine technology from TDT. The trial will assess the vaccine's efficacy in blocking metastatic disease and improving patient survival. Alpha Holdings, Inc., a Korean-based company has invested $8.7 million in Viral Gene to fund the trial and commercialize the vaccine. Alpha Holdings is engaged in the manufacturing of system semi-conductors and provides system-on-chip (SoC) design for Samsung group. Alpha has a vast product portfolio and is Viral Gene's largest shareholder. Trial completion should take about 2 years, and both companies also plan to conduct a Korean trial for the Asian market under the direction of Dr. Waldman.

Harry A. Arena, MBA, President and CEO of TDT, Chris Kim, and Dr. Scott Waldman recently spoke with *Drug Development & Delivery* about the unique characteristics of the vaccine, the patients who will benefit the most, and how a research team captured the attention of investors.

Q: What is the TDT business model?

Mr. Arena: TDT was formed in 1994 to commercialize technological discoveries made by Dr. Waldman in his laboratory at Thomas Jefferson University. At that time, we signed a worldwide exclusive license agreement with the university that included ongoing financial support for Dr. Waldman's research and a commitment to prosecute and pay for the related patent work, while looking to sublicense the resulting applications (including the vaccine technology) to large pharmaceutical companies. We are sort of the middleman. That's our model, and that's always been our model: to look at early stage university-based technology, support it, make sure the patents are prosecuted properly, and then to look for the large pharmaceutical companies to take it through the clinical trials and final product development and marketing. TDT has been involved with this project from the beginning, and we are excited about the prospects due to the funding infused from Viral Gene. Our reward comes when we receive royalties on the sales of any resulting products.

Q: What is the relationship with Viral Gene, and what made them the right fit for this project.

Mr. Arena: In this case, the vaccine wasn't picked up by a large company because of issues regarding how far along the vaccine had been developed. We didn't have other bids, and we wanted to move forward. Viral Gene came along and was looking for something just like this. They had the funding, were enthusiastic about the technology, and had a game plan to build something in the biotech area. We then did a licensing deal to piggyback what we had been doing to fund the project beyond the early research, and fund the clinical trial work to get it to the point where we can get approval. We brought it this far, and they will take it from here. They have a sublicense from us to take the vaccine the rest of the distance from clinical trials to marketing. Viral Gene plans to apply to the FDA for Orphan Drug Status through its Office of Orphan Products Development because there is little therapy available for the types of cancers the vaccine is targeting, and the patient populations are fairly small.

Q: What is the market potential for the vaccine domestically and globally?

Mr. Arena: There are approximately 150,000 colorectal cancer surgeries in the US each year with diagnoses indicating various stages of the disease. Patients with other GI cancers (gastric, esophageal, and pancreatic) total about 103,000. Those currently undergoing chemotherapy, or who are immunologically compromised from other treatments, are not candidates for the vaccine. The overall market size of the Viral Gene GI cancer vaccine market in the US is approximately 165,000 cases annually. To this, you could potentially add the population of surviving patients from years prior to the vaccine's approval.

Mr. Kim: Cancer vaccine revenues in the US were reported at $14 billion in 2012, and are expected to reach $20 billion by 2020.[1] The current average and projected annual growth rate to 2020 is 4.56% (CAGR). The US currently represents the largest market for cancer vaccines and represented 60% of the global cancer vaccine market in 2016.[2] The estimated insurance coverage of the vaccine is as much as $80,000 per patient.

Q: Can you describe how this vaccine was pioneered?

Dr. Waldman: Our team has been focused on trying to understand the biology of the target of this vaccine, which is Guanylyl Cyclase C (GCC), since the early 1980s. GCC regulates water and salt secretion in the intestine, and is a protein shown to be highly accurate in detecting the spread and

"Immuno-oncology is the flavor of the year, but most of the focus is on immune-modulating drugs. There are other pieces to the immune-oncology continuum that can be exploited to the benefit of patients, such as vaccines." - Dr. Scott Waldman Professor & Chair, Sidney Kimmel Medical College's Department of Pharmacology & Experimental Therapeutics, Thomas Jefferson University

recurrence of colorectal cancer whether in lymph nodes or blood. In the 1990s, we recognized the unique utility for GCC in managing patients with colorectal cancer as a marker and target of that disease. The reason it's a unique marker and target is because GCC is selectively made in the intestines by the intestinal epithelial cells, which are the single layer of cells that line the intestine. They are anatomically compartmentalized and made in the intestine. GCC continues to be made and is overexpressed by those cells once they transform from normal epithelial cells to colorectal cancer cells. What's unique in this case is the target is normally compartmentalized on the inside of the intestine. But when the disease metastasizes, the metastasis carries the marker from the intestines to the inside of the body, making it a unique target and marker. It gives us the ability to hunt, seek, and destroy GCC-expressing metastatic tumors inside the body using a variety of approaches without harming the intestine and without attacking the "normal" GCC made by normal epithelial cells. This can be done because of the separation between the inside of the intestine and the inside of the body. There is a barrier – a compartmentalization – so we really leverage that to use GCC as a target. It gives us the ability to attack metastatic colorectal cancer cells without attacking the normal tissue. We can do that with antibody drug conjugates, but we can also do that with our vaccine.

Q: How does the vaccine work in the body?

Dr. Waldman: We leverage the immune system to selectively go after metastatic colorectal cancer cells. We are teaching the immune system to recognize GCC as a foreign protein and attack it like it would attack a bacteria or virus. We developed a vaccine for GCC that trains the immune system to go after GCC on the inside of the body, not the inside of the intestine. We can take advantage of that compartmentalization principle by using the immune system. The vaccine takes advantage of adenovirus as a carrier of the vaccine. The virus is non-replicating, so we take adenovirus and the front half of GCC, and put it into the adenovirus genome. This package becomes our vaccine, which we inject into muscle where it then makes virus proteins and GCC from its genome. Remarkably, the GCC in the vaccine gets presented to the immune system in the context of a viral infection. The virus sends "danger" and "stranger" signals. It's like a Trojan horse. We trick the immune system into thinking it needs to react to GCC, and what winds up getting attacked are the colorectal cancer cells; the immune response kills those cells to improve survival.

Q: What makes this vaccine unique, and is it supposed to replace the antibody drug conjugates?

Dr. Waldman: The vaccine has a unique place in the armamentarium that we have to treat colorectal cancer. The vaccine is designed to prevent secondary metastasis for the life of a patient. This is for someone who has already been diagnosed with colorectal cancer and had their definitive surgery to remove the primary tumors. They've had their primary radio- or chemotherapy. They are now ostensibly free of cancer and on a surveillance program. This vaccine will not have use against the primary cancer because it's sitting within the intestines, and the vaccine won't attack that primary tumor. About half of the patients with colorectal cancer will get recurrent disease, and ultimately die of their disease because of hidden metastasis in their body. We vaccinate them to attack and kill the cells that are there, but now they are protected. We create a memory immune response that gives life-long protection against the development of metastasis down the road. We have proven this in mice that had cancer and were vaccinated, then given cancer again; they rejected the cancer. We see the vaccine as being value-added in the continuum of care, not only to prevent secondary metastasis acutely, but also to the remaining life of the patient.

Q: Can you discuss the type of dosing that will be required?

Dr. Waldman: We don't yet know how often the vaccine will need to be renewed. In the Phase I clinical trials, we used a single dose. The next clinical trial will be segmented into two parts. First, we will determine the right dosing regimen to give a patient. We gave an average dose in the Phase I study. In the first part of the next trial, we want to know how much we should give. We believe we can go up in dose considerably. We want to find out if we can, and should, repeat those doses to boost the response. Once we identify the right dosing regimen, we will address if the vaccine dose makes patients with cancer live longer. The longer-term question to ask is, will it be beneficial to give a booster every 1, 5, or 10 years? The Phase II trial will commence next year.

Q: Does the vaccine have applications for other types of cancers?

Dr. Waldman: The reason colorectal cancer cells make GCC is because the cells from which they originated make GCC. Most colorectal tumors retain the characteristics of the cell type from which they originated. The characteristic pattern they retain is the making of GCC. However, we learned some interesting things by looking at other tumors at other sites in the GI tract. For instance, not all original cells in the GI tract make GCC, but when they become tumor cells, they newly start to express GCC. About 75% of lower esophageal cancer cells make GCC; 50% of gastric cancer cells make GCC; and 25% of pancreatic tumors make GCC. Each of these tumors become therapeutic candidates for the vaccine. We envision the next trials will focus on tumors outside of colorectal cancer, such as pancreatic cancer and esophageal cancer. We will focus on these high-need disease states in our next phase to see if we can improve survival rates.

Q: What will this vaccine mean to future cancer vaccination development?

Dr. Waldman: Immuno-oncology is the flavor of the year, but most of the focus is on immune-modulating drugs. There are other pieces to the immune-oncology continuum that can be exploited to the benefit of patients, such as vaccines. Cancer vaccines really struggle to identify the right target to go after. Our vaccine offers a unique target with unique characteristics that target GI malignancies. The principles we learned about GCC and the immune system can pertain to other cancer targets. ◆

Contact: Lou Nosti
SGW
T: (973) 263-5289
C: (973) 934-3231
lnosti@sgw.com

REFERENCE

1. US Cancer Vaccine Market Outlook 2019 Research Report, February 2014.
2. US Cancer Vaccine Market Outlook 2022, RNCOS Industry Research Solutions, July 2016.

Special Feature

Analytical Testing: Market Drivers, Growing Demand & Client Needs

By: Cindy H. Dubin, Contributor

The global healthcare analytical testing services market is estimated to grow at a CAGR of 11.3% from 2016 to 2021, to reach $4.13 billion by 2021 from $2.42 billion in 2016. Growth in this market is mainly attributed to the growing demand for analytical services for biologics and large-molecule drugs, increasing outsourcing of analytical testing by pharmaceutical companies, and growing acceptance of the Quality-by-Design approach in pharmaceutical research/manufacturing. In addition, the high quality standards in the pharmaceutical industry, rapid growth in the biosimilars and biologics market, and presence of a large pool of analytical testing providers are further expected to drive the growth of this market.[1]

Drug Development & Delivery magazine recently spoke with several of these testing providers to find out what services they offer, trends they identify, and how they have specifically addressed clients' needs during the past year.

SGS recently entered into a collaboration with DiscoverX, a life science company that supplies cell-based assays and services for drug discovery and development.

Alcami: Identifies & Analyzes Client's Drug Impurity to Continue Manufacturing Campaign

As a full-service CDMO, Alcami supports all phases of pharmaceutical development—from API characterization to finished product formulation to clinical and commercial manufacturing and stability—offering a breadth of services. For example, Walter Holberg, Scientific Advisor-Operations Lab Support, Alcami, explains the conversion of one API crystal form to another poses a potential risk to patient safety by potentially altering drug release. To mitigate this risk, Alcami offers comprehensive crystallization studies in concert with polymorph identification using differential scanning calorimetry, thermogravimetric analysis, and X-Ray Crystal Diffraction.

Mass Spectrometry has become one of the foundation technologies in pharmaceutical analysis, particularly with the recent emphasis placed upon impurity identification and extractables and leachables testing. Alcami offers LC and GC-MS separations with ESI, ICP, and MALDI-QTOF analysis to fill this need. "Our skilled scientists provide method development and validation services from early-stage proof-of-concept studies to ICH-compliant validation for all phases of product development," says Donal DeCou, Principle Scientist-Biotechnology, Alcami. "In addition, a comprehensive suite of microbiological testing, such as sterility, antimicrobial effectiveness and microbial limits testing, and disinfectant efficacy, complement a full spectrum manufacturing capability for solid oral dosage forms and sterile parenteral products."

Alcami has a variety of state-of-the-art equipment available to provide industry-leading turnaround times.

Several trends in analytical testing are being attributed to new FDA regulatory requirements for all new drug products effective June 2016, and for all commercial products effective January 2018. For example, advancements in analytical testing for quantitation of elemental impurities in prescription and non-prescription human drug products are on the rise, specifically using plasma spectrometry, ICP-MS or ICP-OES, to screen and/or accurately quantitate the presence of any elemental impurities of interest. Alcami offers value-added risk assessment screenings using scientifically sound methods for the analysis of APIs, excipients, and drug product.

To illustrate Alcami's expertise in this area, Mr. Holberg explains how one client contracted Alcami to manufacture a generic product for the U.S. market that was listed in both the USP and European Pharmacopoeia (Ph. Eur.). While Alcami manufactured the finished product, the client obtained the API from another source. When the API was originally tested, it met all USP requirements; however, several months later when the drug product was tested for manufacturing release, a single impurity was identified that was greater than the ICH threshold for unknown impurities, thereby putting the manufacturing campaign at risk.

Alcami quickly concluded that this unknown impurity was a listed impurity in the Ph. Eur. Monograph. It was listed as a known impurity with an unknown structure. The USP and Ph. Eur. methods were compared, and the unknown impurity in the client's API was positively identified by comparing UV spectra obtained from PDA detectors, chromatographic retention time match, and LC-MS mass quantification. Eluent fractions were collected from both analytical methods, and the molecular structure was elucidated from the ICP-MS/MS fragmentation pattern. Finally, a small amount of the impurity was obtained and analyzed both chromatographically and using ICP-MS/MS to positively verify that the impurity in the API with a previously unknown structure had been identified. "With this information, our client was able to continue its manufacturing campaign and market the product."

In addition to purity challenges, there are challenges presented when testing small molecules, such as that an increasing number of novel therapeutic agents are either poorly soluble or difficult to detect with traditional techniques. Will Boomershine, Principle Scientist-Structural Chemistry & Biotechnology, says Alcami scientists have experience with analyzing and detecting poorly soluble molecules using non-traditional techniques, such as evaporative light-scattering detection (ELSD) and charged aerosol detection (CAD), as well as other non-spectrophotometric technologies, such as electrochemical, conductivity, refractive index and multi-angle light-scattering (MALS) detection.

One of the significant challenges with biologics is demonstrating biosimilarity. Alcami can overcome this challenge through primary sequence confirmation, activity binding (equivalency), and higher-order structure analysis, which uses both glycosylation and impurity profiles, and is a central requirement of the ICH Q6B guideline document. A second challenge that often presents itself is the characterization and analytical development for antibodies and antibody drug conjugation (ADC). Alcami provides solutions to this challenge through the development and validation of purity methods. These include chromatographic purity techniques (SEC, IEX, RP) and electrophoretic purity techniques (SDS-PAGE, IEF, CE, iCE). Activity binding can also provide answers to this challenge through cell-based bioassays. Conjugation analysis, concomitant analysis of free drug, total antibody, and antibody drug conjugates can also help provide solutions to issues that may arise during the characterization and analytical development for biological drug products.

Avista Pharma offers sophisticated instrumentation and capabilities including ICP-MS and XRPD systems (shown here).

Avista Pharma Solutions: Optimizing All Method Parameters in Analytical Method Development & Testing

Avista Pharma provides a full range of analytical services to pharmaceutical and biotechnology companies supporting both early and late stages of drug development. Increases in the complexity of molecules entering the development pipeline along with stringent regulatory requirements require sophisticated instrumentation, technologies, and services. Avista Pharma offers sophisticated instrumentation and capabilities to assist its clients in solving the most challenging analytical problems, says Ahmed Abrahim, Vice President, Business Development, Avista Pharma Solutions. Some of the recent additions include more than 10 UPLC systems for high efficiency chromatographic method development; redundant ICP-MS instrumentation for analysis of elemental impurities; high resolution LC-MS for identification of impurities and MS-directed purification system for isolation and purification of low level impurities; and X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) instrumentation for polymorph screening and identification, material stability monitoring, standard characterization, and investigational studies.

One area that has gained regulatory attention in recent years is the appropriate assessment and control of Potential Mutagenic Impurities (PMIs also known as PGIs or GTIs) as described in ICH M7 guidelines. The synthetic route of each drug substance must be evaluated for the use and formation of PMIs. In addition, PMIs must be evaluated during forced degradation studies that may indicate PMIs that are produced during product storage. These studies require very sensitive methods (i.e. low ppm or ppb quantitation limits) to measure these compounds at the appropriate control points during synthesis. These methods often utilize LC-MS or GC-MS techniques to achieve the appropriate sensitivity requirements. "Because these PMI analytes are inherently reactive, it is common to "under recover" PMIs in

sample matrix spiking studies," says Mr. Abrahim. "In these cases, derivatization may be used to ensure that the analytical method can accurately assess endogenous PMI levels present in the sample. Our scientists specialize in these types of studies."

In fact, Avista Pharma recently helped a client solve a challenging problem at the ANDA filing stage of its generic drug. The client observed a new impurity in the HPLC impurity profile of a sample stored at a 40°C and 75% relative humidity storage condition (i.e. accelerated stability studies). In less than a week, the Avista Pharma analytical team isolated enough highly purified material for mass spectrometry (MS) and nuclear magnetic resonance (NMR) studies (i.e. both performed internally). MS data that was obtained included an exact mass measurement to determine the molecular formula. NMR data included the ^{1}H, COSY, HMQC, and 1D NOE spectra to establish molecular connectivity. Collectively, the analytical data indicated a specific structure consistent with a reaction between the active pharmaceutical ingredient and an excipient in the drug product. "Our synthetic chemists subsequently synthesized this proposed compound and generated the analytical data to support the veracity of the proposed structure for the isolated impurity. In addition, the Relative Response Factor (RRF) of the impurity was established. With the information that Avista Pharma provided, the client was able to quickly make the necessary changes to its ANDA and moved forward to launch the product," says Mr. Abrahim.

Another growing area in drug development is the concept of Quality by Design (QbD). Avista Pharma has the capability to perform studies to identify Critical Process Parameters (CPPs) as well as full fate-and-purge studies for impurities, reagents, and intermediates. "It is critical that our process chemists and analytical scientists work in a very close partnership to design and generate the data needed to support a robust operating range for chemical processes. The fate-and-purge studies are critical in establishing impurity specifications for regulatory starting materials (RSMs), drug substances, and products."

An area of analytical services that has shown significant uptake in business is elemental impurity testing. This is driven by the new ICH guideline (Q3D) and USP <232>/<233> relating to Elemental Impurities, which presented the pharmaceutical industry with new challenges, says Mr. Abrahim. These challenges include the complexity of introducing new analytical technology, specifically Inductively Coupled Plasma (ICP)-based techniques replacing the qualitative wet chemical "heavy metals" limit test USP <231>.

"Pharmaceutical and biotechnology companies are in search of CROs that have the technology and the experience to provide this service. Avista Pharma scientists have extensive knowledge and experience providing consultation and analytical support to navigate and achieve compliance with the elemental impurity guidances. We regularly assist our clients in developing a risk assessment strategy via documentation, analytical screening, and method development/validation to achieve compliance. We perform this analytical testing using redundant ICP–Mass Spectrometer (ICP-MS) instruments with microwave digestion, if needed."

In addition to specialized services, Avista Pharma offers expertise in chromatographic method development, such as HPLC stability-indicating methods. The development of stability-indicating methods for either small molecules or biologics can be challenging for various reasons, including low aqueous solubility/stability of the API. While chromatographic specificity is the most important parameter during the method development process, other parameters such as solubility and stability of the product in various diluents, should also be addressed. Avista Pharma was recently involved in transferring and evaluating an HPLC assay and related substances method that was previously developed and validated at another contract organization. While the method was determined to be specific for the specified impurities, the impurity profile of a sample was shown to vary depending on the type of diluent used for dissolution of the sample. When using the method diluent (50/50 Acetonitrile/water), one of the early eluting impurities (i.e. unknown) was at 0.4% by area. The same sample dissolved in acetonitrile showed the impurity at 0.1% by area with a new late-eluting peak 0.3% by area. This observation indicated instability of the late-eluting peak in the presence of water and possibly hydrolysis of the impurity. Mr. Abrahim says: "This example highlights the importance of optimizing all the method parameters during the method development process, even the sample diluent."

Boston Analytical: The Importance of Using the Right Test Method for a Drug

"It's important for an analytical laboratory to provide a variety of techniques and equipment to support the development and manufacture of drug products," says Michael Molloy, Technical Director at Boston Analytical. The lab has to identify and quantify critical constituents of the product and measure contaminants and degradation products. Analytical tools like chromatography (such as HPLC), mass spectrometry, ultraviolet or infrared spectroscopy, and thermal analysis are essential to adequately characterize the active molecule and excipients.

For small molecules, the workhorse instrument for evaluating purity and degradation products continues to be the HPLC, with UPLC continuing to gain traction. There are significant advantages in test execution with the UPLC, both in saving time to do the test and using less solvent volume, explains Mr. Molloy. "Method development is faster given the shorter run times, with really no loss of precision in the analysis, but development still depends largely on HPLC. Systems are widely available, and analysts are quite comfortable working with and troubleshooting HPLCs, so they will remain an important approach for the foreseeable future."

An important characteristic for small molecules is the dissolution profile, which helps develop a strategy for bioavailability, and as an indicator of stability, looking at the changes in dissolution profile during a stability study at multiple storage conditions. "There are several different approaches to dissolution, with instruments specialized for a particular type of drug product or device. It's important for an analytical lab to have availability of all the dissolution approaches to test the many different types of products that benefit from it," he says.

One important trend today is in testing raw materials or drug substance for contaminating metals. Traditionally, the approach was to use the USP Heavy Metals test, which Mr. Molloy says was not specific and only provided an estimate of levels of metal. A new approach is now established in the USP, using more specific and precise instruments including inductively coupled plasma mass spectrometry (ICP-MS). "Mass spectroscopy can yield a much lower level with very good precision, and can specifically identify the elements present."

Another important trend is in testing product packaging to ensure that it doesn't inadvertently contribute any contaminants to the product. This is done with a sophisticated battery of tests under an extractables and leachables evaluation. The package is subjected to harsh conditions intended to break the material down and release contaminants. This helps identify those compounds that may eventually find their way into the product.

Challenges can arise that stem from the interaction of the drug with the test system, or sometimes from the excipients. Care must be taken to design the appropriate tests for the information required. Mr. Molloy says, "Developing appropriate test methods is an important part of moving the drug to the market."

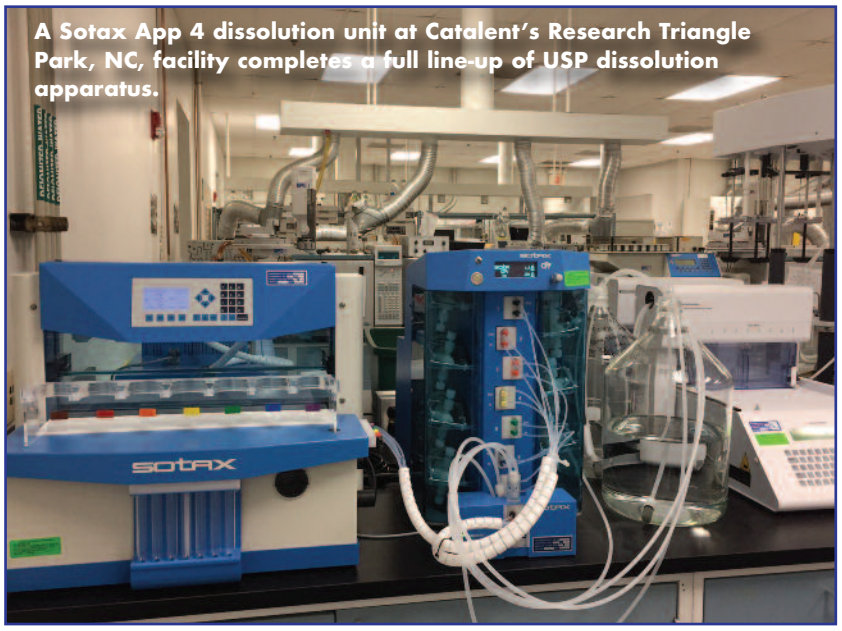
Catalent Pharma Solutions: Developing Methods & Assays for Aqueous Drugs & Solid Dispersions

Catalent's analytical team in Research Triangle Park, NC, recently competed in the Conference on Small Molecule

Boston Analytical's new state-of-the art lab.

Science Method Development Olympics (MDO), an annual contest for teams from pharmaceutical companies and universities to compete in an analytical challenge designed by the MDO committee. All participating teams' results are judged for: accuracy; ancillary information discovered; and creativity in approaches. Catalent's team has entered three times and won one bronze and two silver medals.

Building on its analytical expertise, Catalent recently added five robotics instruments for liquid sample handling. The new instruments are dedicated to GMP and GLP execution of molecular binding, cell-based assay, and flow cytometry analysis of biologic entities from peptides to viruses. These new systems are housed within flexible cGMP and GLP laboratory spaces to maximize process flow. And, in the past several months, Catalent has received numerous requests for help performing gap analysis and additional lab work on forced degradations studies in accordance with the new guidance from ANVISA, the regulatory body of the Brazilian government. In 2015, ANVISA published the RDC53/2015 regulation outlining specific requirements in regard to reporting, identification, and qualification of degradation products for product registration and post-approval change submissions, and Guide nº 04/2015 for obtainment of the degradation profile, and identification and qualification of degradation products. Even though it is generally aligned with industry practices,



A Sotax App 4 dissolution unit at Catalent's Research Triangle Park, NC, facility completes a full line-up of USP dissolution apparatus.

the scope and depth of such requirements are expanded beyond the ICH guidelines with some specific requirements for forced degradation study at its core. For example, it specified what material should be studied, what condition must be used, and what results are acceptable and how their used in stability indicating method development. "Needless to say, the ANVISA forced degradation study regulation and guidance will have a huge impact on companies intended for product registration and post-approval change submissions in Brazil," says Wei Pan, PhD, RAC, Director, Stability & Analytical CMC, Catalent Pharma Solutions.

The past year also brought a request to develop an aqueous drug product in a polymeric, semi-permeable container closure system. Dr. Pan explains that during a leachables assessment, an unknown species was detected by GC-MS analysis. Through diagnostic mass spectral elucidation, the Catalent team determined that the unknown species was neither related to the polymeric materials of construction nor the known additive profile used in the molded component. Working closely with the resin material suppliers, the polymeric container manufacture, and client, the Catalent team designed a step-wise assessment of unmolded resin material and eventually identified the unknown species as a transformation product. Specifically, it was determined to be a hydrolysis product of a cross-linking terminator used in the manufacture of the virgin resin. With this new information, the Catalent team developed and validated the appropriate monitor and control methodology that facilitated timely approval of a novel drug product for a previously underserved patient population

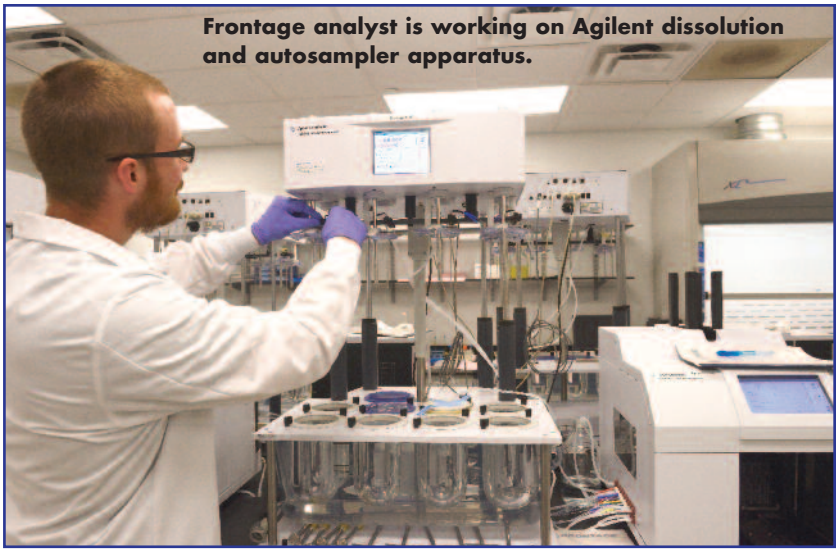
"Catalent developed a new high throughput viral screening assay by combining a new detection technique with the automated liquid handlers," says Mike Merges, Director of Strategic Growth, Biologics Analytical Serv-

ice, Catalent. "The assay turnaround time was reduced from 10 to 3 days, reagent costs were cut in half with 3% CVs."

For another client, Catalent used OptiForm® technology to develop quantitative methods to determine the crystalline content of an amorphous solid dispersion (ASD). Feasibility studies of powder x-ray diffraction (PXRD), modulated differential scanning calorimetry (mDSC), IR, Raman microscopy, and FT-Raman spectroscopy were conducted and showed that partial least-squares (PLS) analysis of FT-Raman spectral data proved the best methods. With a suitable method to generate homogeneous calibration standards and controls established for environmental on the FT-Raman spectrometer to maintain a constant RH for sample analysis, the optimized FT-Raman methods afforded the limit of detection of 1.5% and 3.0% for ASD and tablets, respectively. Dr. Pan says these methods were successfully used to support the stability tests of ASD and tablets.

Frontage Laboratories: *In-Vitro* Release Test Method for Nanoemulsions

Frontage's analytical scientists specialize in analytical method development, validation, and transfer for product development and clinical trial materials manufacturing support, as well as commercial product release and stability testing. Services are designed to help sponsors throughout the drug development process to fully characterize drug substances, developmental formulations, and commercial drug products.



Frontage analyst is working on Agilent dissolution and autosampler apparatus.

Frontage brings experience in analyzing a variety of dosage forms including oral solid, liquid, lyophilized, topical, and liposomes/emulsions/suspensions. Chemists' expertise includes chromatography, dissolution/diffusion testing, UPLC, HPLC/MS, UPLC/MS, GC/MS, IC, ICP/MS, Karl-Fisher, and titrimetric methods.

Dr. Kang Wang, Vice President, Analytical Services, Frontage Laboratories, says FDA expects that an *in vitro* drug release test method be developed for nanoemulsion drug products, through which the product quality is guaranteed from batch to batch. Frontage has developed a reverse dialysis *in vitro* drug release method and characterized one nanoemulsion product. "The method is discriminative and has shown batch similarity for validation batches, and differences between batches made under different conditions," says Dr. Wang.

FDA requires Q1/Q2 match and *in vitro* release test in some ANDA semi-solid product development. Frontage used GC/FID, GC/MS, HPLC/CAD, and ICP/OES instruments to determine excipient contents in reference listed drug (RLD) and proposed Q1/Q2 to FDA for several products. Also, Franz cells were used as an *in vitro* release testing tool and support drug product formulation development, he explains.

Gateway Analytical: Keeping Its Eye on the Critical Path Initiative

Gateway offers a full range of analytical services, including optical microscopy, manual and automated scanning electron microscopy, Fourier Transform Infrared (FTIR) spectroscopy, Raman spectroscopy, Raman Chemical Imaging (RCI), automated Raman (SPE), and HIAC particle counting. Gateway's focus is on foreign particulate identification, sizing, and counting, ranging from hair and fibers to glass lamellae. In addition to characterizing contami-

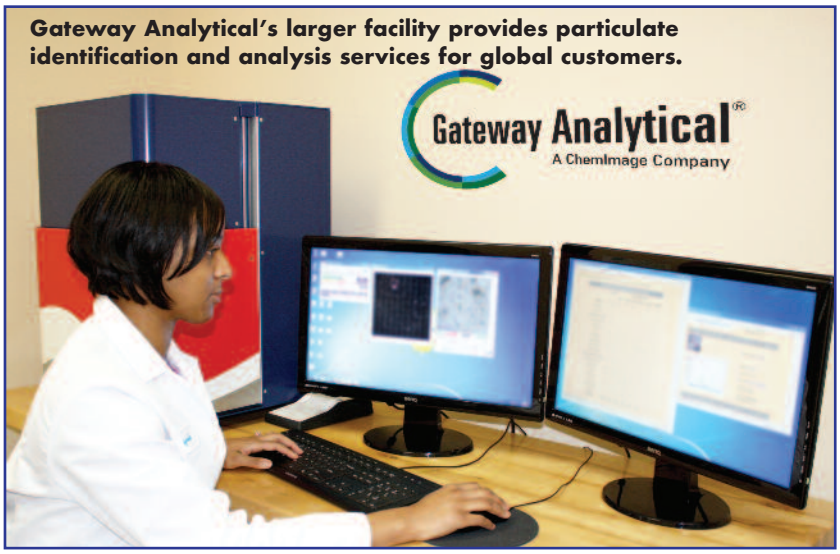
nants, Gateway provides forensic expertise to determine the source of unknown and unwanted materials found in drug products.

Gateway utilizes automated SEM-EDS, RCI, SPE, and HIAC to perform count and size on particle populations, including foreign particulate (e.g. USP<788>), as well as performing count/size on drug ingredients (e.g. Ingredient Specific Particle Sizing).

"Foreign particulate contamination in any pharmaceutical product is a major safety issue for end users," says David Exline, President, Gateway Analytical. "The danger is of a distinct concern when the product is being introduced to a patient who is immunosuppressed. Gateway's recent relocation to a new, larger facility allowed for the construction of a dedicated cytotoxic testing laboratory, which can support proper handling and testing of cytotoxic drug products."

One particular trend in analytical testing is the Critical Path Initiative, says Mr. Exline, specifically how automated Raman technology (SPE and/or RCI) will play a role in the pharmaceutical industry going forward.

The FDA introduced the Critical Path Initiative with the intent of modernizing generic drug development, and the Office of Generic Drugs recently supported approval of the first generic drug to utilize this approach. The size distribution of the active pharmaceutical ingredient (API) is critical as it relates to bioavailability, rates of absorption, and stability of the drug product, and this is where automated Raman technology is effective. "Drug manufacturers around the world look to leverage new processes that can get generic drug products to market faster," he says.

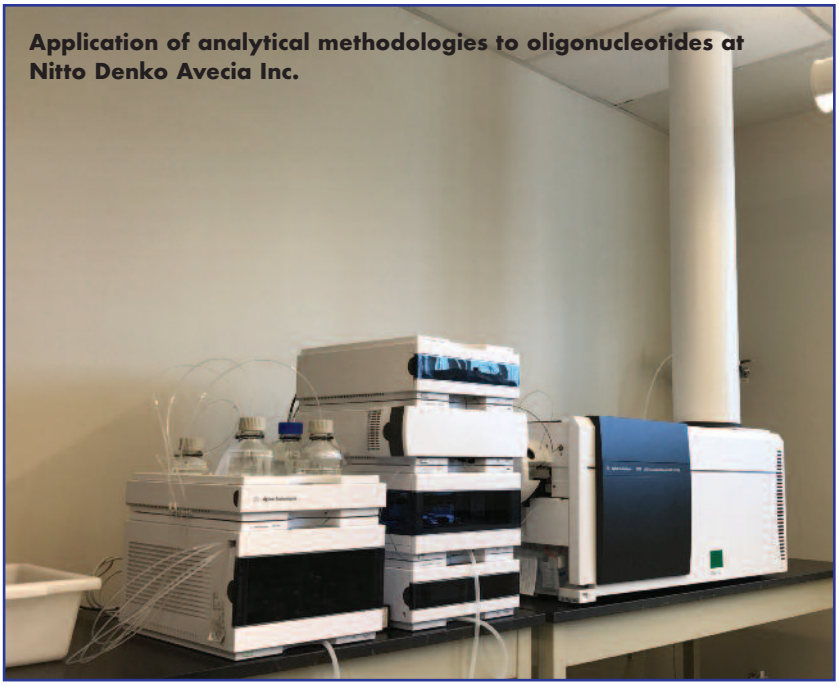


Gateway Analytical's larger facility provides particulate identification and analysis services for global customers.

Nitto Denko Avecia Inc.: Taking Oligonucleotide Characterization to the Next Level

The field of oligonucleotide therapeutics continues to mature with drugs at all phases of development, as well as a small number of drugs approved by regulators. Since most oligonucleotide drug sponsors rely on cGMP manufacturers to supply material for clinical trials, much of the analytical method development efforts are outsourced to CMOs like Avecia. "The resulting analytical methods are critical for development of the manufacturing process and support the release of material suitable for testing in humans," says Dr. Sridhar Vaddeboina, Vice President, Analytical Development, Nitto Denko Avecia. "The development of analytical methods is continually challenged by new chemical modifications to oligonucleotides introduced by drug designers. These modifications work to improve delivery to the inside of target cells and tissues while resisting the biological degradation that limits potency."

Orthogonal Chromatographic methods are preferred for determining the purity of oligonucleotides and measuring the levels of impurities. Oligonucleotides are a challenging class of polymers for chromatographic methods because of the combination of charged groups in the sugar and phosphate backbone while the bases contain both polar and nonpolar surfaces, says Dr. Jonathan Neidigh, Group Leader, Analytical Development, Nitto Denko Avecia. Dr. Neidigh explains that strong anion exchange and ion-pair reverse phase chromatography are the core methods in most analytical testing strategies. When the drug molecule is a duplex of oligonucleotides with complementary sequences, size exclusion chromatography or non-denaturing chromatographic methods are also required. While refractive index and multi-angle light scattering can be used for some conjugated oligonucleotides, most methods use UV detection where the large



Application of analytical methodologies to oligonucleotides at Nitto Denko Avecia Inc.

absorbance of the nucleotide bases provides high sensitivity. In addition, LCMS methods are frequently used to establish the identity of oligonucleotide therapeutics, quantify impurities that, due to their similarity with the therapeutic oligonucleotide, do not resolve chromatographically, and for supporting process development efforts.

The introduction of chemical modifications to oligonucleotides leads to the need for complex sequencing methodologies. "Mass spectrometry approaches have been shown to be accurate, robust, and hence, attractive for assessing the sequence of synthesized oligonucleotide and to confirm it has the proposed theoretical molecular sequence," says Dr. Edward Huber, Director, Analytical Development, Nitto Denko Avecia. At Avecia, electrospray ionization–mass spectrometry/mass spectrometry (ESI-MS/MS) is utilized for this required sequencing testing. The experimental approach is based on Collision-Induced Dissociation (CID) of the parent oligonucleotide, which results in a complex mixture of fragment ions of varying lengths and charge states, explains Dr. Huber. These experimentally generated fragment ions are identified and consolidated to rebuild the sequence of the parent oligonucleotide. This is accomplished by a combination of software and manual analyst evaluations. Experimentally, a High Resolution Mass Spectrometer equipped with a UHPLC connected online at the front end is utilized for these experiments.

"The sequencing experimental approach has been fine-tuned by Avecia for obtaining experimental data with a quick turn-around time to meet short timelines and associated business demands," says Dr. Huber. "Avecia has made this complex sequencing analysis routine and applies it on a near daily basis for confirming proposed molecular sequences of synthesized oligonucleotides." Consistent with the regulatory requirement defined in the ICH Guidance Q2(R1) Validation of Analytical Procedures: Text and Methodology, the sequencing method has been validated by Avecia for multiple oligonucleotides.

SGS Life Sciences: Staying Ahead of the Orthogonal Curve

In the past year, SGS invested in new technologies and techniques within its laboratories to support biopharmaceutical development, including Hydrogen Deuterium Exchange Mass Spectrometry (HDX-MS) for higher order structure analysis services for proteins, and molecular binding kinetic and affinity determination via Bio-Layer Interferometry (BLI).

"Whether it be ICH Q6B, or the FDA's "Purple Book," the regulatory expectation and industry practice is to employ current and leading analytical techniques during biopharmaceutical product characterization and comparability studies," says Mark Rogers, Vice President USA, Life Science, SGS. "The addition of HDX-MS and BLI to the SGS analytical tool kit expands on an already comprehensive analytical package for characterization of biological products, and is in alignment with SGS' strategy for investment in forefront technologies."

HDX-MS complements orthogonally, but also provides additional data over other techniques such as Circular Dichroism (CD), Analytical Ultra Centrifugation (AUC), Size Exclusion Chromatography with Multi-Angle Laser Light Scattering (SEC-MALS), and Fourier Transform Infrared Spectroscopy (FTIR); ultimately

allowing for a more complete and comprehensive submission-ready structural characterization package, explains Mr. Rogers.

Similarly, BLI provides an orthogonal complement to classical activity assays, including cell-based bio-activity assays, ELISAs, SPR, and other photometric assays. However it has the advantage that molecular interactions can be monitored in real time, and it can study interactions between most types of molecules, such as protein-protein, protein-small molecule, antibody-peptide, DNA-protein or DNA-DNA. "This technique is among the most advanced, sensitive, and robust to measure desirable, potentially clinically beneficial, and undesirable, potentially clinically unfavorable, molecular interactions," he says. "BLI can support candidate selection or support batch comparability testing for binding strength, efficiency and kinetics; ensuring clients can have access to the most meaningful information quickly while only using the smallest amount of valuable material."

In fact, Mr. Rogers says that biosimilar comparability testing is a growing trend. Growing regulatory acceptance of such drug products is reflected by the increased number of products in the development pipelines. "Analytical structure and functional characterization is regarded by regulatory authorities throughout the world as a critical component of biosimilar development, as the structure and function of a molecule are key indicators if the target molecule of interest has been successfully recreated. In essence, even before purity and other critical quality attributes are optimized, confirmation of biosimilarity at the structural and functional levels is the first step in gaining an understanding of the originator, biosimilar, and ultimately if the desired output has been met." These analytics are essential to define the Critical Quality Attributes that form the Quality Target Product Profile (QTPP) of the product.

For biosimilars, Mr. Rogers says it is essential that the range of tests used during development are both sensitive and robust enough to detect any potential differences in structure and function between the biosimilar and reference. In addition, the techniques should be capable of quantitative as well as qualitative assessment of the quality attributes.

Over the last 20 years, advanced technologies have been developed for structural characterization, and also the prediction of how the molecule will interact within the biological system. Regulators are now looking for orthogonal techniques – multiple orthogonal assessments to build a total profile of the molecule. The FDA introduced the concept of "fingerprint-like" analyses. This entails a carefully selected portfolio of characterization techniques for primary and higher order structure, together with biological and potency assays producing data, which add up to more than the sum of the parts. What remains to be explored is the link between the higher order structure and biological activities. Several complementary techniques are emerging from research backgrounds to address these questions such as HDX, 2D NMR, SPR, and BLI. "While the functional assessment of the bio-molecules action in a cell is still largely evaluated through quantitative cell-based assays, BLI allows us to quantitatively measure the strength and speed of those interactions at a molecular level," he says.

SGS recently entered into a collaboration with DiscoverX, a life science company that supplies cell-based assays and services for drug discovery and development. DiscoverX developed a series of cell-based assays that rely on the native biology of target receptors to quantitatively measure drug potency for the rapid identification of biosimilar candidates. SGS has been able to qualify these cell-based assays to establish biological activity and potency for three biosimilar targets.

"Based on the intra- and inter-run precision and accuracy obtained, SGS concluded that the bioassay kits and reporter cell lines developed by DiscoverX are suitable for functional comparability assessment required by regulators," says Mr. Rogers. "Because these assays are easy to use, commercially available, and highly reproducible, one key benefit is the significant reduction in assay development time, translating into overall cost savings in a biosimilars development program." ◆

Reference

1. Healthcare Analytical Testing Services Market by Type, by End User - Global Forecast to 2021, Reportlinker, June 15, 2016, http://www.prnewswire.com/news-releases/healthcare-analytical-testing-services-market-by-type-by-end-user--global-forecast-to-2021-300285441.html, accessed Dec. 20, 2016.

COMBINATION PRODUCTS

6 Guidelines to Follow When Developing Combination Products

By: Winston Brown

INTRODUCTION

While the development of a combination product comes with significant patient benefits through technology and molecule innovation, that reward can be offset by the range of regulatory complexity and uncertainty encountered with bringing a product to market, in addition to any post-marketing activities. The area of combination products is still unique to many regulatory authorities abroad, wherein the lines are often blurred when it comes to product classification and jurisdiction. While the regulatory path and compliance requirements may be fairly clear in one country, there are no universal templates, procedures, or exacting opinions to follow for harmonized solutions.

Combination products have the potential for significant therapeutic advantages over traditional dosage forms of medicine by delivering value and convenience for both patient and point-of-care provider, maintaining dosage compliance, and providing novel drug delivery therapies for unmet medical needs. Combination products, such as in vitro diagnostics and radio-biologics, have been on the market since the 1970s. However, there has been a proliferation of combination product platforms that have been developed throughout the years covering a wide range of drug delivery applications. The main drivers for the increasing demand of these novel therapies are customer convenience, evolving medicine models, and reimbursement strategies, and the increasing demand for product intelligence features. Current trends in healthcare toward more outpatient and home-health-based services have only accentuated those needs.

In 2013 alone, there were 313 Combination Product Applications submitted to the FDA. Roughly 88% of these applications were divided, from a reviewing standpoint, fairly evenly between CDRH and CDER.[1] But despite the increase in the development of these device platforms, regulatory authorities are still struggling to identify if these products are drugs, devices, or both. Sponsor companies can reduce the risk and impact that regulatory uncertainty can play by, in advance of pursuing development, understanding the regulatory landscape and then developing a regulatory compliance strategy that is appropriate and suitable for the combination product as a "system." The following six guidelines will help reduce the number of questions coming back from the reviewing agency, thereby enabling speed to market.

DEFINE THE PMOA (ACCURATELY)

Have a clear understanding of all applicable regulations, guidance documents, and any predicate products prior to developing a regulatory and quality compliance strategy. Early and meaningful engagement of the respective regulatory reviewing office is also key to avoiding delays and submission refusals. The primary US FDA-applicable regulations can be found in FDA 21CFR Part 3 and Part 4, along with 13 primary FDA Guidance Documents. A recent FDA performance report concluded that from 2009-2014, there were 67 requests for designation (RFD) for formal combination product classifications and assignments. Of those 67 RFDs, 69% were found to have been insufficient with the information provided by the sponsor. Another 6% of the filings were withdrawn by the sponsor prior to the issuance of a decision.[2] One common mistake made by sponsors when filing an RFD is failing to distinguish between the primary mode of action

(PMOA - often the most important therapeutic action) and multiple modes of action with reasonable certainty (21 CFR Part 3.2). Depending on the constituent parts of the overall combination product system, there can potentially be multiple modes of action. Clearly defining the PMOA is critical to obtain approval at first pass. If the sponsor cannot define with certainty the PMOA, then the FDA will likely use the PMOA assignment algorithm. The assignment then comes down to historical precedents and the respective FDA office with the most experience for the product in question.

RESEARCH THE GLOBAL REGULATORY GUIDELINES

Though the path for combination product regulatory approval in the US (FDA) is more defined and currently evolving, there is little harmonization with the rest of world. For example, if a sponsor wanted to file for market approval in Europe, there is no specific, centralized decision-making body that will provide a clear understanding of filing requirements. For Europe, MEDDEV 2.1/3 establishes clinical data submission considerations, but still falls short in describing the clear regulatory path the product must progress through in order to obtain a favorable opinion.[3] Latin American countries, such as Brazil, have no specific combination product regulations. Sponsor applications for these products would currently fall under Brazilian, Federal Laws No. 5.991/73 and 6.360/76 and ANVISA's (the Brazilian National Health Surveillance Agency) Decree No. 79.094/77, which regulates both drugs and medical devices. Additionally, Law No 5.991/73 outlines the requirements for what is considered a product intended for medicinal purposes, those that are medical devices, and those that may warrant a pre-review by the Brazilian Ministry of Health and ANVISA.[4]

The advice here is to get engaged early with any potential country where you plan to do commerce. Gaining clarity on national requirements may not be enough. The sponsoring company may need to drill down to the regional and local jurisdictions to fully understand all requirements and nuances. This level of granularity is especially important if you choose to conduct clinical trials overseas, with clinical trial materials made in another country. In these cases, import/export laws must be considered and planned. This is where having regionally deployed personnel ("boots on the ground") are effective for navigating the regulatory waters of local jurisdiction.

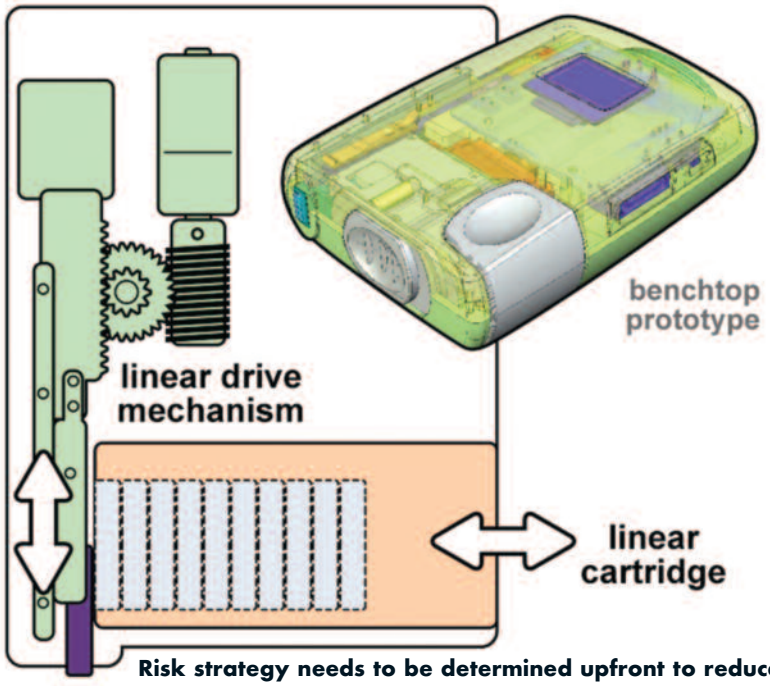
FIGURE 1

The impact of regulatory uncertainty can be reduced by pursuing development, understanding the regulatory landscape, as well as developing regulatory compliance strategy appropriate for the combination product as a "system."

DEVELOP AN APPROPRIATE CGMP QUALITY COMPLIANCE STRATEGY

From a quality systems standpoint, combination products should be viewed holistically as a "system" in which both constituent parts must have suitable quality system requirements in place, be it manufactured in the same facility, different facilities, or completely outsourced (virtual sourcing). We find through various FDA Form 483(s) (Warning Letters and other recent stark reminders, that the development and understanding of a combination product is sometimes not in synch with the cGMP manufacturing strategy. For example, in 2014, the FDA issued a Warning Letter to Amgen as a result of a June 2014 inspection related to the PROLIA prefilled syringe and needle guard, ENBREL lyophilized vial and diluent with vial adaptor, and Enbrel prefilled syringe with SureClick 1.5 auto injector.[5] Deficiencies cited were primarily in the quality system

FIGURE 2



Risk strategy needs to be determined upfront to reduce time to market.

element areas of design controls, change controls, and purchasing controls. The interpretation of this Warning Letter would suggest that systems need to be developed and acted on for both device and pharmaceutical/biologic types. The Warning Letter also infers that legacy combination products that are still on the market may be held to a more rigorous standard in the near future, including the retrospective application of medical device and/or pharmaceutical quality system requirements. The Quality Management System (QMS) should be derived by a blended or bolt-on approach. If the sponsor is a pharmaceutical company that develops combination products and conducts or provides oversight for device operations, then build in those device requirements into the pharma-based model for complete regulatory compliance coverage. Likewise, if the sponsor is a device manufacturer that conducts or provides oversight for pharma operations, include the device requirements. It is often good to coach people on the idea that both worlds are not mutually exclusive. Strip the label off of the (device or drug) regulation and focus on the actual intent of what is being requested in the requirement.

IMPLEMENT A DESIGN FREEZE DURING THE COMBINATION PRODUCT DEVELOPMENT PROCESS

Pharma and biologics companies are not device companies, and thus, many are unfamiliar with the concept of a "design freeze." The freeze is the point in the product development life cycle at which the actual design has been formally approved and all product changes are prohibited, unless initiated through the design control process. Knowing when to do a design freeze during the development of a combination product is critical. Typically, a design freeze is initiated just before the validation/verification stage of a medical device. Any changes that are made to the device design post design freeze, and once initial data has been submitted for regulatory review, may trigger additional requirements of the design outputs. Ideally, sponsor companies should think about incorporating clinical studies (including human factors) prior to implementing the design freeze. By implementing a development pilot study prior to any pivotal clinical trial, the sponsor company can gain valuable insight into product performance. If the product remains consistent and robust throughout the studies, the data could feasibly be used to propel the product ahead of plan.

Sometimes, pharma companies, in general, are reluctant to change a device once it is on the market because that usually results in additional clinical studies and a significant amount of money and time to resubmit. Regulatory delays can be significant for a combination product worth several million dollars. Conversely, some device companies seem to have an affinity for making changes to a device; they want the next generation, better ergonomics, with more human factor studies.

The design freeze is extremely important because if the design keeps changing and there is no stage-gate or control built into the process, sponsor companies will find it difficult knowing what to incorporate for design reviews, design verification protocols, and subsequent validation data. Regulators want to see a firm plan with traceability from the base level of design (proof-of-concept). They also want to ensure that the device they are approving is just as safe and effective as the constituent drug/biologic part, from a clinical standpoint. Do not be surprised during the submission process if additional clinical data is requested above what was already submitted.

USE RISK-BASED DECISION MAKING TO DEVELOP & BRING THE PRODUCT TO MARKET

Any type of risk, such as the potential harm the device could cause to the patient, has to be considered when developing a combination product. Use failure modes and effect analysis to look at all the risk in the development for both the individual constituent parts and the system as a whole.

For instance, when the drug/biologic target product profile (TPP) is being established, the sponsor company can, in parallel, integrate the device design development concept into this discussion by asking how using a certain material in the manufacturing of the device could possibly introduce a leachable/extractable that would pose significant harm or risk to patient, and stability profile of the product. As an example of this thinking, consider a sponsor company working with a device design and development company to produce an insulin auto-injector. The next-generation auto-injector may require an option for changing the grade or properties of a polymer or a resin additive. Using risk-based decision-making, the two companies would need to work together to determine if they would have to go back and complete biocompatibility studies with the resin change and the drug to see if they were compatible.

It really comes down to determining what risk strategy the sponsor company will employ in the development of the combination product, and will the sponsor company deploy it in separate parts - one for the drug and one for the device. Or, is it going to be a combined strategy in which the drug and device companies are working together in planning the development?

ESTABLISH A PRODUCT STABILITY STRATEGY

The FDA and EU want to see stability studies on file before a final submission is sent to them. Determine if the device and drug should be studied with the two components together, independent of one another, or both. Analyze how or if the device changes the actual drug once the two are paired together over the shelf-life of the product. The sponsor company will need to provide details of these studies and validation that the products are safe for patient consumption before the regulatory bodies will consider approving. You also need to consider what specific tests need to be performed on each constituent part and together as a system. For instance, if the company is performing shock and vibration studies on a particular drug delivery device, should they do this separate from the drug being included, together, or both? If conducting accelerated aging on a system or constituent products, is the company carrying out physical testing and then monitoring all relevant time points? Is stability ending at the end of shelf-life only, or does the company go past expiry? All are factors that should be included in a sound stability strategy.

CONCLUDING ADVICE

The regulatory submission and approval process for combination and drug delivery devices is still evolving, which means sponsor companies may have a lot of unanswered questions. Implementing some of the aforementioned essential guidelines is key to improving the odds of first-time regulatory approval. Many companies file with not enough or the wrong information, or they don't establish an appropriate QMS, all of which slows their approval process and costs them more time and money. Speed to market is then lost. The more meaningful data the sponsor company has that validates the product as a system, and the more sound and holistic the product development and cGMP processes are, the better the chances are of first-time approval, which ultimately saves the sponsor company both time and money. ◆

REFERENCES

1. Food and Drug Administration: FY 2014 Performance Report to Congress- Office of Combination Products (Required by the Medical Device User Fee and Modernization Act of 2002).
2. Ibid.
3. EUROPEAN COMMISSION: Guidelines on Medical Devices: Clinical Evaluation: A Guide for Manufacturers and Notified Bodies, MEDDEV. 2.7.1 Rev.3 (December 2009).
4. Medical Devices BRAZIL Demarest e Almedia Advogados: Lex Mundi Publication. 2011.
5. Chimera Consulting, North America, LLC. Summary of Key Points: Warning Letter to Amgen 2014 (PROLIA Prefilled Syringe and Needle Guard, ENBREL Lyophilized Vial and Diluent with Vial Adaptor, and Enbrel Prefilled Syringe).

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Winston Brown is the VP of Global Quality at Phillips-Medisize. He has more than 20 years of experience in global Quality, Regulatory Compliance, and Operations working with diverse pharmaceutical, medical device, biologic companies. He can be reached via email at Winston.Brown@phillipsmedisize.com.

BIODEGRADABLE FIBERS

Enabling Controlled Pharmaceutical & Biologic Delivery for Next-Generation Medical Applications

By: Kevin Nelson, PhD

INTRODUCTION

Incorporating a broad range of pharmaceutical- or biologics-loaded fibers into implantable medical devices that could enable next-generation medical applications was previously not feasible because the types of drugs capable of surviving traditional fiber manufacturing processes were historically limited.

Pharmaceutical- and biologics-loaded implantable textiles can result in faster healing and improved patient compliance of medical devices. However, traditional melt extrusion processes used to manufacture fibers destroyed the viability of all but a very limited selection of pharmaceuticals and biologics, given the high temperatures at which melt extrusion must occur - which often exceeds 200°C and high shear stress during extrusion.

Now, modified wet-extrusion processes can occur at room temperature, eliminating the traditional temperature limitations of pharmaceuticals and biologics that may be incorporated into implantable medical devices and therapies with melt extrusion processes. As a result, the range of drugs now available for controlled sustained delivery from a fiber has been broadly expanded from those previously deliverable via electrospun fibers, microspheres, or nanoparticles.

Using drug protection technology, the biological activity of incorporated agents can now be preserved so that the broadest range of pharmaceuticals and biologics ever possible remain viable when loaded into biodegradable fibers for use in implantable devices that can support controlled sustained delivery.

THE ADVANTAGES OF FIBER DELIVERY

Because fiber is both readily implantable and maintains positional stability, it offers an unparalleled advantage when targeting specific sites within the body. Pharmaceutical- and biologics-loaded fiber has the ability to facilitate an entirely new and groundbreaking approach to a variety of medical applications related to advanced drug delivery, nerve regeneration, and tissue engineering.

The use of biodegradable fiber offers several unique advantages over traditional pharmaceutical delivery formats, including:

- Longer therapeutic windows
- Targeted delivery to internal surgical sites
- Controlled, sustained delivery of pharmaceuticals and biologically based drugs
- Tailored release of multiple pharmaceuticals from a single fiber
- Removable format if required

Fiber's cylindrical geometry provides a slower pharmaceutical release rate than a spherical geometry of the same radius, resulting in an inherently longer therapeutic window for similar pharmaceutical concentrations. Also, because fiber is both readily implantable and maintains positional stability, it offers an unpar-

alleled advantage when targeting specific tissue sites, such as solid tumors. Additionally, fiber decreases the risk to patients because fiber is removable in the rare case of an adverse reaction, whereas microspheres and nanoparticles are delivered systemically and typically not extractable once delivered.

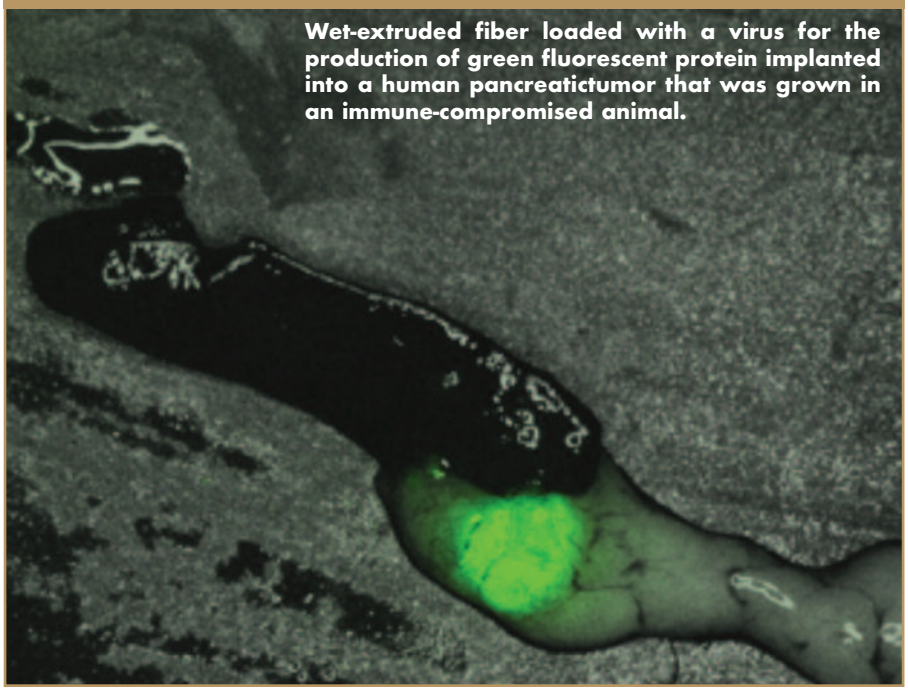
THE EMERGENCE OF WET EXTRUSION

Traditional melt-extrusion for medical-grade polymers occurs at temperatures that exceed the temperature tolerance of the vast majority of pharmaceutical and biological therapeutic agents. Now, wet spinning has emerged as a promising alternative to overcome the limitations of melt extrusion.

In the wet spinning process, a polymer solution is injected through a spinneret into a coagulating bath. The coagulating bath is composed of a solution that is highly miscible with the solvent used to dissolve the polymer, yet is a non-solvent for the polymer. As the polymer solution stream enters the coagulating bath, the solvent diffuses from the solution stream into the coagulating bath, locally increasing the polymer concentration. Simultaneously, the polymer stream is exposed to the non-solvent of the coagulation bath. This combined effect causes the polymer molecules to precipitate out of solution, forming a solid fiber.

The polymer fiber is then pulled from the coagulation bath and taken through a number of draw stations, where the fiber is stretched to align the polymer chains, resulting in increased tensile strength. While these draw stations typically include ovens to heat the fiber during the pulling process, the temperatures are typically limited to body temperature, allowing the residual solvents (and non-solvents from the coagulating bath) to provide the molecular mobility required to allow the polymer chains to align and provide high mechanical properties to the fiber.

FIGURE 1



Wet-extruded fiber loaded with a virus for the production of green fluorescent protein implanted into a human pancreatictumor that was grown in an immune-compromised animal.

The challenge posed to retained drug viability in traditional wet extrusion is the solvent system that enables fiber formation itself. Exposure to the solvents and non-solvents used during extrusion may destroy incorporated pharmaceuticals or biological agents. However, it is now possible to protect the pharmaceutical from the solvent; enveloping it in a protected zone within the polymer solution thereby protecting the drug from the solvent environment. Prior to use in medical applications, however, the solvents must be removed from the fiber. Several processes can be used to effectively remove residual solvent to levels below the allowable limit set by FDA guidelines while preserving the loaded drug's viability.

Wet fiber extrusion is a very controlled process, yielding more uniform size distribution than the distribution typically found in other formats. Multi-layered, coaxial fibers may be readily produced with each layer containing a unique pharmaceutical and polymer combination, thus enabling tailored release kinetics for multiple pharmaceuticals in a single fiber.

By employing a patented extrusion process based on the fundamentals of wet spinning, a broad range of polymers may be loaded with viable drugs including both synthetic and biopolymers. Wet- extruded fibers are ideal for use in current and next-generation implantable medical devices, regenerative medicine, and as pharmaceutical depots for slow controlled release. The localized pharmaceutical delivery capability of these fibers enables medical device designers to orchestrate the body's response to the device. Depending on the choice of drug, it is possible to mitigate unwanted reactions and promote desired responses.

"The challenge posed to retained drug viability in traditional wet extrusion is the solvent system that enables fiber formation itself. Exposure to the solvents and non-solvents used during extrusion may destroy incorporated pharmaceuticals or biological agents. However, it is now possible to protect the pharmaceutical from the solvent; enveloping it in a protected zone within the polymer solution thereby protecting the drug from the solvent environment."

THE NEXT GENERATION OF MEDICAL APPLICATIONS

Allowing sensitive pharmaceuticals and biologics to remain viable when loaded into fibers enables the development of drug delivery devices with tailored release kinetics and retained activity. These fibers are ideal for incorporation into any number of implantable medical device applications that benefit from the controlled release of pharmaceutical and biological agents within the body directly to the internal sites where they are needed.

This technology has the potential to revolutionize many medial applications, including spinal cord repair, nerve regeneration, tumor remediation, dermal wound healing, and many more applications. Imagine the possibilities of medical textiles becoming scaffolding for tissue engineering and regenerative medicine applications. The scaffolding would then deliver growth factors that can selectively direct cell migration and tissue growth according to proper placement of fibers loaded with growth factors within the scaffold.

Growth factors, such as vascular endothelial growth factor, have been successfully loaded into fibers as well. Even virus particles have been loaded into fibers and implanted into immune-compromised animals, resulting in efficient transfection.

The controlled release and specific drug-eluting capabilities of wet extruded fiber-based systems are well-suited for a variety of medical applications, including meshes and weaves for current textile applications, sutures, ligatures, and scaffolding. In fact, the fibers are sufficiently strong for use as a biodegradable, self-expanding, pharmaceutical-loaded cardiovascular stent.

IMPLICATIONS FOR MEDICAL & REGENERATIVE APPLICATIONS

Beyond the many uses in implantable medical devices and pharmaceutical depots, drug delivery via biodegradable fibers is poised to enable paradigm-shifting advancement in tissue engineering and regenerative medicine applications.

With wet extrusion, sensitive growth factors, such as Nerve Growth Factor (NGF), Vascular Endothelial Growth Factor (VEGF), and other sensitive biological molecules, including immune proteins and enzymes, such as IgG and even live adenoviruses, can be loaded and delivered via fibers.

Fibers loaded with such biologics and incorporated into implantable medical devices are ideal for a number of regenerative applications, including:

- Nerve regeneration
- Regenerative medicine
- Solid tumor remediation
- Spinal cord repair
- Dermal wound healing

Fiber is mechanically strong enough to be woven, knitted, or braided to create physiologically meaningful three-dimensional structures that can support tissue scaffolding. For example, a fiber running through a scaffold releasing VEGF may induce angiogenesis along its pathway, while another fiber in that same scaffold releases NGF to direct the growth of nerve tissue along another specific pathway as defined by that fiber. This pharmaceutical delivery technology also enables fibers with controlled pharmaceutical concentration gradients along the length of the fiber to encourage cell migration. These three-dimensional structures make possible the creation of physiologically meaningful architectures through site-specific pharmaceutical release.

In animal experiments, fiber has been shown, for example, to promote peripheral nerve regeneration. A parallel array of fibers provides excellent scaffolding for guiding neurons and fiber loaded with biologically active neurotrophic factors has been shown to attract neurons from isolated DRG cells in cell culture experiments.

SPINAL CORD INJURY REPAIR

The central nervous system (CNS) is biologically very different from the peripheral nervous system (PNS), especially in terms of wound healing. In the CNS, unlike the (PNS), there is limited regenerative capacity. Research indicates that the axons do attempt to regenerate following injury; however, there are many roadblocks that impede functional recovery. For example,

in the myelin (a substance that wraps around many axons to speed up electrical signal conduction) there are substances that inhibit the growth of the axons. When the PNS is injured, the myelin is rapidly degraded by white blood cells and Schwann cells (the type of cells that make myelin in the PNS). In CNS injury, however, both the white blood cells and the oligodendrocytes (the cells that make myelin in the CNS) are much less effective at clearing the myelin rendering less effective removal of inhibitory substances. In the PNS, Schwann cells produce large amounts of neurotrophic factors, which is a beckoning call to the regenerating axons to induce and guide their growth. The oligodendrocytes (CNS counterpart), however, produce much less of these factors. Also, in the CNS, the glial cells (supportive cells in the CNS) form "scar" tissue very rapidly following injury, called a glial scar, which consists of growth inhibitory substances. This glial scar is highly effective at stopping the axons from bridging even very small gaps.

Now that roadblocks to healing are better understood, by delivering sensitive growth factors directly to the injury site, nerve regeneration can be promoted without requiring tissue to be harvested from elsewhere in the patient's body for grafting. This could potentially advance the treatment and recovery of patients with previously irreversible spinal cord injuries resulting in paralysis.

The growth factor-loaded fiber could enable the creation of three-dimensional concentration gradients of neurotrophic factors that are positionally stable over time, and these gradient scaffolds may be surgically implanted into an injured spinal cord. The concentration gradients of the various neurotrophic factors may selectively entice motor and sensory axons to cross a gap in opposite directions in the spinal cord by directing axonal growth.

This approach could possibly be indicated in spinal cord injury patients, where the spinal cord injury resulted in a lesion, or was severed. This treatment may even apply to old injuries as well, in which case the number of potential recipients increases significantly, as some 250,000 people in the US are currently completely disabled due to a previous spinal cord injury.

SMALL DIAMETER VASCULAR GRAFTS

Small-diameter vascular grafts for use in the treatment of cardiovascular disease have proven challenging to develop due to the need to induce successful endothelialization and, consequently, to prevent the unwanted formation of blood clots resulting from graft implantation. While blood clots present limited clinical harm in large vessels, in small diameter arteries, the risk to the patient from clotting is considerably greater.

Grafts constructed of drug-eluting fiber may hold the key to enabling small diameter grafts to finally become a viable option for treating cardiovascular disease. By loading medical textiles with the right choice of growth factors for incorporation in the small diameter graft, complete endothelial coverage may be achievable to prevent the likelihood of blood clot formation in the artery. ◆

CONCLUSION

Wet-extruded fiber with drug protection technology eliminates the traditional limitations of pharmaceuticals and biologics that may be incorporated into implantable medical devices with melt extrusion and provides additional benefits compared to other technologies such as electrospun fibers, microspheres, or nanoparticles. These extrusion processes that occur at room temperature enable loading of the widest range of pharmaceutical and biological agents ever possible for delivery from biodegradable implantable devices, thereby enabling localized, controlled delivery within the body, which can facilitate breakthroughs in medical applications, such as nerve generation, spinal cord injury repair, tissue engineering, and even vascular grafts. ◆

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BIOGRAPHY

Dr. Kevin Nelson earned his PhD from The University of Texas Southwestern Medical Center at Dallas under the direction of Dr. Robert Eberhart. As a faculty member in Biomedical Engineering at the University of Texas at Arlington in 1996, he joined a team working on an NIH grant to develop a fiber-based, biodegradable vascular stent with the goal of delivering gene therapy to the vessel wall. Simultaneously working with Dr. Nathan Schwade to develop drug-loaded microspheres for improved wound healing, he eventually combined the drug-loading techniques of microspheres with the fiber for the biodegradable stent, and fiber-based drug delivery was born. Eventually patented, this technology has been the focus of Dr. Nelson's professional life and the driver behind TissueGen, Inc.

Drug Development
EXECUTIVE

Patrick Walsh
Chief Executive Officer
Avista Pharma Solutions, Inc.

Avista Pharma Solutions: Experience, Responsiveness & Expanded Capacity Driving Growth

Avista Pharma Solutions, Inc. (Avista Pharma) is a new name, but it has a decade-long track record in the CDMO market via three strategic acquisitions and one of the most-experienced leadership teams in the industry. At the helm is CEO Patrick Walsh, whose pharma career spans 35 years, and who is a recognized entrepreneur in the pharmaceutical industry. His recent accomplishments include leading the resurgence of AAIPharma Services, which resulted in a strategic sale of the company in 2013, and he has served as a Board of Director and advisor to numerous leading healthcare and private equity organizations. In addition to his role at Avista Pharma, he is on the Board of Directors of Brammer Bio, a new cell and gene therapy CDMO that also has an aggressive growth strategy. *Drug Development & Delivery* recently spoke with Mr. Walsh about Avista Pharma's range of capabilities and what is driving growth for his company in this dynamic industry.

Q: Can you describe the current status of the contract services industry?

A: The industry is experiencing unprecedented growth and market expansion, but it is still highly fragmented in terms of the number of CDMOs in the industry with significant market share. In addition, pharma clients are seeking to consolidate vendors and concentrate their outsourcing spend on contract organizations with technical depth, responsiveness, significant expertise, and a breadth of service offerings. Avista Pharma was created with these specific attributes in mind, and our clients have stated that these are among the most important attributes for contract service providers in this dynamic and growing market.

Q: Where does Avista Pharma Solutions see its biggest impact being made in this dynamic environment?

A: Avista Pharma is a relatively new name to the industry, but it was formed by combining three businesses with strong technical and scientific leadership, as well as facilities offering significant expansion possibilities. Currently, there are few companies who have the technical depth, facility capabilities, and experienced leadership necessary to quickly advance early phase programs and respond to clients' concentrated timelines.

Q: Avista Pharma Solutions consists of several facilities across the United States. Can you describe your investments in these operations?

A: Avista Pharma is an organization with strong support from our private-equity partner, Ampersand Capital, which has allowed us to make significant investments in all of our locations across the United States. Avista Pharma encompasses over 200,000 sq ft of laboratory and manufacturing assets, with further expansion planned.

Our Massachusetts-based operation recently completed a major facility expansion and offers microbiology service offerings on par with any company in our competitive peer group. We also offer sample courier service around the North East biotech corridor and on-site expertise for environmental monitoring services.

The expansion of our North Carolina and Colorado operations reflects significant investments in expanding the scale and scope of our API manufacturing, formulation, analytical, and drug product manufacturing operations. We see the animal health market as another high growth area, with Avista Pharma already recognized as a preferred partner in this high growth sector. We currently do business with a majority of the global animal health companies in the industry.

Q: What do you believe are some of the biggest challenges in the contract services industry?

A: There are hundreds of contract service providers in our industry, yet few provide the consistent quality, technical depth, and responsiveness to deliver perfectly on every client project. In addition, many CDMOs do not possess the necessary level of technical depth beyond the senior leadership level, and project management is underserved and understaffed. There is a tremendous desire by pharmaceutical companies to consolidate external contract providers and to create meaningful alliances with a select number of CDMO partners who can cover the majority of their requirements. We view this industry trend as extremely favorable to Avista Pharma, and we have invested millions of dollars in IT, quality management systems, and the latest analytical equipment to meet these requirements.

Avista Pharma's scientific and technical expertise goes deep into the organization, allowing clients to feel comfortable with projects at any stage of development. This ensures a capable, trained project champion who oversees successful project outcomes.

Q: Are there particular services that distinguish Avista Pharma Solutions?

A: We like to take on difficult assignments, complex chemistry, and projects in which clients and clinical programs are counting on a successful outcome. Avista Pharma also distinguishes itself by providing chemistry, formulation development, API, and first-in-human clinical manufacturing from a single site at our Colorado facility. In addition, our Durham site is recognized around the globe for helping companies in the animal health market screen compounds and make informed product development decisions with our novel screening platforms.

Q: What are the next steps for Avista Pharma Solutions?

A: We see alignment of our service offerings with our clients' challenging projects, and our business will continue to be rewarded for delivering projects on time every time. Avista Pharma will continue to explore additional acquisitions that add new capabilities to our pharma or animal health core platform of services.

In 2017, we anticipate completion of a major facility expansion of our Longmont, CO, CMC Center of Excellence. We have invested in three new 50-gallon API reactors, four new drug product manufacturing suites (offering capsule, tablet, and formulated capsule manufacturing options), and material characterization as well as formulation, analytical, and stability capabilities.

Our 92,000-sq ft Durham facility recently expanded capabilities in extractables/leachables, impurity ID, fate and purge, drug product analytical testing, stability storage, and API manufacturing.

We expect the next few years to bring unprecedented growth in our industry and Avista Pharma to continue to be a key partner in the growth of our clients' clinical and commercial product portfolios. ◆

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Technology & Services Showcase

CMC Services

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Contract Testing Laboratory

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Leading CDMO

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Avista Pharma Solutions is a premier contract testing, development, and manufacturing organization that provides a broad range of leading services from discovery, early stage API and Drug Product development and cGMP manufacturing to stand-alone analytical and microbiology testing support. We are your experienced, capable, dependable partner, serving pharmaceutical, animal health, and medical device clients from over 200,000 square feet of laboratory and manufacturing space across three locations (Agawam, MA; Durham, NC; and Longmont, CO). We support your development program from Nomination to IND/Phase I to Proof-of-Concept/Phase II/Phase III. We have the FLEXIBILITY and CAPACITY to meet your project's FAST TIMELINES. For more information, contact Avista Pharma Solutions at (866) 459-4600 or visit **www.avistapharma.com.**

Technology & Services Showcase

Contract Laboratory Services

BioScreen Testing Services, Inc. (est. 1985, FDA registered, ISO 9001:2008 certified), headquartered in Los Angeles, CA, offers a wide range of testing services in Analytical Chemistry, Microbiology, and Human Clinical Trials . Additionally, the company offers an array of in vitro toxicological tests and consulting services. BioScreen's two Clinical sites (located in Phoenix, AZ, and Los Angeles) have one of the largest and most ethnically diverse subject databases in the industry (including Asian subjects). BioScreen's full-service chemistry lab is also the industry leader in heavy metal testing, boasting multiple ICP-OES, and ICP-MS instruments. Our customer service staff is friendly, helpful, and ready to assist you, and we provide routine quotes within 24 hours. For more information, visit BioScreen Testing at **www.bioscreen.com.**

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Technology & Services Showcase

Differentiated Injectable Delivery

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The Grünenthal Group is an independent, international, research-based pharmaceutical company headquartered in Germany. Grünenthal has affiliates in 25 countries worldwide, and its products are sold in more than 155 countries. Grünenthal developed the INTAC® platform for solid oral dosage forms. The technology combines PEO-based formulations and a proprietary hot-melt extrusion process. Products based on INTAC show particular properties in regard to physical breaking strength. The technology is utilized in FDA-approved products to impede physical manipulation for misuse and abuse purposes. Grünenthal is currently developing immediate-release single-entity and fixed-dose combination opioids, modified-release prescription stimulants, and pseudoephedrine products. INTAC is a leading technology for abuse-deterrent products in the prescription and OTC space. For more information on how you can prevent abuse of your product, visit The Grünenthal Group at **www.intac.grunenthal.com**.

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Technology & Services Showcase

Advanced Medical Technology

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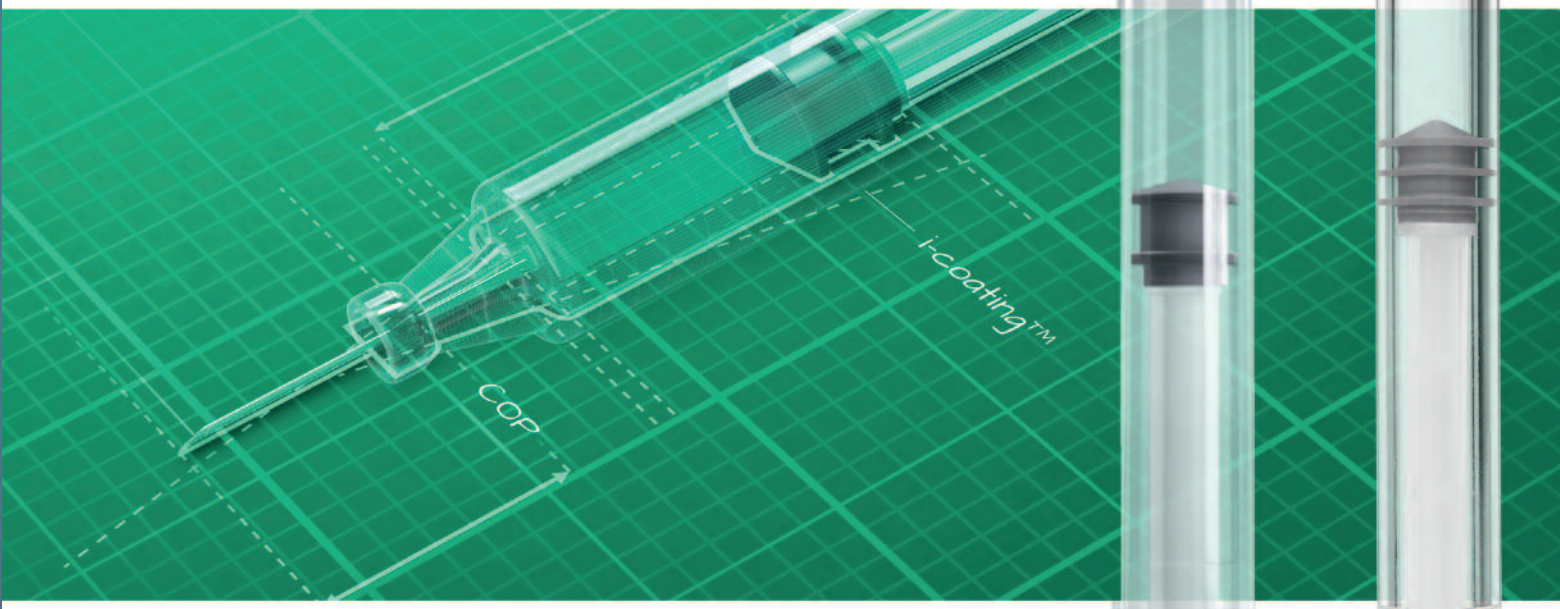

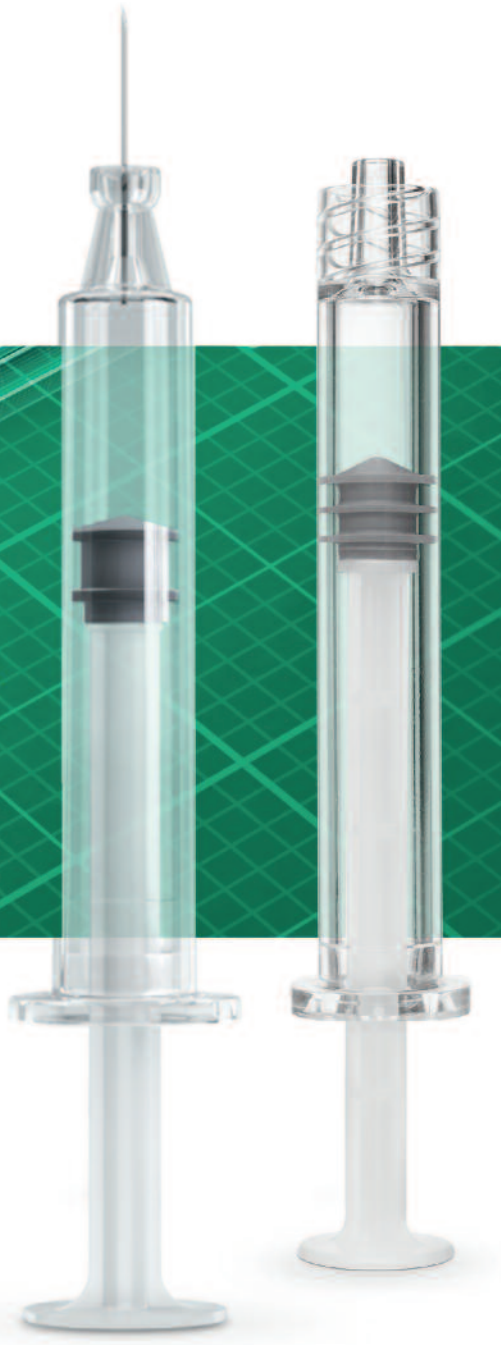

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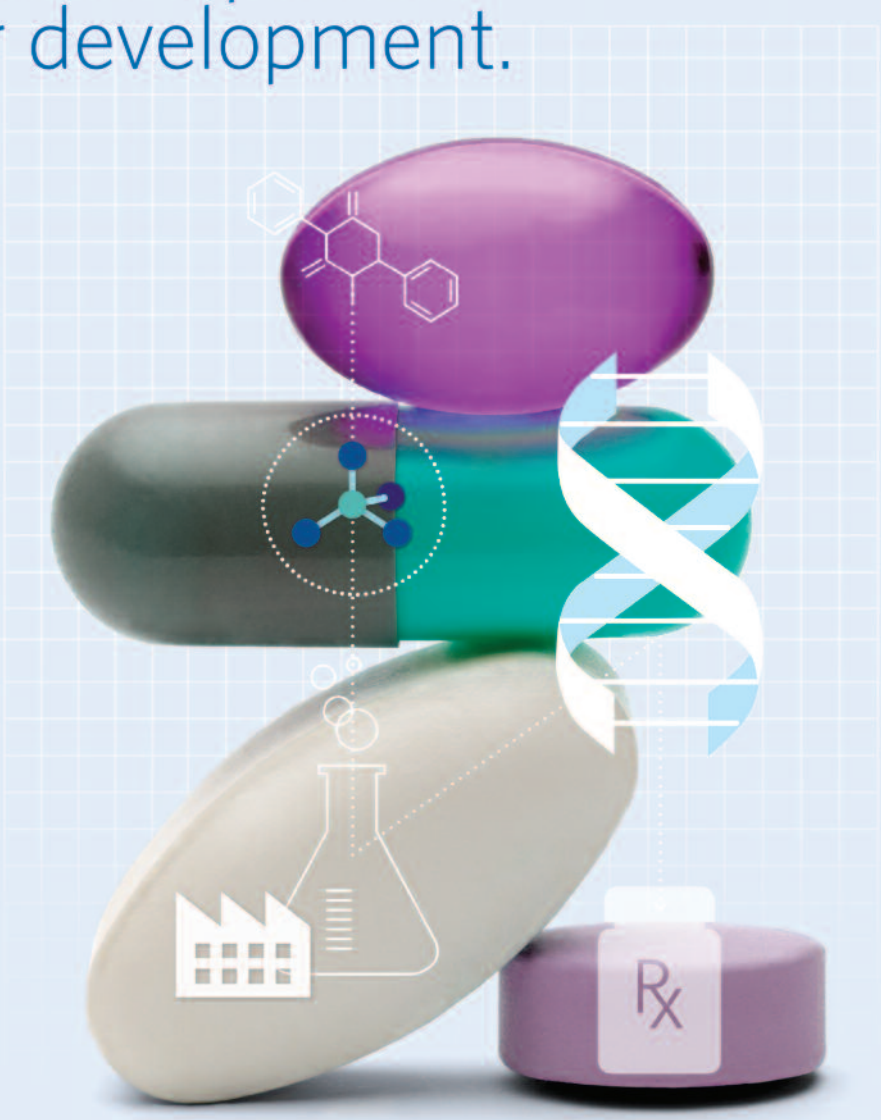

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