Targeted Therapeutics and Nanoparticles

A key objective of pharmaceutical and biopharmaceutical development is to increase product therapeutic specificity and safety. Some of the recent exciting developments have obviously been related to the development in new chemical entities for the treatment of underserved disease populations. However, increasingly, successful developments in this field involve new formulation technologies that use engineered physicochemical attributes to enable and improve the efficacy and safety of new and existing products. These formulation technologies can positively affect product specificity, bioavailability, biodistribution, pharmacokinetics and safety. Formulation technologies can not only impact the delivery of a single therapeutic molecule but combine pharmaceuticals and biopharmaceuticals to provide uniquely new and useful product attributes and clinical applications. Two major advances in recent years have been the development of monoclonal antibody-drug conjugates (ADC) and the many forms and applications of nanoparticles.

Table 1

NANOPARTICLE TYPES AND MAJOR ATTRIBUTES

Particle Types:	Solid-Lipid	Polymeric (PLGA)	Liposomes	LyoCell®
Efficiency / Location of Formulated Drug:				
Hydrophobic Molecules	++++ / interior of particle	+++ / interior of particle	+ / in lipid bilayer	+++ / in lipid phase
Hydrophilic Molecules	+ / on particle surface, & possibly entraped in solid-lipids using proprietary technology	+ / on particle surface & possibly entraped in polymer using some processes	++ / in aqueous core of liposomes	++ / in aqueous phase of LyoCells
Amphiphilic Molecules	++ / on particle surface	+ / on particle surfaces	+ / in lipid bilayer	++ / in lipid and aqueous phases
Stability of Aqueous Suspensions	++++	–	++	+++

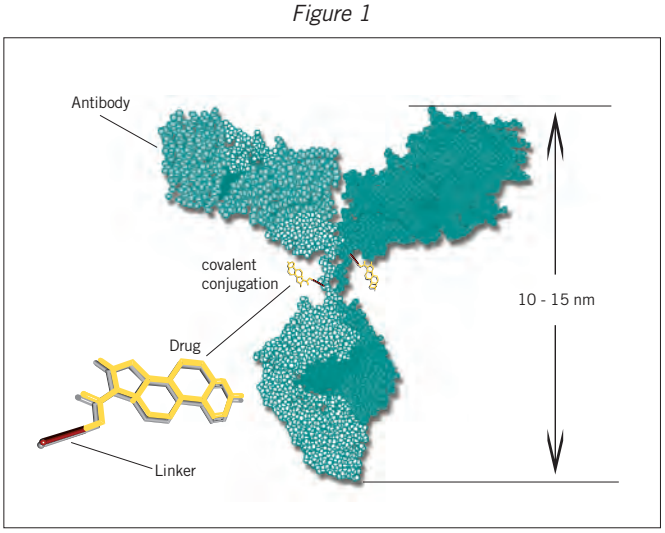
Antibody-Drug Conjugates

The combining of pharmaceuticals and biopharmaceuticals in the form of ADC has been a goal of research since the advent of monoclonal antibody technologies forty years ago. This approach holds the promise of combining the beneficial attributes of drugs and the exquisite specificity of monoclonal antibodies. In oncology focused ADC for instance, cytotoxic drugs that could treat the desired disease are covalently bound to disease relevant antibodies via a chemical linker (Figure 1). Eight different human monoclonal antibodies have been approved for cancer therapy, several of which bind to cell surface tumor antigens[1]. From this portfolio of antibody specificities, two ADC products have recently been approved as commercial clinical therapies[1].

ADC products must use antibodies with specificities that can bind to cell surface antigens and be subsequently internalized via endocytic vessels. The therapeutic success of ADC products depends upon the ADC construct being internalized by the tumor cells, and the linker associating the antibody to the drug being hydrolyzed by the acidic environment of the endosomes (approximately pH 5.0). Then the cytotoxic drug must maintain its ability to cross endocytic membranes, possibly with linker remnants still attached, into the cytoplasm where it can function as a therapeutic. So development of ADC technology has depended heavily on these typically proprietary linkers. However, the utility of different combinations of antibodies, linkers and drugs has been difficult to predict, which has complicated the development of new ADC products.

While the ADC pipeline is robust, there are technical limitations to what can be accomplished. Inability to significantly increase the ratio of the number of copies of cytotoxic drugs attached to targeting antibody creates dose boundaries for ADC development and limits its applicability. ADC products need a high copy number of targeted tumor antigens expressed on tumor cells to enable the needed cytotoxic dose of drug being internalized by cells, and the cytotoxic drugs used for these conjugates need to be of very high potency to minimize this necessary dose. These limitations result in only a small portion of the portfolio of therapeutic drugs being applicable to ADC.

Figure 1



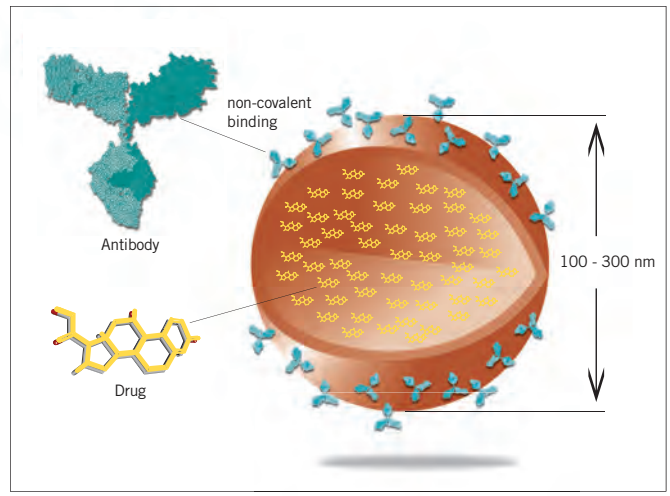
Nanoparticle Formulations

There are wide variety of nanoparticle technologies used in drug delivery and they have had a major impact on formulating pharmaceuticals. These nanoparticle technologies offer a number of attractive attributes for drug delivery including: improved bioavailability, delivery of high doses, protection of the drug from harsh environments, extending pharmacokinetics, targeted biodistribution of drug, sustained release of the therapeutics, and co-delivery/ combinations of pharmaceuticals

and biopharmaceuticals. The underlying technologies behind the majority of nanoparticles include: liposomes, reverse cubic phase particles, and solid lipid particles. Ten different nanoparticle based drug products have been approved in oncology alone and many more are in pre-clinical and clinical development[2].

Nanoparticle physicochemical attributes can be tailored including their size, hydrophobicity, charge, degradation rate, and payload[2,3]. This flexibility allows developers to optimally formulate and deliver drugs depending upon the drugs' attributes and clinical performance needs (Table 1). Nanoparticles composed of solid-lipids can be especially suitable for the formulation of hydrophobic small molecules, the loading of which can be maximized by blending various components to optimize solubility of the API in the particle[2,3]. These solid-lipid particles are routinely quite stable in aqueous suspensions, making them commercially attractive[2,3]. Polymeric nanoparticles (i.e. PLGA) have been used to formulate hydrophobic small molecule pharmaceuticals[4] but can be adapted to also entrap hydrophilic pharmaceuticals that can be released upon degradation of the polymer. Since most degradable polymer based nanoparticles hydrolyze gradually in aqueous suspension, these products need to be dry for storage and resuspended prior to administration. Liposomes are well adapted for the formulation of hydrophilic pharmaceuticals since the liposomal membranes encapsulate aqueous cores. Liposome formulations' most significant challenges typically are related to their limited payload and relatively unstable physical and chemical nature when in aqueous suspensions although these formulations have been successfully developed as commercial products. LyoCells® are also lipidic nanoparticles but are in a very thermodynamically stable reverse cubic phase that, unlike liposomes, have continuous lipid and aqueous phases. It is a formulation technology that is especially adapt to both lipophilic drugs and amphipathic molecules, like many biopharmaceutical proteins, since lipid and aqueous phases are never more than several nanometers apart.

Figure 2



When formulating chemotherapeutics for solid tumors, nanoparticles have been especially effective as a result of the enhanced permeability and retention (EFR) effect[3]. This EPR effect results in nanoparticles formulations efficiently distributing themselves within solid tumor tissues. Nanoparticles, once within targeted tumors, can be either internalized by the tumor cells where the formulated drug can kill the cells, or remain extracellular and provide sustained release of the drug within the tumor tissues which again affects the therapy.

Nanoparticle surface characteristics are critical determinants of behavior, impacting drug loading, drug release profile, circulating half-life, biodistribution, disease targeting and elimination[2,3]. The most common nanoparticle surface modifications are charge control, and the attachment of chemical moieties and targeting ligands. Charge can been customized on particles to enable their binding to other molecules including pharmaceuticals and biopharmaceuticals. The level of charge, zeta potential, can also affect how particles interact non-specifically with biological systems and impact circulating half-life. Targeting of nanoparticles can be achieved through attaching ligand specific moieties to the particle's surface. For example, polysaccharides, including hyaluronic acid, have been covalently attached to nanoparticles, targeting them to cells expressing receptors for these polysaccharide ligands. Protein based targeting molecules have also been attached, typically by covalent linkers[2].

Targeted Nanoparticles

A number of different targeting molecules are being developed in combination with nanoparticle formulations, the most common of which is antibodies. Traditionally the binding of antibodies to particles is achieved covalently through various linker chemistries. Other options that have also been developed are solid-lipid nanoparticles formulated with surfactants that mediate non-covalent binding of antibodies and other biological molecules; a technology known as Surface Arrayed Therapeutics[4](SATx™; Figure 2). The SATx™ particles efficiently bind to biopharmaceutical molecules like vaccine components[4], and monoclonal antibodies. SATx™ can effectively link biopharmaceutical and pharmaceutical molecules, like that of ADC, but without the need for and limitations of conjugation chemistries.

Engineered nanoparticles, much like ADC, can "link" pharmaceutical drugs to targeting monoclonal antibodies generating highly specific therapeutics that also offers significant advantages that address the limitations and challenges faced by ADC products. Antibody targeted nanoparticles can dramatically improve the drug loading and delivery over ADC constructs. The delivery of these particles, with their high drug payloads, is no longer absolutely dependent on the target antigen copy number; as long as sufficient antibodies on the particles bind to the target antigen linking the particles to the cells, the drug contents of a particle will be delivered. This dramatic improvement in drug loading promises that drugs can be delivered to target cells with low copy number antigens. Furthermore, nanoparticle formulations, as compared to ADC formulations, can benefit from the EPR effect and do not depend on intracellular hydrolysis of a chemical linker, but rather provide therapeutic effect when either localized within tumor tissues or internalized by tumor cells.

Formulation technologies are a critical contributor to current and future improvements in pharmaceutical and biopharmaceutical development. Because of their compelling advantages, nanoparticles will see rapidly increasing adoption and use in both pharmaceutical and biopharmaceutical products. Lastly, as the biosimilar field expands and begins to improve existing biopharmaceutical products, creating "biobetters," these formulation technologies are certain to play a leading role.

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4. Becker RS, Mitchnick MA. Drug Development & Delivery. 2014; 14 (7): 56-63.

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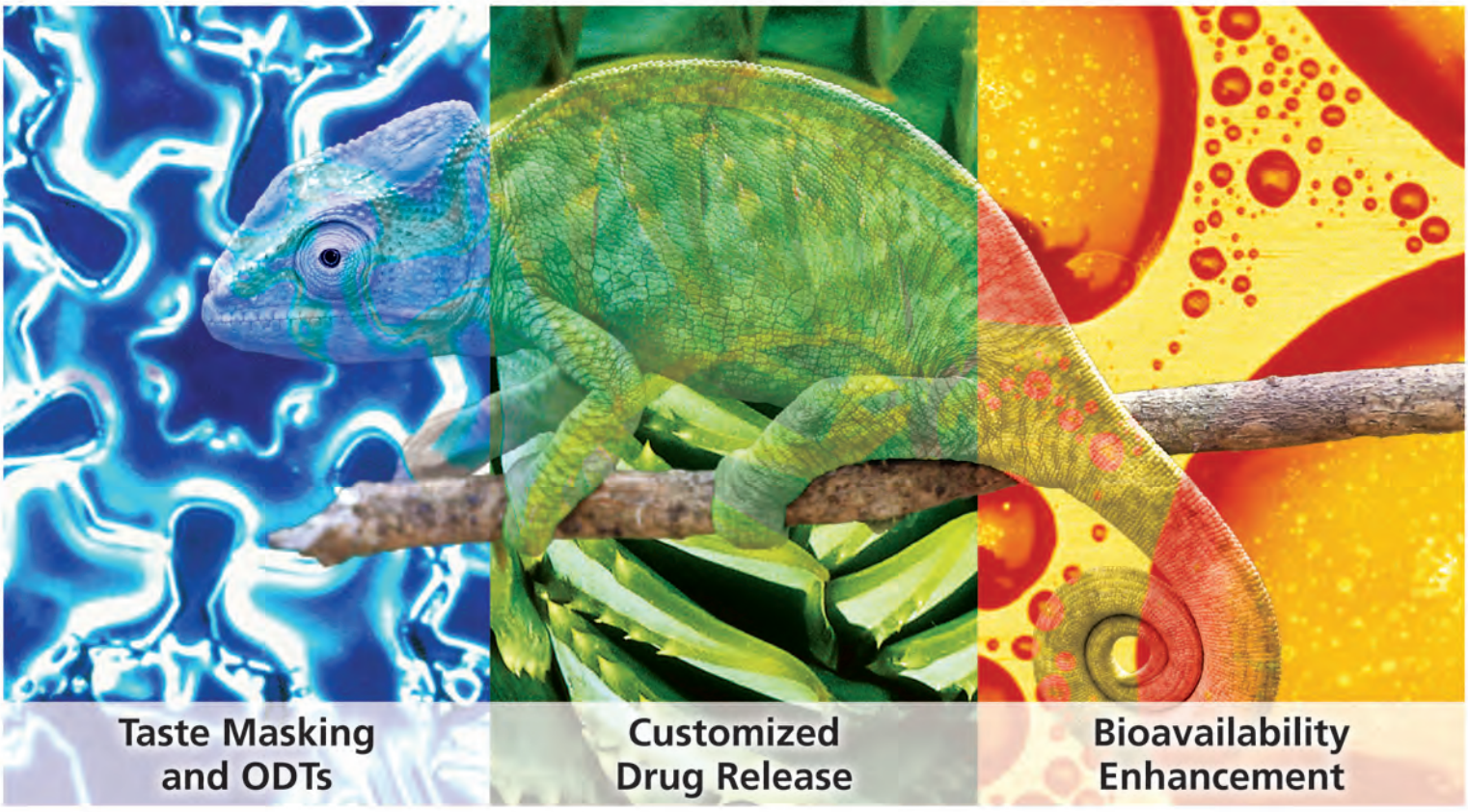

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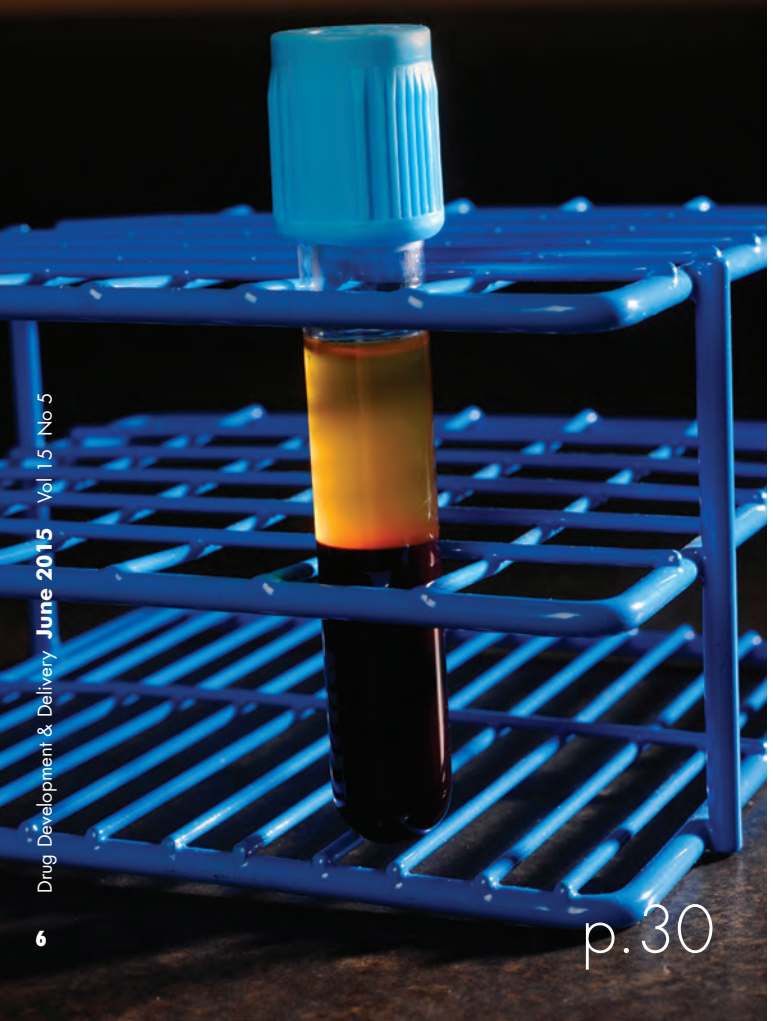

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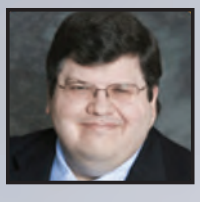

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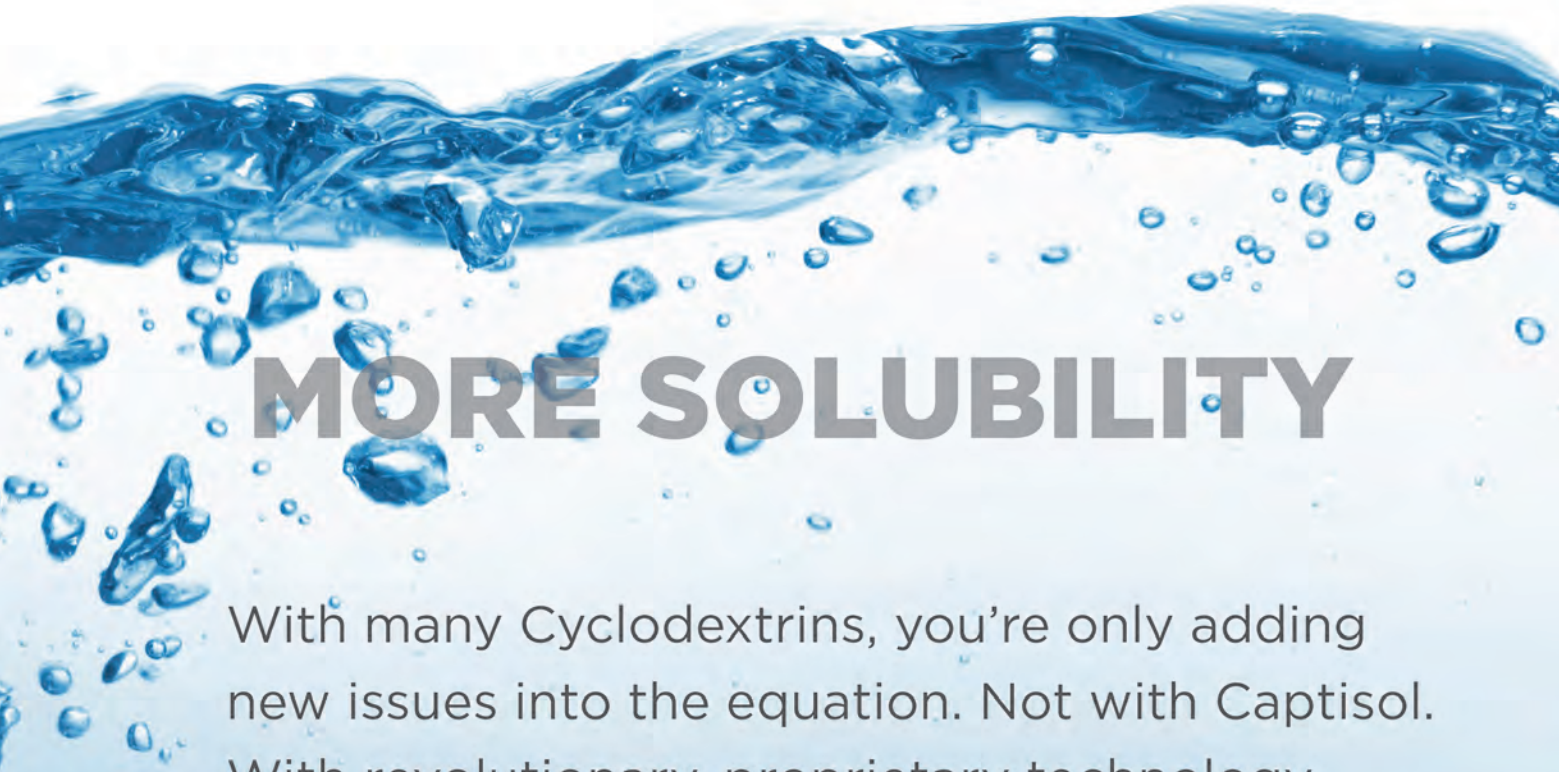

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First Patient Dosed in Phase II Study of Tipifarnib

Kura Oncology, Inc. recently announced that the first patient has been dosed in the Phase II clinical trial of tipifarnib in patients with locally advanced tumors that carry HRAS mutations. Tipifarnib is an inhibitor of farnesylation, a key cell-signaling process implicated in cancer initiation and development.

"There are no approved treatments that target HRAS mutations specifically," said Alan Ho, MD, PhD, a medical oncologist at Memorial Sloan Kettering Cancer Center and a lead investigator on the Phase II trial. "We look forward to investigating whether tipifarnib can inhibit HRAS-mediated activation of the MAPK pathway to produce therapeutic responses."

"Tipifarnib has previously demonstrated durable responses in subsets of patients with cancer," added Antonio Gualberto, MD, PhD, Chief Medical Officer of Kura Oncology. "The selection of patients with tumors characterized by HRAS mutations represents a promising strategy to identify those patients most likely to benefit from tipifarnib."

The HRAS protein is involved in regulating cell division in response to growth factor stimulation and other signals that instruct cells to grow or divide. HRAS is an early player in many signal transduction pathways and acts as a molecular on/off switch – once HRAS is turned on, it recruits and activates proteins necessary for the propagation of the signal. In certain tumors, mutations in the HRAS gene cause the HRAS protein to be permanently on, resulting in persistent activation of downstream growth and proliferation signals that drive tumor cell growth.

Farnesyl transferase inhibitors, such as tipifarnib prevent protein farnesylation, a key cell-signaling process implicated in cancer initiation and development. In preclinical studies, tipifarnib has been shown to block HRAS farnesylation and membrane localization, thereby inhibiting the growth and proliferation of HRAS mutant tumors. Collectively, cancers that have an HRAS mutation are estimated to have an annual incidence of approximately 8,000 patients in the US and, in general, patients with these cancers have poor prognosis and limited options for treatment.

The primary objective of the Phase II study will be to investigate the antitumor activity, in terms of objective response rate, of tipifarnib in patients with locally advanced, unresectable or metastatic, relapsed and/or refractory tumors that carry HRAS mutations. Secondary objectives include evaluation of progression-free survival, duration of response and safety. A total of 36 patients are planned to be enrolled into two non-randomized cohorts: malignant thyroid tumors with HRAS mutations; and non-hematological malignancies with HRAS mutations. Additional information about this clinical trial of tipifarnib is available at clinicaltrials.gov using identifier: NCT02383927.

Pluristem Announces Significant Advancement to its Clinical Development Plan

Pluristem Therapeutics Inc. (PSTI) recently announced a significant advancement to its clinical development plan: the PLX cell program in critical limb ischemia has been selected for the European Medicines Agency's Adaptive Pathways pilot project. The goal of the project is to improve timely access for patients to new medicines. It allows for early marketing authorization of a therapy in a restricted patient population, followed by additional assessments and the possibility of later approval for use in broader patient populations.

Critical limb ischemia (CLI), a severe blockage in the arteries of the legs, which markedly reduces blood-flow, is associated with a significantly increased risk of leg amputation and death. It currently affects approximately 1 million people in the US, and the prevalence is expected to increase significantly in the coming decades. CLI therefore represents a major commercial opportunity. Acceptance of Pluristem's cells for the treatment of CLI into the Adaptive Pathways could significantly curtail the time and investment needed to bring this product to market.

"Acceptance into Europe's Adaptive Pathways pilot project is a tremendous milestone for Pluristem. It allows us to potentially commercialize our product earlier than expected," said Pluristem CEO Zami Aberman. "We are extremely pleased with this outcome, which was one of the key elements we defined in our long-term strategy to lead the cell therapy industry. Reducing time to market is a critical element of our strategy. The Adaptive Pathways has the potential to assist us in accomplishing this goal. Last week we announced a milestone in Japan, which is also an important territory for us. We are pursuing our strategy for expedited approval of PLX cells in Japan. We have applied to Japan's Accelerated Pathway for Regenerative Medicine for our PLX cells in critical limb ischemia, and Japan's Pharmaceuticals and Medical Devices Agency just validated the proposed quality and large-scale manufacturing methods for PLX-PAD cells for use in clinical trials."

Pluristem has already amassed experience in working with the European Medicines Agency and conducting trials in the EU. The company completed both a Phase I trial in CLI and a Phase II trial in muscle injury in Europe. Pluristem is currently conducting a multinational Phase II trial in intermittent claudication, the less advanced stage of peripheral artery disease that can precede CLI, and several of the trial sites are located in Europe. Pluristem has also effectively protected its IP in Europe.

Eleven Biotherapeutics Announces Top-Line Results From Pivotal Phase III Study

Eleven Biotherapeutics, Inc. recently announced top-line results from the OASIS study, the company's first pivotal Phase III study of its lead drug candidate, EBI-005, in moderate-to-severe dry eye disease. The co-primary endpoints of the Phase III study were the total corneal fluorescein staining score and the patient-reported measurement related to ocular pain and discomfort based on the ocular surface disease index (OSDI), comparing the mean change from baseline at week 12 for treatment with EBI-005 to treatment with vehicle control. In this study, EBI-005 did not meet either of these two co-primary endpoints.

There was no statistically significant difference between the EBI-005 treated group and the vehicle control group on the co-primary endpoints or any secondary endpoints. Patients with dry eye disease in both the EBI-005 and vehicle treatment groups showed statistically significant improvement from baseline on the co-primary endpoints. While the change from baseline on the co-primary endpoints was greater in the vehicle group than the EBI-005 group, the differences between the two groups were not statistically significant and the company believes the differences were not clinically meaningful. EBI-005 was generally well tolerated in the Phase III study with fewer than 5% of patients reporting eye irritation and no treatment-related serious adverse events. Approximately 13% of patients in the study reported some use of artificial tears, with no difference in artificial tear use between the EBI-005-treated and vehicle-control groups. Overall, 92% of patients completed the study, with 33 patients having dropped out of the EBI-005 group, and 20 patients having dropped out of the vehicle control group.

"We are disappointed that our Phase III study in dry eye disease did not meet its primary efficacy endpoints, but we are encouraged that we continue to see a favorable tolerability profile for EBI-005. Our key focus will be on continuing to develop EBI-005 to meet unmet medical needs in allergic conjunctivitis, based on our previously reported Phase II data and scientific rationale supporting EBI-005 as a treatment for allergic conjunctivitis," said Abbie Celniker, PhD, President and Chief Executive Officer of Eleven Biotherapeutics. "Based on these top-line results, the company does not see an immediate path forward for EBI-005 in dry eye disease, and we will not be initiating the second Phase III study of EBI-005 in dry eye disease that we had planned to start in the second half of this year. However, we need to further assess the results from the OASIS study to fully inform our evaluation of future plans in dry eye disease, including the ongoing Phase III safety study."

Novozymes Biopharma Enables Stable Formulation of Serendex Pharmaceutical's Drug

Denmark-based Serendex Pharmaceuticals recently announced they will initiate Phase I clinical trials for their Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) drug candidate, Molgradex. The drug uses Novozymes Biopharma's recombinant human albumin, Recombumin, as a stabilizer to enable the development of a stable drug formulation for novel pulmonary delivery. More specifically, Recombumin prevents unwanted derivatization of the labile therapeutic protein by scavenging against the generation of reactive species, thereby helping to reduce the risk of unwanted immunological responses.

Molgradex is a recombinant version of the human GM-CSF and is intended for the treatment of rare pulmonary diseases, such as Pulmonary Alveolar Proteinosis (PAP), Acute Respiratory Distress Syndrome (ARDS), Bronchiectasis (BE), and Cystic Fibrosis (CF). Molgradex is being developed as the first inhalable treatment option for these diseases with expected market authorization for PAP in 2018.

Leading up to the clinical trials, Novozymes Biopharma and Serendex Pharmaceuticals have been working closely to implement the use of albumin in the final drug formulation.

"Novozymes Biopharma has been instrumental in smoothly moving our drug candidate through development and regulatory filings. Their regulatory and technical product support has been of great value to us in preparation for our clinical trials," said Kim Arvid Nielsen, CEO of Serendex. "It has also been important for us to have a partner capable of providing an undisputed product safety profile as well as supply security."

Recombumin is already being used in marketed drugs, and several pharmaceutical companies are currently evaluating Recombumin in late-stage clinical trials both under US and EU regulations.

"We are excited about our collaboration with Serendex Pharmaceuticals," added Peter Rosholm, Vice President of Novozymes Biopharma. "I consider it additional proof that our unique recombinant albumin products offer superior stabilizing benefits when other stabilization options fail. This provides further evidence that our well-documented products and technical support deliver value to our customers and help moving better therapies to market faster."

Serendex develops drugs to treat severe respiratory conditions, such as PAP, ARDS, BE, CF, and DAH. These conditions are acute or chronic and have no existing medical treatment. All Serendex drugs are inhaled or induced to the lungs of the patient. This improves the risk/efficacy ratio of drug and treatment. Serendex has obtained orphan drug designation (ODD) for several indications in both Europe and USA.

Selecta Biosciences Makes Two Major Announcements

Selecta Biosciences, Inc. recently announced that, under the terms of an existing strategic global collaboration, Sanofi has exercised its option to an exclusive license to develop an immunotherapy for the treatment of celiac disease.

In celiac disease patients, the consumption of gluten-containing food induces harmful immune responses that can lead to abdominal pain and, in most severe cases, intestinal cancer. This new immune tolerance program expands activities within the Sanofi-Selecta collaboration, which is already successfully advancing a novel immunotherapy for a life-threatening food allergy. The products resulting from this collaboration will leverage Selecta's proprietary Synthetic Vaccine Particle (SVP) platform, which has unique capabilities to engineer nanoparticles with the structure and composition to produce immune tolerance by attenuating the overactive response to specific antigens.

Under the terms of the collaboration, Selecta is eligible to receive research support and several preclinical, clinical, regulatory, and sales milestones totaling up to $300 million for this new program in celiac disease. Additionally, Selecta is also entitled to up to double-digit tiered royalties as percentage of product net sales for any commercialized immunotherapy resulting from these efforts with Sanofi.

In November 2012, Selecta announced that they had formed a strategic global collaboration to discover highly targeted, antigen-specific immunotherapies for life-threatening allergies. Under the agreement, Sanofi obtained a first exclusive license to develop an immunotherapy designed to abate acute immune responses against a life-threatening food allergen and an option to develop two additional candidate immunotherapies for allergies and celiac disease. With the exercise of this option by Sanofi, Selecta and Sanofi now have two initiatives actively advancing immune tolerance treatments under the terms of the 2012 agreement. In October 2014, Selecta and JDRF announced another collaboration with Sanofi to research novel antigen-specific immune therapies for Type 1 Diabetes.

Selecta Biosciences and Genethon also announced an ongoing research collaboration with the goal of enabling repeat dosing for gene therapies. Based on preliminary results, the companies have identified three applications that might benefit from combining Genethon's expertise in the development of gene therapy vectors and Selecta's Synthetic Vaccine Particle (SVP) platform to prevent undesired immune responses. The companies plan to co-develop and co-own these next-generation gene therapies, each with the potential to meet significant unmet patient needs.

Under the terms of the proposed collaboration, Selecta and Genethon will apply Selecta's SVP platform in an effort to eliminate the neutralizing antibodies and other undesired immune responses to the viral vector used in gene therapy. The combination of Genethon's novel gene therapies with Selecta's proprietary SVP would, for the first time, allow repeated systemic dosing of gene therapy vectors. Selecta's SVP platform has unique capabilities to engineer nanoparticles with the structure and composition to produce targeted immune tolerance by attenuating the undesired immune response specifically to viral vectors. Using SVP offers the potential to expand the therapeutic range for gene therapies by maintaining the efficacy of the gene therapy over several doses. This is of particular interest in children, where organs that produce the gene therapy products are growing, and in applications where high amounts of proteins need to be supplied by the gene therapy. Genethon and Selecta will initially focus their collaborative research and co-development efforts on gene therapies in development for muscular dystrophies and pediatric liver metabolic diseases that employ adeno-associated virus (AAV) vectors, which are a gene transfer platform of choice for many in vivo therapy applications.

DURECT Corporation Announces Positive Study Results

DURECT Corporation recently announced it has obtained positive results from a multi-dose Phase I clinical trial with an oral formulation of DUR-928, the lead molecule in DURECT's Epigenomic Regulator Program. DUR-928 is an endogenous, small-molecule, new chemical entity (NCE), which may have broad applicability in metabolic diseases, such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). It may also play an important role in protecting against acute kidney injury (AKI) and other types of acute organ injury.

This Phase I trial was a single-site, randomized, double-blinded, placebo-controlled, multiple-ascending-dose study to evaluate the safety, tolerability, and pharmacokinetics of DUR-928 when orally administered once daily for 5 consecutive days to healthy volunteers. The 20-subject study evaluated DUR-928 in 2 consecutive 10-subject cohorts, the first receiving DUR-928 at a lower dose and the second at a higher dose.

Following multiple dosing, DUR-928 was well-tolerated at both dose levels, with no clinically significant changes in vital signs, laboratory values or ECG parameters, no severe or serious drug-related adverse events reported and no subjects withdrawing from the study. Peak plasma concentrations achieved were at least 100-fold higher than endogenous levels, no accumulation in plasma concentrations were observed with repeat dosing, and dose-related increases in plasma concentrations were observed with peak plasma concentration at approximately 2 to 6 hours after dosing.

DUR-928 is an endogenous, orally bioavailable small molecule that modulates the activity of several nuclear receptors that play an important regulatory role in lipid homeostasis, inflammation, and cell survival. A systems biology study involving over 23,000 genes showed that DUR-928 modulates the activity of more than 240 genes, including ACC, FAS, HMGR, Cyp7A1, LXR, PPAR, NFB/IB, TNF, IL-1, IL-6, COX-2, PCSK9, and others.

The biological activity of DUR-928 has been demonstrated in 6 different animal disease models, 3 representing acute toxic or ischemic organ injury (kidney and liver), and 3 representing chronic disorders of hepatic lipid accumulation and dysfunction (NAFLD/NASH). Animal pharmacokinetics and toxicity studies have shown DUR-928 to be orally bioavailable and safe at all doses tested to date. An injectable formulation, envisioned for use in acute conditions, is currently undergoing animal testing.

DURECT's Epigenomic Regulator Program is a collaborative effort now in its fourth year between DURECT and the Department of Internal Medicine at Virginia Commonwealth University (VCU), the VCU Medical Center, and the McGuire VA Medical Center. During the course of this program, a number of compounds that may have therapeutic utility have been identified, including the lead molecule DUR-928.

Lilly & Sanford-Burnham Announce Major Collaboration

Eli Lilly and Company and Sanford-Burnham Medical Research Institute recently announced they will collaborate to discover and develop immunological therapies. Lilly and Sanford-Burnham, a non-profit medical research institute, will investigate potential therapeutics using biotechnology approaches in targeting multiple immune checkpoint modulators for the treatment of immunological diseases, such as lupus, Sjögren's Syndrome, inflammatory bowel disease, and other autoimmune disorders.

The comprehensive research collaboration is driven by Lilly's world-class biotechnology capabilities and expertise in immunology, and Sanford-Burnham's deep expertise in understanding the fundamental cellular pathways regulating the immune system focusing on the immune checkpoint networks. This high degree of interaction will allow the organizations to flexibly and efficiently advance projects to clinical investigation. The research collaboration will be co-chaired by Thomas F. Bumol, PhD, Senior Vice President, Biotechnology and Immunology Research at Lilly, and Carl Ware, PhD, Director, Infectious and Inflammatory Diseases Center at Sanford-Burnham.

"Immunology is an important research area of focus for Lilly, and through this exciting collaboration with Sanford-Burnham, our scientists can discover and develop new medicines together in a seamless way that takes advantage of each group in a family of key targets," said Dr. Bumol.

Lilly has established its presence in immunology in recent years through its own R&D and collaborations, with seven molecules currently in the pipeline for conditions such as psoriasis, rheumatoid arthritis, lupus, and inflammatory bowel disease. Sanford-Burnham's work in this area focuses on cell communication pathways that control the development of lymphocytes, innate and adaptive immune responses, and inflammation. Their work has led to the discovery of molecular targets for the development of treatments for immunological and inflammatory diseases, and cancer.

"The Lilly-Sanford-Burnham collaboration is precedent setting in scope and its potential to advance discoveries to the patient more efficiently," said Sanford-Burnham CEO, Perry Nisen, MD, PhD. "By combining the deep knowledge of human biology and disease mechanisms among Sanford-Burnham scientists, in particular, our expertise in the field of checkpoint regulators in the immune system, and Lilly's leadership position in the development of biologics and large molecules, we are forging the path to develop the next generation of transformative treatments for autoimmune disease."

Sanford-Burnham Medical Research Institute is dedicated to discovering the fundamental molecular causes of disease and devising the innovative therapies of tomorrow. Sanford-Burnham takes a collaborative approach to medical research with major programs in cancer, neurodegeneration, and stem cells, diabetes, and infectious, inflammatory, and childhood diseases.

Management Insight

Homeopathy & Other Irrational Things People Believe

By: Derek Hennecke, CEO & President, Xcelience

The ADE 651 was marketed by a UK company called ATSC as a bomb detector that worked on the principle of "electrostatic magnetic ion attraction." It sold for $40,000 per unit. The Iraqi government spent $85 million on 2,125 of these tracker devices.

The ADE 651, it turns out, is a glorified dowsing rod. An "electrostatic magnetic ion attraction" is just a string of pseudoscientific nonsense that sounds good, but isn't. The success ratio of the unit was the equivalent of a coin toss, yet it was used to make life or death decisions about a region's safety. People died.

Pseudoscience kills. And yet, so many people – even smart people like those in the military and government leaders – believe it. Why do smart people believe stupid things?

THE DANGERS OF HOMEOPATHY

Which leads me to homeopathy. To be clear, I'm not talking about herbalism, not today. Herbalism is a variation of homeopathy and has many red flags of its own, but at least it might contain something. Homeopathic remedies contain nothing. They are massive dilutions. Massive, in this context, is something of an understatement. As the Canadian Broadcast Corporation (CBC) colorfully pointed out, a tablet the size of the earth might contain a single molecule of the original substance (as quoted in the blog *Science-based Medicine*, "Homeopaths threaten public health selling sugar pills as vaccine alternatives," Dec 4, 2015). How can such a dilution possibly do anything at all?

Homeopaths claim that the water in their tablets and vials has come into contact with an active ingredient and somehow magically retained a memory of it (while apparently forgetting all the other ingredients it has come into contact over the water's 4-billion-year history).

Homeopathy is based on the idea that "like cures like." On the surface, this sounds like vaccines, but with two differences. One is the amount of dilution, which reduces the presence of the active ingredient to zero, and the other is that

many of the diluted homeopathic ingredients are unrelated to the cause of the disease. The belief is that any ingredient can be effective if it's diluted enough: cancer, crude oil, and skim milk are examples. The Berlin Wall is my favorite, touted to cure feelings of being forsaken, separation, but also asthma, narcolepsy, and painlessness. Painlessness?

Target sells a homeopathic asthma spray under its brand name Up & Up. There are 15 "ingredients" listed in Latin with associated benefits. *Aconitum Napellus* is said to aid with shortness of breath. If you happened to have your Latin dictionary with you in Target, you might learn that its common name is aconite (it has never been associated with any medical benefit), and the only thing we do know about it is that it's a toxic alkaloid and at high concentrations, a strong, fast-acting poison. Aconite comes from a Greek word meaning "without struggle." It was once used to kill wolves, which is why one of the plants with this ingredient bears the nickname Wolf's Bane. One other ingredient in the remedy is also a known poison. None of the 15 ingredients have any established efficacy. Target is effectively selling a water pump, and while the package does say it's not a rescue inhaler, it is being sold as an alternative medication in the pharmacy aisle. Medication is a word that has meaning to people. Like you could use this spray instead of another (real) medication to treat life-threatening asthma symptoms.

Nosodes are the homeopathic answer to vaccines. They contain less (read none) of the active ingredient, and are therefore marketed as more natural and safer, leading parents to believe that after taking nosodes, their children are immune, without burdening parents with proof of scientific efficacy. Pseudoscience kills. So why do so many people believe these things?

CONSENSUS SCIENCE & CHIROPRACTORS PRESCRIBING DRUGS

Of course, everyone has the right to challenge the current way of doing things, and homeopaths often claim the right to challenge consensus science. They certainly have the right to do so, but the media also has the obligation not to take them too seriously. There's a big difference between a Google education, and a medical degree with years of experience. It takes training and experience to evaluate medical reviews and put them in context. An article in a journal may or may not be taken seriously by the medical community; Google readers, if they understand it, lacks that perspective. Let's face it, true expertise takes hard work.

So it isn't about whether or not you can question the scientific consensus, it's about how you do so. If argument uses misinformation and cherry-picked studies, it should be called out. Similarly, the media has a duty not to put years of scientific expertise and acquired bodies of knowledge head to head against this type of pseudoscience as if they were two equally credible adversaries in a battle for opinions. Sure, anyone has the right to challenge the scientific consensus. And anyone can slap a hockey puck: you, me, Wayne Gretzky, and Jenny McCarthy.

Speaking of credibility, the ACA (American Chiropractor's Association) has created a College of Pharmacology and Toxicology. The ACA's goal is to let chiropractors become full-scope practitioners, offering a range of physician services, including diagnoses and prescribing drugs. If the prescription course is anything like the Family Practice course, it would be in the range of 100 hours. In fairness, it could be more like the 300-hour course that apparently teaches students to diagnose using blood tests, electrocardiograms, spirometry, salivary assay hormonal and neurotransmitter tests, among others and awards a post-doctorate degree for 2 to 3 months of work.

WHERE'S THE FDA IN ALL THIS?

Clinical trials rate the efficacy of homeopathic treatments precisely on par with a placebo. They are a placebo. These results are not a

coincidence. Homeopathy does, believe it or not, fall under the purview of the FDA. Honestly, it shouldn't. This gives homeopathic remedies a legitimacy they don't deserve, and puts the FDA in an awkward spot. It came about because of a homeopathic-friendly US Senator, Royal S. Copeland, who sponsored the 1938 Food, Drug and Cosmetic Act, which made it so that any product listed in the US Homeopathic Pharmacopoeia (USHP) would by definition be a drug to the FDA. There is a Compliance Policy Guide, which sets out labeling and manufacturing standards for homeopathic products, but that's about it. Any product that finds its way into the USHP is a legal drug. Only a "homeopathic proving" is required, a type of evaluation that proves neither safety, nor efficacy.

By setting out regulatory standards and licensing these products as drugs, the FDA lends credence to them in the mind of the consumer. The FDA is an authority, "Protecting and Promoting your Health," as its website says. FDA involvement in homeopathy leads consumers to believe that these products are being evaluated and tested, and allowing them to be placed side by side with the real drug on the pharmacy drug further entrenches the apples to apples comparison.

Because Congress considers them drugs, the FDA is in an awkward situation. The solution so far, other than a few labeling requirements, has been to add the disclaimer that the "FDA is not aware of scientific evidence to support homeopathy as effective" on packaging. But how does this get around the requirement that labels can't make claims that can't be proved? I ran out of time to figure this one out.

The last time a law was passed regarding homeopathy was 1938. It's time to rethink this. Between the wars, homeopathic remedies were quaint concoctions doled out by a few alternative practitioners. Now, depending on your source, the industry is worth between $3 and $6 billion a year, and a lot of consumers - perhaps most - still have no idea what homeopathy really is.

The FDA has announced a public hearing to collect comments and information on homeopathic remedies from stakeholders. This is a good place to start. Here are my thoughts.

We need new legislation that clarifies that homeopathic remedies are not drugs and have passed none of the rigorous tests of drug development. They should not be regulated by the FDA. They are not drugs. This must come from Congress.

Homeopathic remedies should not be allowed to be placed side by side with real drugs on pharmacy shelves. If they want to be compared with pharmaceutical products as equals, they should be required to meet the same safety and efficacy standards as other medications.

If they can't prove efficacy, they should not be sold as medications. It is unethical to sell a product that contains no active ingredient and shows no efficacy. If they are to be sold, they must be labeled appropriately. Current labels are obscure, using Latin to hide behind names like *Anas Barbariae Hepatis et Cordis Extractum* (duck liver and heart, sold as a flu medication) and dilutions like 10X and 30X, which have no meaning at all to consumers. Consumers have the right to know what the "ingredients" are, as well as that the dilution results in none of the ingredient being present in the bottle.

Much as the health labels on tobacco, it should be required that every homeopathic product contain the declaration that no homeopathic product has ever been proven effective for any medical condition.

WHY DO PEOPLE BELIEVE IRRATIONAL THINGS?

All this leads me to wonder about bigger issues. If mankind's intelligence rises three points every 10 years (*Skeptic Magazine*, "The future of intelligence," by Robert Ehlich, Vol. 10, No. 2.), then why do people still believe stupid things?

The answer may be that evolution has hard-wired us to believe in things, says Michael Shermer, founding Publisher of *Skeptic Magazine*, in his TED Talk, The Pattern Behind Self-Deception. Belief is our natural default position.

We are pattern learners. We associate. Your mother always served

ice cream out of a tall blue glass. You see a tall blue glass, and your heart leaps. Shermer uses the example of a pigeon with two buttons. When he presses a button, sometimes he gets a reward. There is no pattern. Still, whenever he gets a reward, he repeats what he did the last time to get the reward, even if it means two spins clockwise and one counterclockwise, followed by two pecks on a button. This is where superstitions come from.

Evolution has rewarded our pattern-seeking behavior and punished the opposite. Imagine that you are a cave dweller in Paleolithic times, Shermer asks us. Walking toward your sub-Saharan campsite, you hear a noise in the bushes. If you associate the rustling in the bushes with a lion, you will probably live. If you don't think bushes + rustling = lion, your genetic line dies out.

We don't question our pattern-seeking behavior. It's too engrained. In a split-second decision, you don't get time to think rationally. Evolution dealt with this by setting our default position to believe all patterns are real, says Shermer.

Interestingly, the less we control things, the more likely we are to look for patterns. Baseball players are notorious for their superstitions, from rubbing the bat a certain way to wearing a gold thong (Jason Giambi, New York Yankees). Rituals are richest in batting because the less control we have, the more we look for patterns. The best batter fails 7 times in 10, whereas outfielders catch the ball 90% to 95% of the time.

I feel the pull of this type of pattern behavior. I consider myself a rational guy, but I have a lucky hockey jersey to wear to games. My wife has a lucky perfume, which she still insists single-handedly ended the Great Recession. Now she wears it everyday, and Xcelience is doing very well.

Evolution has also taught us to infuse our patterns with intentional agents. Identifying predators kept us safe. Think of the cave dweller scenario again. The lion is the intentional agent. Invisible agents are everywhere today. From ghosts and aliens to government conspiracies, they are behind the scenes orchestrating. The Illuminati. The Truman Show. The X-files.

If you're looking for pattern-seeking behavior, look no further than your nearest psychotic neighbor. I'm not bad-mouthing your neighbor, most of us have a little dab of psychosis in us; it doesn't have to be full-blown schizophrenia. A UK study published in *New Scientist* on April 4, 2015, showed that 33.8% of respondents felt that someone was out to harm or discredit them. Some 44.3% thought they were not in control of some of their actions. Another 33.6% thought that some of their thoughts were not fully under their own control. You get the idea. Psychosis is pretty normal.

Dopamine is strongly associated with pattern-seeking behavior, and hence with psychosis. L-dopa, the drug form of dopamine, is given to Parkinson's patients and has been shown to increase the tendency to see patterns (more specifically, delusions and paranoia). Similarly, psychosis is treated by blocking receptors for dopamine. Amphetamines and cocaine increase the tendency to see patterns associated with both creativity and hallucinations, says Shermer. Consider the fine balance that this takes. John Nash goes crazy and Richard Feynman gets a Nobel Physics Prize, as Shermer points out.

All this would make you believe that we need to tame our pattern-seeking minds in a modern world and go for purely rational thought, but that's not entirely true. There is power in moderation. If you see patterns in everything, you're delusional, but if you are too skeptical, you'll miss the good ideas too. It's best to seek a healthy balance that will keep you safe from lions but also open to creative possibilities. ◆

Derek G. Hennecke
President & CEO
Xcelience

FORMULATION DEVELOPMENT

Overcoming Early Phase Development Challenges & Optimizing Formulations With a Minimal Amount of API

By: Irena McGuffy, MS, PharmD

ABSTRACT

Softgel is a proven and effective delivery technology for poorly soluble drugs and can incorporate a wide range of fill formulations to optimize the bioavailability of active pharmaceutical ingredients (APIs). The following will explain how suitable modeling methodologies can predict the solubility of drugs in a range of solvents and mixtures, and how this approach is particularly applicable to the early stage development of softgel formulations when only a small amount of API may be available.

INTRODUCTION

In the early phase of drug development, it is common to have a limited amount of API available for reasons such as the complexity of its synthetic route or high manufacturing cost. Finding the appropriate formulation for a drug is often challenging, labor-intensive, and requires a significant amount of API in order for it to be tested in a range of solvent vehicles. As a result, many programs are suspended or slowed down before progressing into animal pharmacokinetics (PK), toxicity, or first-in-human (FIH) studies. In addition to impeding rapid progression of drug development, low initial quantities of API may result in handling difficulties due to the need to process small batch sizes on industrial-scale machines, thus affecting yields, with typical losses being in the range of 300 to 500 grams per batch.

For poorly soluble compounds, development of formulations is usually achieved using lipid-based drug delivery systems (LBDDS incorporated into softgel technology) to improve their bioavailability. In most cases, optimization of the bioavailability can be achieved by utilizing suitable delivery vehicles that maximize the solubility of the API. The process of selecting this method generally involves screening a set of platforms and technologies exhibiting a diverse range of hydrophilicity, lipophilicity, and solubilizing properties. It may also involve the evaluation of solubility in both the neat vehicle and in a mixture.

Softgel technology not only enables improved delivery of poorly soluble BCS Class II and IV drugs, but in cases where solubility is not the only biopharmaceutical hurdle to overcome, membrane modulation permeability can also be manipulated, thereby enabling the delivery of macromolecular BCS Class III drugs.

In addition to its advantages in enabling the formulation of technically challenging drugs, softgel technology is also well positioned for optimal formulation of drugs for which limited amounts of API are available.

TABLE 1

	MW g/mol	XlogP	T_m (°C)	ΔH_f (J/g)
Indomethacin	357.79	4.3	159.6	104.8
Posaconazole	700.78	4.6	133.4, 167.3	6.36, 72.1
Levothyroxin	798.85	2.4	N/A	N/A

Model Compound Characteristics

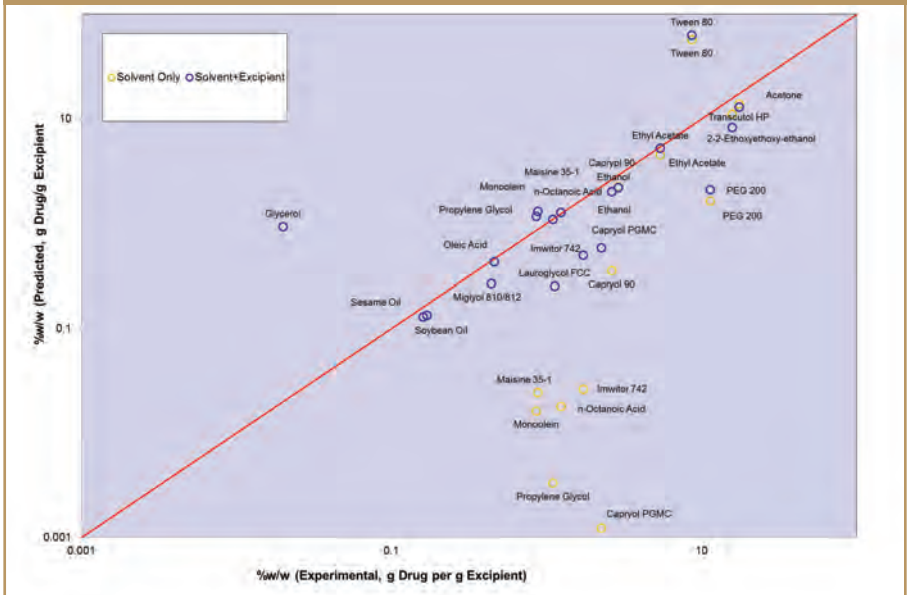
LBDDS: VERSATILE TECHNOLOGY

The basic principles of LBDDS technology, which has proven to be one of the most successful advanced drug delivery methods applied to BCS Class II drugs, ensure that drug substances are delivered in a solution form that is maintained within biological fluids before the API reaches the intestinal membrane. In addition to the solubility issue, some of the poorly soluble drug candidates that Catalent is formulating have further challenges to be met to give the desired target product profile. LBDDSs have the versatility to offer a broad range of formulation possibilities.

For example, some poorly soluble drugs display excessive inter/intra individual variability, which may not be compatible with the desired therapeutic effect. There are several strategies specifically designed to reduce such variability, including the self-microemulsifying drug delivery system (SMEDDS), a lipid-based "preconcentrate" of solubilized drug composed of lipid excipients; surfactants and co-surfactants, and co-solvents. Dilution of these formulations with gastrointestinal fluids results in the formation of a stable microemulsion; the drug stays in solution and precipitation does not occur. Several new drugs formulated in this way have been commercialized.

Other strategies that have been applied to optimize formulations beyond solubility enhancement include the limitation of serum peak concentrations, thus reducing the Cmax/Cmin ratio. To achieve this, Catalent has developed semi-solid formulations combining solubility-enhancement properties with a modulated release rate. The technology upon which these formulations are based enables the encapsulation of various LBDDSs at higher temperatures.

FIGURE 1



Correlation between experimental and predicted solubility values obtained using different training sets.

EXCIPIENT & SOLVENT SELECTION

Catalent utilizes solubility prediction software that can speed up and narrow down excipient selection for softgel formulations when working with little, or even no API, and solubility and excipient screening for 30+ formulation vehicles can be achieved utilizing high-throughput techniques requiring as little as 1 to 2 grams of drug substance. In addition, Catalent's in-house encapsulation tooling design and fabrication expertise reduces API loss during manufacturing, and the use of commercial-scale equipment from first clinical batch manufacture expedites the drug product development pathway.

These methods use as little as one-third of the typical amount of API to determine the most suitable solvent vehicle for dosage formulation. Solubility prediction software can be based on one of two models: a quantum chemistry approach in which the molecular structures of APIs and excipients are used in combination with a solubility database to give predicted solubility values; or a thermodynamic approach based on melting point, solubility, and heat of formation data of APIs and vapor-liquid equilibrium or liquid-liquid equilibrium data of excipients.

A typical high-throughput solubility screening approach, based on low quantities of API, comprises the selection of 15 to 30+ vehicles (different chemical classes and hydrophilic-lipophilic balance); sample preparation by dispensing of the API and vehicle in a 1:10 or other ratio with a sample size <1 gram and incubation/mixing (typically for 48 hours). Separation of undissolved API is achieved by centrifuging and/or filtration. The solution is analyzed by HPLC for API solubility and the residual solids assessed by polarized light microscopy and X-ray diffraction (XRPD). A generic gradient HPLC method is employed, excipient

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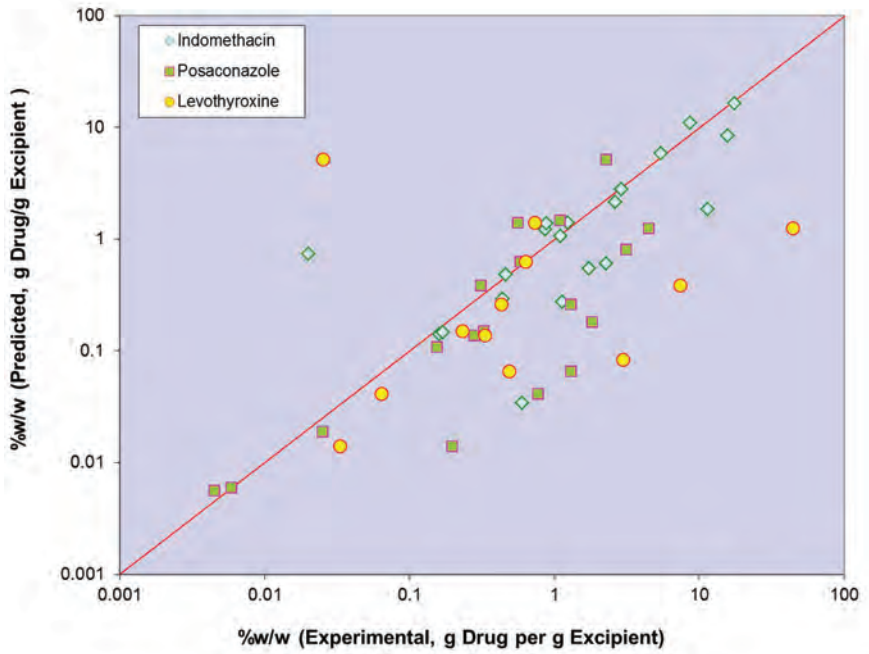
FIGURE 2



Correlation between experimental and predicted solubility values obtained for all three model compounds.

peaks being recorded at known retention times. The whole procedure can be completed within 1 week using 1 to 2 grams of API.

TESTING SOLUBILITY MODELS & FORMULATION DEVELOPMENT PROCEDURES

To demonstrate the versatility of its softgel solvent and excipient selection procedures, Catalent has performed a study in which the solubilities of three model compounds, indomethacin, posaconazole, and levothyroxine, (see Table 1 for their molecular properties) were experimentally tested in a basic set of seven solvents and softgel vehicles. These APIs were selected due to their having distinct chemical properties, thus broadening the scope of the study to be representative of the evaluation of a wide variety of compounds. Combined with specific chemical properties of the solvents, the solubility experiments provide specific information on the properties of the active ingredients, including polarity, hydrophilicity, and hydrophobicity. Using the molecular characteristics of the API and the test solvent panel, it is possible to extrapolate API solubility in a range of vehicles by applying an empirical non-random two-liquid segment activity coefficient (NRTL-SAC) model, which is correlative and predictive, and which requires minimal further input data.

The use of NRTL-SAC and other activity models in predicting solubility of APIs in common solvents has been widely investigated. The model calculates activity coefficient based on: (1) entropy of mixing (compositional, combinatorial, non-specific) and; (2) segment-segment (specific) pair-wise interactions. Each molecule in the model is defined by four conceptual descriptors (±polarity, hydrophilic, hydrophobic).

As an empirical model, NRTL-SAC has several advantages over other solubility models: the approach does not rely on predefined functional group activity coefficients; it is correlative and predictive; and, minimally, requires only four experimental solubility data as an input.

The conceptual approach used in studying a new API with NRTL-SAC is first, to determine the molecular weight, heat of formation, and melting point of the API; second, to measure the solubility in 4 to 6 training solvents; third, identify molecular descriptors of training solvents and generate a molecular description of the API by regression; and finally, to validate the model.

FORMULATION OF MODEL COMPOUNDS

In the study presented here, researchers utilized a NRTL-SAC model to predict the solubility of APIs in formulation vehicles and evaluate the feasibility of the model as a tool for selecting potential vehicles. Thermodynamic solubility of three compounds with differing physico-chemical properties, indomethacin, posaconazole, and levothyroxine, were determined in several formulation vehicles and common solvents. Experimental solubility data as well as thermal data were used to regress the solubility behavior of the compounds via the NRTL-SAC model and predict their solubility in formulation vehicles.

A set of 21 vehicles consisting of common solvents as well as potential softgel vehicles were used in the study. Table 1 presents the description of the vehicles as well as the experimental

TABLE 2

Excipient	Function	Indomethacin	Posaconazole	Levothyroxin
Acetone	Aprotic solvent	174.2	22.8	0.3
Caprylic Acid	Fatty acid	12.4	31.2	0.0
Capryol 90	Surfactant	26.3	13.0	4.3
Capryol PGMC	Surfactant	22.6	7.7	0.6
Ethanol	Protic solvent	29.0	5.6	7.3
Glycerol	Polyol	0.2	0.0	29.6
Heptane	Hydrophobic solvent	0.0	0.0	0.0
Imwitor 742	Fatty ester	17.3	13.0	4.9
Peceol	Oily vehicle	8.6	2.8	3.3
Lauroglycol FCC	Emulsifier	11.3	2.0	0.3
Maisine	Oily vehicle	8.8	3.2	2.3
Miglyol 812	Medium-chain triglyceride	4.4	0.2	0.0
Oleic Acid	Fatty acid	4.6	1.5	0.0
Ethyl Acetate	Low polarity solvent	54.0	10.9	0.0
PEG 400*	Solubilizer	114.0	18.2	0.0
Propylene Glycol	Polyol	11.0	3.1	73.9
Sesame Oil	Triglyceride	1.6	0.0	0.0
Soybean Oil	Triglyceride	1.7	0.1	0.0
Transcutol HP	Solvent	157.6	44.8	440.1
Tween 80	Surfactant	86.2	5.8	6.4
Water	Solvent	6.0	0.0	2.7

Experimental Solubility Values

equilibrium solubility data obtained. Of the three model compounds, indomethacin exhibited generally better solubility across all vehicles compared to the other two model compounds.

A training set involving four common solvents only, as well as training sets combining four solvents and three softgel vehicles, were initially designed to model the solubility behavior of indomethacin. Figure 1 shows the correlation of the results between experimental and predicted values in the two models for indomethacin. Overall, modeling involving solvents and softgel vehicles resulted in a better correlation.

The same training sets of seven solvents and softgel vehicles were utilized to model the solubility behavior of all three model compounds. Results of the solubility prediction are shown in Figure 2. In general, the predicted solubility values for the softgel vehicles were lower compared to actual experimental results (see Table 2 for experimental solubility values).

However, the rank-order of the vehicles in terms of solubility is good overall. Evaluation of the overall correlation of experimental versus predicted data sets suggests indomethacin > posaconazole > levothyroxine. Interestingly, this rank order qualitatively correlates with the physical stability of the compound during the solubility determination. The data generated by using this method allow for the selection of a solvent vehicle with a higher likelihood of success in creating a dosage form with adequate API solubility.

CONCLUSION

In the early drug development phase, dosage form development is often delayed due to insufficient quantities of API available. Softgel is a proven dosage form to improve drug bioavailable, compatible with a wide range of solvent systems. Catalent has successfully generated solubility data in various softgel solvents using the NRTL-SAC model and as little as one-third of the typical amount of API is required. Thermodynamic solubility modeling can provide adequate correlation between experimental and predicted solubility data and can be useful in selecting vehicles for initial formulation design. This novel approach helps overcome challenges in labor and material requirements during traditional dosage formulation experiments, resulting in the opportunity to perform dosage form selection in the early phases of drug development. ◆

BIOGRAPHY

Irena McGuffy is a Director, Formulations Development at Catalent Pharma Solutions, and leads formulation development teams in Somerset, NJ, and St, Petersburg, FL, that are responsible for preclinical and clinical lipid-based formulation and softgel product development for NCEs. Other areas of expertise include generic product development, process scale-up and development, as well as clinical material manufacture. Her research efforts are currently focused on softgel film coating for the purpose of modified or targeted release and fixed dose combination product development. She has also served as a Portfolio Champion for Rx Softgel and a member of Catalent's Softgel IP Review Board. Ms. McGuffy joined Catalent in 2007 and has over 13 years of experience in the pharmaceutical industry. Prior to Catalent, she spent 4 years with PLIVA and 1.5 years with Ranbaxy developing solid dosage forms, specifically generics, immediate-, gastro-retentive, and controlled-release products, as well as other novel approaches to overcoming poor solubility and bioavailability. She is an active member of the AAPS and a steering committee member for the AAPS Lipid-Based Drug Delivery Systems Focus Group. She is a registered pharmacist and earned her BS in Pharmacy and her MS in Pharmaceutical Sciences from the University of Zagreb, Croatia, as well as her PharmD from University of Florida.

PLASMA-DERIVED BIOLOGICS

New Fractionation Process to Expand Availability of Plasma-Derived Treatments

By: Jeffrey B. Davis, MBA, Chief Operating Officer, PlasmaTech Biopharmaceuticals

INTRODUCTION

Plasma-derived therapeutics start from human blood plasma instead of the chemical or synthetic materials from which most pharmaceuticals are made. Human blood plasma is rich in proteins that boost the immune system, and fight infections and inflammation, making plasma-derived biologics useful in treating rare, chronic, and often genetic diseases like hemophilia. Among the proteins used are immunoglobulins, coagulation factors, alpha-1 antitrypsin, fibrin sealants, and albumin.

While there is no distinction biologically, human plasma donations come from two different processes. The first type of donation is called "source" plasma, wherein a donor undergoes a process called plasmapheresis. In this process, the plasma is separated from the other components (red and white blood cells and platelets) of the donor's blood. The plasma is retained by the collecting facility, while the other components are returned to the donor's blood stream. By this method, 600 to 800 milliliters of plasma can safely be donated at a time. The American Red Cross states that plasma donation can occur every month without harm to the donor.

The other type of donation is that of "recovered" plasma. In this type of donation, the donor gives whole blood, and the plasma is taken from it. This provides about 250 milliliters per donation. Whole blood donors should wait 8 weeks between donations.

Once the plasma is collected, it needs to be screened for disease (eg, HIV or hepatitis). Plasma that has passed such screening then undergoes "fractionation." Thousands of plasma donations that have passed screening are pooled together, which ensures homogeneous batches, and the process begins to extract and purify the desired proteins. The process is called "plasma fractionation," and the proteins are said to be "fractioned off."

FRACTIONATION TODAY: COHN COLD FRACTIONATION PROCESS

All fractionation today is done via the Cohn Cold Fractionation Process, named after Dr. Edwin J. Cohn who developed it in the 1940s. The Cohn Process involves modifying the pH, ethanol concentration, and temperature to separate proteins through precipitation into five "fractions" (I-V). The separated proteins then undergo an extensive purification process that includes cryoprecipitation, nanofiltration, solvent detergent treatments, and incubation to produce a sterile, virally inactivated protein product.

Plasma fractionation has been around since World War II, when it was used to create blood products, initially albumin, to help wounded soldiers and sailors suffering from burns and hemorrhagic shock. While human blood plasma contains hundreds of proteins that may have medicinal value, there are around 20 that are commercialized today. The main proteins, in chronological order of development include the following:

Albumin: Used since the 1940s as a volume expander for blood and fluid loss, septic shock, burn therapy, renal dialysis, and therapeutic plasma exchange. Albumin represents roughly

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55% of the total protein volume in human plasma.

Hemophilia Factors: Used since the 1960s, first as cryoprecipitate to control bleeding, but later as individual anti-hemophiliac factors, such as Factor VIII (the most common factor deficiency) and Factor IX as methods of purification were developed.

Intravenous Immunoglobulins (IVIG): In the 1970s, the Swiss Red Cross further improved on the Cohn method by adding chromatography process to further extract and purify immunoglobulins. FDA-approved indications include some oncology indications, certain neurological conditions, and select hematological and dermatological conditions.

Alpha-1 Antitrypsin (AAT), also Known as Alpha-1 Protease Inhibitor (A1PI): AAT is a protein that is made in the liver in healthy humans, and certain genetic defects diminish or eliminate the liver's ability to make AAT. An AAT deficiency causes a variety of conditions, including emphysema, neonatal hepatitis, jaundice, and chronic obstructive pulmonary disease (COPD). Approximately 1 in 3,000 humans have this genetic deficiency, and it is estimated that over 300,000 people in North America and Europe are living with the deficiency, but less than 3% receive A1PI replacement therapy, which is lifelong and involves weekly infusions of A1PI of at least 60 mg/kg of body weight, or roughly 250 grams per year. Information on Alpha-1 deficiency, and resources provided by the patient advocacy group Alpha-1 Foundation, can be found at www.alpha1portal.org.

FIGURE 1

For albumin, the Cohn Process is perfectly adequate. With albumin accounting for 55% of all the proteins in plasma, it's a target-rich environment for this 75-year-old process.

For AAT, the Cohn Process suffers from very low yields. It is believe the ethanol in the Cohn Process is very damaging to some proteins, negatively effecting the ability to get good commercial yields. AAT makes up 1.8 to 3.5 grams per liter of plasma, and the Cohn Process can only recover about 7% of it. When one considers the numerous potential uses for AAT, it is not beyond reason to worry about a shortage of the protein for patients who need it. Of the 300,000 potential patients with Alpha-1 deficiency, only about 10,000 are getting plasma-derived treatment. If the other 291,000 are to be identified and treated with replacement therapy, supplies will have to expand radically.

One of the main issues with the Cohn Process is its reliance on ethanol combined with changes in pH, ionic strength, and temperature in a lengthy multi-step process to bring about the separation of proteins. The use of ethanol poses two problems: it tends to have denaturing effects on plasma proteins when they are exposed for a long time, and ethanol is volatile, making commercial use of the Cohn Process capital intensive for safety reasons. A process that could fractionate the proteins without the use of ethanol would, therefore, be a step forward.

IN WITH THE NEW: SALT DIAFILTRATION PROCESS

About 10 years ago, researchers began development of the Salt Diafiltration Process (SDF). The SDF Process uses salt as the precipitant at neutral pH, followed by salt removal by diafiltration, followed by the use of state-of-the-art chromatography for final separations and purification. The efficacy of the process has been confirmed in pilot-scale batches in independent laboratories. PlasmaTech Biopharmaceuticals has initiated a three-

phase process of scaling up its process, validating it for required FDA filings, and ultimately running the process at production scale to enable the clinical trial product to be produced.

Over the years, research has established that several salts work. However, sodium citrate is now the preferred salt for the SDF process because of its ''friendliness'' to biologics, having been long used as an FDA-approved protectant and preservative of whole blood and blood plasma. With the SDF process utilizing sodium citrate, yields from plasma fractionation have gone from 7% recovery of AAT with the Cohn Process to 70% with the SDF, or approximately a 1000% increase in yield.

Moreover, the SDF process is quite capable, according to research done to date, of delivering other fractionated proteins. Intravenous Immune Globulin (IVIG) extracted from human plasma contains a broad spectrum of Immunoglobulin G (IgG) antibodies, and it is used to treat, among other conditions, primary immune deficiencies of genetic origin (estimated 10 million potential patients worldwide; 60,000 currently treated with IVIG), chronic lymphocytic leukemia, idiopathic thrombocytopenia, pediatric HIV, allogeneic bone marrow transplantation, kidney transplantation, and Kawasaki syndrome. The SDF process improves IVIG yields by roughly 20% and is expected to extend half-life in circulation due to reduced denaturation.

Further the short, two-step salt precipitation process, in contrast to the highly denaturing Cohn process, may also enable the extraction of several additional plasma biologics by means of downstream affinity and/or ion-exchange chromatography, thus potentially further improving revenues and process economics available from the same starting plasma. Examples of these additional therapeutic proteins are C-1-Esterase Inhibitor, Protein C, Antithrombin III, Transferrin, and Haptoglobin, all of which are used as treatments for low-incidence genetic deficiencies that could qualify them as Orphan Drugs.

THE FUTURE OF PLASMA-DERIVED TREATMENTS

A final advantage plasma-derived treatments have is a regulatory one. Because of concerns about product availability and because human-derived plasma biologics are considered to be "bio-identical," as opposed to bio-similar as is the case of recombinant or transgenic products, the FDA's Center for Biologics Evaluation and Research (CBER) approval process can be much shorter and less costly. Depending upon the specific protein being evaluated, CBER may only require clinical trials to demonstrate safety and bioequivalence of the protein in circulation.

The global market for human-plasma derived therapeutics is estimated at $15 billion, and is growing at more than 10% per year. With the clinical indications and uses for these proteins ever expanding, there is a real risk of potential shortages or shortfalls in the future due to limitations inherent to the Cohn process. SDF offers real innovation in an industry that has relied on the Cohn process for roughly 75 years. As uses for these proteins expands, SDF is well positioned to meet growing supply needs. ◆

BIOGRAPHY

Jeffrey B. Davis earned his BS in Biomedical Engineering from Boston University and his MBA from The Wharton School, University of Pennsylvania. Mr. Davis has held a variety of c-level executive positions in the biotechnology industry, and is currently a Director and Chief Operating Officer of PlasmaTech Biopharmaceuticals, Inc. He was previously CEO of Access Pharmaceuticals, Inc., and has previously served in a variety of senior investment banking and management positions. Mr. Davis was an investment banker with various Deutsche Bank AG banking organizations, both in the US and Europe, and also served in senior marketing and product management positions at AT&T Bell Laboratories, where he was also a member of the technical staff, and at Philips Medical Systems North America.

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CAPSULE TECHNOLOGY

Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating

By: Hassan Benameur, PhD

INTRODUCTION

Enteric capsule drug delivery technology (ECDDT) was developed to provide oral delivery with full enteric protection and rapid release in the upper gastrointestinal (GI) tract without the use of coatings. ECDDT's intrinsically enteric properties are attained by incorporating pharmaceutically approved enteric polymers in the capsule shell using conventional pin-dipping capsule manufacturing processes. By eliminating the preparation and application steps used for enteric coating, ECDDT can offer accelerated development timelines and reduced program risk. ECDDT can also enable the oral delivery of sensitive molecules, such as nucleotides and peptides, biological products such as vaccines, and live biotherapeutic products (LBPs), which can degrade at the high temperatures or can be sensitive to aqueous coating solution associated with pan and fluid bed coating processes. The enteric properties and rapid release of specialized ECDDT capsule shells have been demonstrated to meet pharmacopeia standards for both in vitro and in vivo performance using esomeprazole magnesium trihydrate (EMT) as a model compound.

POTENTIAL BENEFITS OF ECDDT

Oral delivery is routinely cited as the universally preferred route of administration for drug products. Many oral drugs are specifically formulated to allow disintegration only in certain sections of the GI tract for the purpose of protecting the drug from destruction by gastric acid of the stomach (e.g., proton pump inhibitors), protecting the active from destruction by enzymes of the stomach (e.g., peptides, proteins) or protecting the stomach from an irritant drug (e.g., enteric coated aspirin).[1] Enteric protection has historically been imparted to solid dosage forms by applying a seal coat followed by coating at relatively high weight gains (typically ≥ 10%) with pH-sensitive polymer systems using rotary perforated pan coaters or fluidized bed equipment.

The development and scale-up steps associated with enteric coating add complexity, time, and risk to drug programs. An assessment by H2 Pharma Consulting cites the following areas where ECDDT could reduce the complexity of enteric dosage form design and processing:[2]

- Simplify selection of enteric formulation composition
- Enable rapid screening and optimization of enteric functional performance
- Reduce/remove dependency of enteric functionality with process variability
- Obviate need for process development of enteric coating step
- Obviate need for process scale-up and validation
- Minimize risk of changes to enteric performance on stability

The assessment further estimated potential savings in overall development time of more than 9 months through Phase III, based on rapid development of prototypes for formulation screening and rapid testing of in vivo performance.

Development risk may also be minimized in several aspects by:

- Removing the need for process development and scale-up of enteric coating
- Limiting the scope of overall process development and validation program
- Removing the dependency between enteric functionality, coating process parameters, and variability
- Minimizing risk of enteric performance changes on scale-up and stability

The major hurdle in oral delivery of many sensitive molecules, such as nucleotides, peptides, live biopharmaceutical products, and vaccines, is protecting the active entity from acidic and enzymatic degradation in the GI tract.[3] In some cases, oral delivery can be precluded entirely due to the need for enteric coating. The high temperatures (> 40°C) associated with functional coating application and drying can degrade these sensitive actives and, as such, parenteral or other delivery routes are often required. ECDDT can therefore be enabling for oral delivery of such actives by providing full enteric protection and rapid release in the upper GI tract without coating.

FIGURE 1

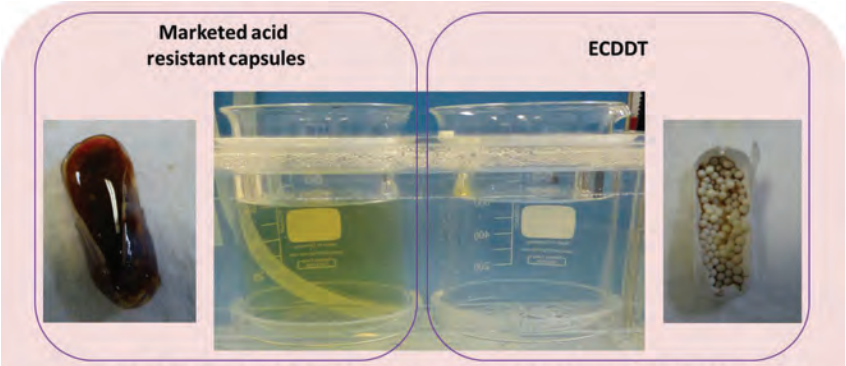

Figure 1: *Appearance of disintegration media and capsule filled content after 2h acid stage*

EVALUATION OF ECDDT

The enteric properties of the ECDDT capsules were assessed using esomeprazole magnesium trihydrate (EMT) as the model compound in the form of uncoated pellets. EMT was chosen as a model compound due to both the market relevancy of Nexium® and the high gastric sensitivity of the active. EMT is known to rapidly degrade in acidic media with short-term chemical instability readily identifiable by a yellow/brown discoloration.

A pharmaceutical-grade cellulosic enteric formulation (complying with EP/USP/JP) was prepared using polymer aqueous dispersion or pseudolatex with plasticizer addition to achieve optimal dipping, setting, and film-forming properties for capsule shell production. Intrinsically enteric size 0 white opaque capsules – equivalent in appearance, dimensions, and mechanical properties to conventional two-piece hard capsules – were then manufactured on a full-scale, commercial hard capsule manufacturing machine. These capsules were then evaluated by in vitro testing and in vivo human bio-studies using EMT.

IN VITRO TESTING & RESULTS

ECDDT formulations using EMT were shown compliant with the specifications for both pharmacopeial disintegration and dissolution testing for gastro-resistant dosage forms, as discussed further.

Capsules (n=6) were filled with 20 mg of EMT-layered, uncoated pellets and then evaluated using EP/USP disintegration apparatus type B. The test was performed for 2 hours at acid stage (pH 1.2) without disk and then for 1 hour at buffer stage (pH 6.8) with disk. For comparison purposes, commercially available "acid-resistant" capsules – not designed to be impermeable to fluid ingress in pH 1.2 media – were filled with the same EMT pellets and tested using the same method.

The ECDDT capsules showed no evidence of early disintegration, rupture, or content release, and there was no significant discoloration of the medium after 2 hours in the acid stage (Figure 1). In pH 6.8 buffer, the capsules rapidly disintegrated within 30 minutes in buffer stage. The acid-resistant capsules, however, showed clear evidence of deformation and of content release in the acid stage with rapid yellow/brown

FIGURE 2

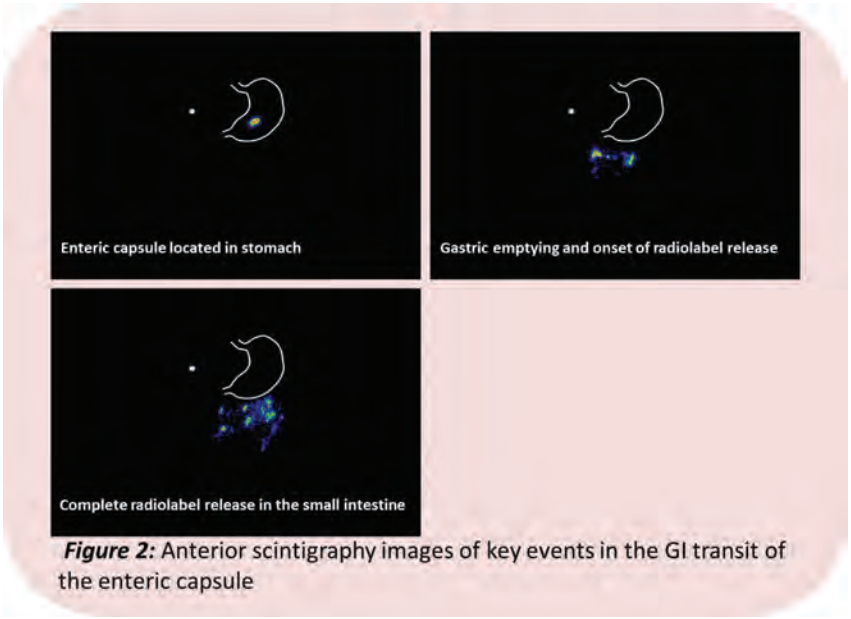

Figure 2: Anterior scintigraphy images of key events in the GI transit of the enteric capsule

discoloration of the medium.

After the acid stage, both capsule samples were cut open to observe the filled contents. The content of commercial acid-resistant capsules consisted of a brown liquid with EMT pellets partially dissolved, demonstrating that a significant amount of acid medium had migrated inside the capsules, resulting in EMT degradation. EMT pellets in ECDDT capsules showed minimal discoloration, indicating little to no degradation.

ECDDT capsules (n=6) filled with EMT pellets were also evaluated according to the EP/USP dissolution test for gastro-resistant dosage forms, using USP apparatus II (paddle). The test was performed at 37°C/100 rpm for 2 hours at acid stage (pH 1.2) and then 1 hour at buffer stage (pH 6.8), with sampling at regular times. The dissolution behavior of Nexium 20-mg delayed-release capsules (n=6) was also evaluated using the same protocol. For the dissolution test, no solubilization of the ECDDT capsules was observed, and each capsule showed less than 0.2% (LOD) of esomeprazole release after 2 hours in the acid stage and more than 90% of release after 30 minutes in the buffer stage.

HUMAN BIO-STUDY RESULTS

Esomeprazole is known to show fast oral absorption (plasma peak = 1 to 3.5 hours) and a short half-life (1.5 hours). To evaluate in vivo performance for the new technology, ECDDT capsules were filled with EMT-layered uncoated pellets and compared to Nexium capsules (uncoated gelatin capsules containing enteric coated drug-layered multiparticulates) in a randomized, open-label, single-dose, and crossover pharmacokinetic and gamma-pharmacoscintigraphy study using healthy volunteers under fasting state. Radiolabelled (99mTc) pellets were added in both ECDDT capsules and Nexium hard gelatin capsules size 0 in order to detect the location of capsule opening and content release in the gut through the GI tract. Blood samples were taken at pre-dose and then at regular times post-dose over 12 hours, and anterior and posterior images were acquired at dosing and then post-dose over 12 hours.

In vivo results (Figure 2) showed that no pellets were released from ECDDT capsules in the stomach and that the capsule quickly opened in the small intestine 30 minutes from gastric emptying to the onset of drug release from the pellet dissolution. Nexium capsules, opened and released their content in the stomach before gastric emptying.

The PK profiles of ECDDT capsules and Nexium capsules showed similar rates of drug absorption, particularly in terms of peak time T_{max}, elimination constant kel and half-life t½ (Figure 3). Overall bioavailability of EMT was increased using ECDDT capsule formulations, with C_{max} and AUC increased by 56% and 32%, respectively, in comparison to Nexium.

SUMMARY

Enteric capsule drug delivery technology utilizes a pharmaceutical-grade cellulosic enteric formulation as an aqueous dispersion to produce capsule shells by conventional capsule manufacturing technology pin-dipping. The enteric properties of capsules have been evaluated in vitro and the results shown to comply with pharmacopeial disintegration and dissolution tests criteria. It has been demonstrated with both in vitro testing and in vivo by human gamma-pharmacoscintigraphy that ECDDT capsules protect EMT from

FIGURE 3

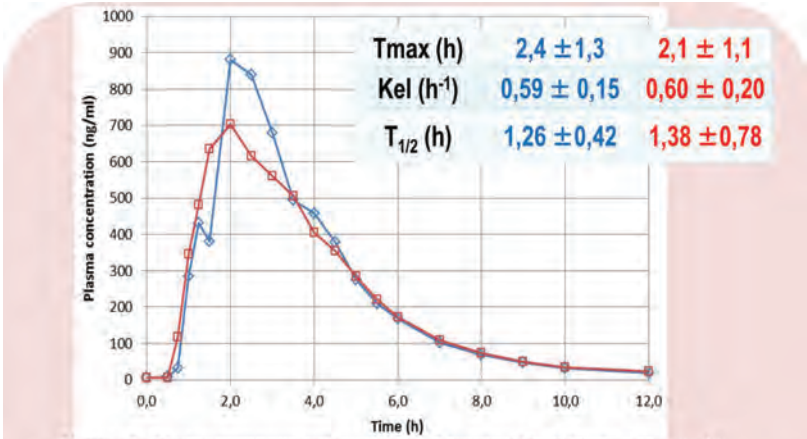

Figure 3: *Plasma concentration versus Time profile of enteric capsules (open blue lozenge) and Nexium® (open red square), with corresponding peak time, elimination constant and half-life*

gastric degradation, do not open in the stomach, and provide fast release in the duodenum.

ECDDT represents a new, faster, and easier means for oral delivery of labile entities, such as peptides, nucleotides, live biopharmaceutical products, and vaccines. Integrated enteric functionality in a capsule dosage form enables new possibilities for rapid prototype development and formulation screening, allows rapid testing of in vivo performance and minimizes the risk of out-of-specification events during enteric performance challenges on manufacturing scale-up and stability trials. Avoiding the high temperatures associated with enteric coating application can also enable oral delivery of actives that require enteric protection but are sensitive to thermal degradation.

ECDDT trials are underway to further evaluate the technology's range and application, including oral live biopharmaceutical products, vaccines, and oral peptide products from preclinical to Phase III. ◆

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BIOGRAPHY

Dr. Hassan Benameur is Senior Director of Pharmaceutical Sciences at Capsugel. He joined Capsugel in 2002 and currently leads the company's pharmaceutical sciences department. Prior to joining Capsugel, he held various positions in Pharmaceutical Research & Development within Therapeutica, SMB Galephar, and Gattefossé. With more than 20 years of expertise in conventional and advanced drug delivery development, Dr. Benameur brings insightful science into innovative dosage forms and uses drug delivery technology to maximize success and reduce attrition in product development, from preformulation to manufacturing using a systematic and rational approach. Dr. Benameur is a lecturer at several academic and industrial symposia and was presented the Academy of Pharmaceutical Science and Technology, Japan Award in 2005. He is a member of several major scientific associations, including AAPS, APGI BCRG, PSTJ, and CRS and scientific academies. He has also authored 40 scientific publications and the inventor of 20 patents. Dr. Benameur is a Chemical Engineer and earned his PhD in Pharmaceutical Sciences from the Free University of Belgium.

IONTOPHORESIS

Captisol-enabled™ Lipophilic Drug Complex Delivered Transdermally by Iontophoresis

By: Abhishek Juluri, PhD, Fahimeh Ghasemi, MS, Horacio Pérez-Sánchez, PhD, Reena N. Murthy, and S. Narasimha Murthy, PhD

INTRODUCTION

Transdermal delivery of therapeutic agents provides several advantages, including avoidance of first-pass metabolism, easy termination of dose by removal of patch, easy application for extended period of time by controlling the drug release, and many more. The skin is poorly permeable to drugs that are hydrophilic (log P<1). Thus, to enhance the delivery of hydrophilic drugs, chemical permeation enhancers (CPEs) are being utilized in dermal/transdermal products. CPEs are chemical substances that facilitate transport of co-administered substances across the skin, mainly by disrupting the highly ordered structure of stratum corneum lipids.[1]

It is well known that the drugs with log P 1-3 (moderately lipophilic) and molecular weight of <500 Da have shown good permeability across the skin.[2] The rate of permeation of moderately lipophilic drugs is mainly controlled by permeability of the skin. Not many approaches are known at present to enhance the rate of delivery of lipophilic drugs of which there is requirement of a higher dose or a higher input rate. The chemical skin permeability enhancers (used to enhance the delivery of hydrophilic drugs), most of which perturb the lipid organization, would rather hamper the delivery of lipophilic drugs. Hence, one of the objective of this study was to explore use of Captisol®, a polyanionic modified cyclodextrin as a drug transport enhancer for lipophilic drugs.

Iontophoresis is one of the widely investigated active techniques that involve passing electrical current across skin in the presence of conductive vehicle. As a result, ions migrate through the skin toward the electrode of opposite charge. The amount of drug delivered is directly proportional to amount of current applied, duration of current application, and area of skin surface that is in contact with the active electrode.[3] However, iontophoresis is not suitable for non-polar drugs as they lack any charge and possess poor water solubility. The second objective of this study was to investigate the feasibility of delivery of lipophilic drugs by iontophoresis after complexing them with a polyanionic modified cyclodextrin, Captisol (CAP). As reported earlier, CAP enhanced the transdermal delivery of a lipophilic drug propofol by ~four-fold when delivered using the Captisol complex across the porcine epidermis compared to control (drug solution in the neat form). Iontophoresis of the complex resulted in ~four-fold more transdermal transport flux over the passive flux of complex.[4] Further, to provide more validity to the concept and to investigate the potential of CAP as a transdermal transport enhancer for lipophilic drugs, ibuprofen (log P 3.5) and testosterone (log P 2.99) were chosen as test molecules.

MATERIALS

Captisol (Betadex Sulfobutyl Ether Sodium) was provided as a gift from Ligand Pharmaceuticals (La Jolla, CA). Ibuprofen and testosterone were purchased from Sigma Aldrich (St. Louis, MO). Dialysis membrane molecular weight cut off (MWCO) 1000 Da was from Spectrum Chemicals (New Brunswick, NJ). All other chemicals used were of research grade.

METHODS

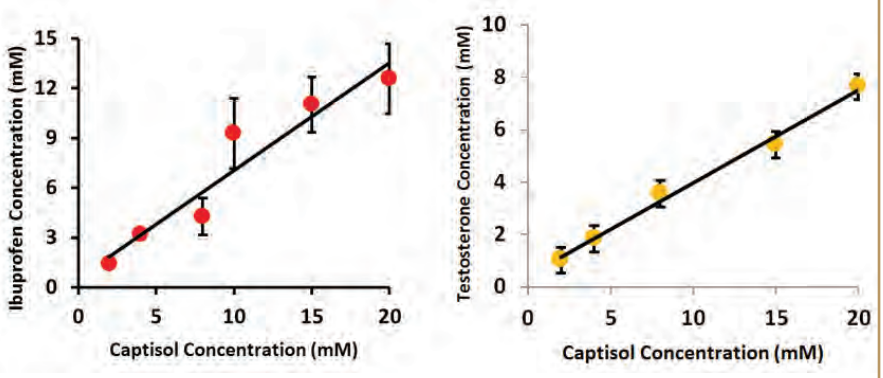
Phase Solubility Studies

Phase solubility studies were performed according to the standard protocol.[5] Solubility measurements were carried out at constant temperature (25°C) using different concentrations of aqueous solution of CAP. A large excess of testosterone or ibuprofen (200 mg) was added to 3 ml of water with accurately weighed amount of CAP and diluted to concentrations from 0.002 to 0.02 M in screw capped scintillation vials. The resulted solution was vortexed for 5 mins and was shaken for 5 days using a rotary Labquake™ tube shaker (Labindustries, Inc. Berkeley, CA). Then, an aliquot of aqueous phase from each mixture was withdrawn, centrifuged for 15 mins at 13,000 RPM, and the supernatant was collected and filtered through a 0.45-micrometer cellulose acetate membrane filter. A portion of clear filtrate was diluted appropriately and analyzed using high-performance liquid chromatography (HPLC).

Preparation of Solid Complex Mixture

Captisol-enabled testosterone (CE-T) and Captisol-enabled ibuprofen (CE-I) inclusion complex was prepared by freeze-drying method. The aqueous solutions of complex were prepared by dissolving 100 mg of drug in 10 ml of 10% and 12% CAP in distilled water for ibuprofen and testosterone, respectively. The resulting mixture was vortexed for 15 mins and sonicated for 20 mins followed by setting aside at 25°C for 48 hrs to attain equilibrium solubility. The clear solution (10 mL) was then subjected to freeze drying for 24 hrs to obtain white powder.

FIGURE 1



Phase-Solubility Profiles of Ibuprofen & Testosterone With Captisol®

Transport Studies Across Porcine Epidermis From Aqueous & Hydro-Alcoholic Solution

The vertical Franz diffusion apparatus (Logan Instruments, Somerset, NJ) was used for all transport studies. The receiver compartment was filled with 5 mL of freshly prepared phosphate buffered saline (PBS) (pH 7.4) with 30% alcohol and donor compartment with 0.5 mL of permeant solution. *In vitro* passive permeation studies were carried out using aqueous solution containing the drug-Captisol complex (dissolved in water) equivalent to 10 mg/mL of drug in the donor compartment. As the pure drug is not soluble in water, a solution of pure drug dissolved in 50% alcohol was used as control at same concentration.

For *in vitro* iontophoretic permeation of complex, constant current cathodal iontophoresis was applied using Phoresor® iontophoresis unit (Iomed, Salt Lake City, UT) at a current density of 0.5 mA/cm^2. Permeation studies were carried out from solution formulation after dissolving the complex in water at the same concentration as passive delivery (10 mg/mL) for a period of 24 hrs, and samples were analyzed using HPLC technique.[6]

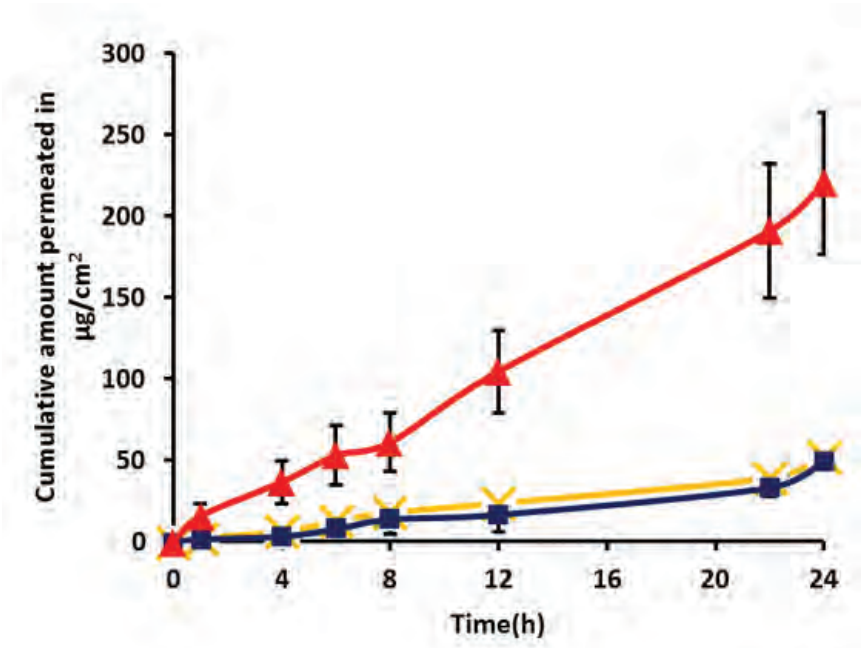
Transport Studies Across Porcine Epidermis From Gel Formulation

Transport of testosterone from the HPMC gel formulation prepared by Hot/Cold technique at 3.5% w/v concentration across porcine epidermis was studied by both passive- and iontophoretic-mediated delivery for a period of 24 hrs and sample from the receiver compartment was withdrawn at predetermined time points and estimated for testosterone using HPLC.

MTT Assay

Cell viability of dermal fibroblast derived from humans (CCD-1093Sk) was studied using the CAP solutions. Fibroblast cultures were stored and handled according to the standard protocol from ATCC. To study the effect of the CAP formulation on cell viability, cell cultures were exposed to different concentrations ranging from 0.5% to 2% w/v for a period of 24 hrs. Each test formulation was studied in eight trials. MTT (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) cell proliferation assay was performed according to the protocol supplied by Promega.[7] The optical absorbance data from the samples were then used to calculate the percentage cell viability.

FIGURE 2



In vitro transport profile of ibuprofen across porcine epidermis when the donor solution was placed with, ibuprofen in 50% alcohol (Control) (X), CE-I complex (equivalent to 10 mg/ml ibuprofen) (■). Transport of ibuprofen by iontophoresis from CE-I complex solution (▲)

RESULTS

Phase Solubility Studies

The phase solubility studies revealed a proportionate increase in the water solubility of drug with increase in the concentration of CAP. The linear correlation between different concentration of solutions of CAP and drug in solution suggests an A_L type relationship and stoichiometry of 1:1 between the substrate and complexing agent.[8] Because the slope of this plot is less than 1, the apparent stability constant was calculated using the equation K_c = Slope/S_0 (1-Slope), where S_0 is the solubility value of drug in water and was found to be 10,569 and 12,369 M^{-1} for testosterone and ibuprofen, respectively (Figure 1).

Transport Studies Across Porcine Epidermis From Aqueous & Hydroalcoholic Solution

Passive delivery of ibuprofen from aqueous solution of CE-I complex resulted in a flux of 1.98 ± 0.71 micrograms/cm²/h, which is comparable with the flux achieved in case of hydroalcoholic solution of neat ibuprofen used as control (1.93 ± 0.24 micrograms/cm²/h) (Figure 2). The ability of alcohol to enhance the permeation of drugs is well documented.[9] In case of hydroalcoholic solution of pure API, the alcohol could be potentially acting as a permeation enhancer as well in addition to serving as a co-solvent. It is intriguing that the permeation from the CAP complexed drug solution prepared in an alcohol-free aqueous vehicle was found to be comparable with the alcoholic solution of API. It is evident that the passive delivery of ibuprofen would be possible either when a suitable co-solvent system is used as a vehicle or when the drug is rendered soluble in water with the use of solubility enhancers, such as CAP.

In agreement with an earlier observation with a lipophilic drug propofol, it was found that complexation with CAP facilitated the transdermal transport of the drug by iontophoresis.[4] Further, iontophoresis of CE-I complex resulted in a drug flux of 9.29 ± 1.19 micrograms/cm² h, which is ~five-fold more compared to the passive permeation flux of ibuprofen from CE-I complex and control.

In case of testosterone, the passive delivery from the aqueous solution of CE-T resulted in a cumulative transport of 4.46 ± 1.21 micrograms/cm² of testosterone at the end of 24 hrs, which is comparable with the cumulative amount of drug permeated in the case of alcoholic solution of testosterone used as control (5.11 ± 0.68 micrograms/cm²) (Table 1). The cumulative amount of testosterone permeated following cathodal iontophoresis of CE-T complex solution was 124.85 ± 8.01 micrograms/cm², which is ~30-fold greater than passive delivery.

There was a significant change in the pH of the donor solution during iontophoresis observed as the complex dissolved in water was used for iontophoretic permeation studies instead of buffers to keep the solution devoid of any competing ions. Considering the low pKa value of sulfonic acid groups on the CAP[10], an increase in the pH in the donor compartment due to hydrolysis of water during iontophoresis is not likely to affect the iontophoretic transport significantly. To minimize the effect of pH changes on the permeation of drug across the skin, the drug solution in the

TABLE 1

Formulation	Control (Hydroalcoholic Solution)	Passive (CE-T Complex)	Iontophoresis (CE-T Complex)
Solution	5.11±0.6	4.46±1.21	124.85±8.01
HPMC Gel	---	2.45±0.92	48.12±6.12

Cumulative amount testosterone permeated from aqueous, hydroalcoholic solution and HPMC gel by passive and iontophoresis of CE-T complex.

donor was replaced intermittently with freshly prepared drug-CAP complex solution.

Release & Permeation Studies of Testosterone From HPMC Gels

These studies were performed to investigate the fact whether CAP would even work in the HPMC gel formulations as a drug transport enhancer. Release of testosterone from HPMC gel formulations with CE-T complexes was studied using 1000 Da molecular weight cut-off membrane. The amount of drug released was ~48% at the end of 24 hrs with CE-T complex. The molecular weight of CAP and the CE-T complex (2.4 kDa) is much higher than the MWCO of membrane (1 kDa), suggesting that the amount of drug in the receiver compartment was predominantly due to the ability of CAP to enhance the thermodynamic activity of drug in the donor compartment.

The amount of testosterone permeated from the gel formulations across the porcine epidermis in 24 hrs was found to be 2.45 ± 0.92 micrograms/cm^2. The decrease in the cumulative amount permeated across the porcine epidermis compared to solution could be attributed to relatively higher viscosity of gels. Further, iontophoresis using the hydrogel containing CE-T resulted in permeation of 48.12 ± 6.12 micrograms/cm^2 (Table 1).

MTT Assay

The MTT assay is a tool to assess the safety of captisol for dermal use. The previous studies have shown that CAP appears to penetrate the skin in significant amounts.[4] Thus, cell viability studies on fibroblast (derived from humans) were performed at different concentrations of CAP solutions. The cell viability of non-treated cells was considered as 100%. More than 80% of cells were viable at 1.5% w/v concentration of CAP (Figure 3), with further increase in concentration to 2% w/v the percent cell viability decreased to 76%, which is likely due to increased osmotic pressure in the medium (2% Captisol in culture media raises the osmolality such that hypertonic).

CONCLUSIONS

The results from the *in vitro* permeation studies indicate that the passive permeation of lipophilic drugs could be facilitated by complexing with CAP. Moreover, complexing the lipophilic drugs with a charged cyclodextrin such as CAP demonstrated the feasibility of iontophoresis of lipophilic drugs. Results obtained from the *in vitro* studies clearly demonstrated the transport enhancement ability of CAP in solution as well as in gel formulations. The CAP is found to be safe for dermal use and could be employed as a solubility and transdermal drug transport enhancer.

ACKNOWLEDGEMENTS

This work was partially funded by Ligand Pharmaceuticals, La Jolla, CA. ◆

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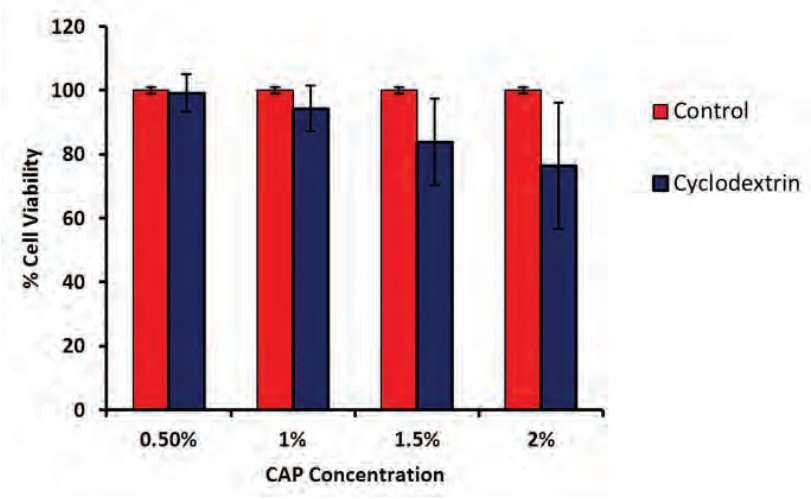
FIGURE 3



MTT Assay of CAP at Different Concentrations

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BIOGRAPHIES

Dr. Abhishek Juluri is a graduate student at The University of Mississippi School of Pharmacy. For the past 4 years, he has been working on novel techniques for delivering drugs across skin. He has published six articles and co-authored a book chapter.

Fahimeh Ghasemi earned her MS in Electrical Engineering from Sharif University, Tehran, Iran, in 2010, where she is currently a PhD student in Biomedical Engineering (Bioelectric) at Isfahan University of Medical Science with a research focus on drug design. Her current main research is in Statistical Modeling and Machin Learning. She has background in Biomedical Image and Signal Processing.

Dr. Horacio Pérez-Sánchez is the Principal Investigator of the Bioinformatics and High Performance Computing research group (http://bio-hpc.eu) from Universidad Católica San Antonio de Murcia (UCAM). Dr. Pérez-Sánchez earned his PhD in Computational Chemistry and has published more than 60 peer-reviewed articles and contributed to more than 50 international conferences and several international patents and research contracts with several biotech companies.

Reena N. Murthy is currently working as a Scientist and Clinical Research Coordinator at the Institute for Drug Delivery and Biomedical Research, Bangalore, India. She has Masters in Psychology and Postgraduate diploma in Clinical Research (PGDCR). She is currently working on development of novel methods of evaluation of gustatory response/palatability of pharmaceutical and food products.

Dr. S. Narasimha Murthy is an Associate Professor of Pharmaceutics and Drug Delivery at the University of Mississippi School of Pharmacy. He has been working extensively in the area of dermal/transdermal delivery of drugs. Dr. Murthy has published over 80 peer-reviewed research papers and edited two books on topical delivery of drugs. He is the founder of Institute for Drug Delivery and Biomedical Research (www.IDBREsearch.org) in Bangalore, India.


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SPECIAL FEATURE

Excipients: Enhancing the New, Poorly Soluble APIs

By: Cindy H. Dubin, Contributor

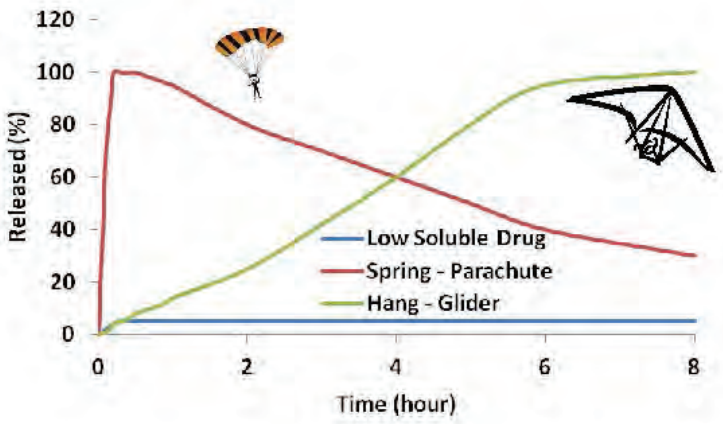
Close to 40% of the currently marketed drugs fall into the two low solubility Biopharmaceutical Classification System (BCS) categories; furthermore, if looking at the pipeline of drug entities under discovery or in development, this number increases to 80%. This trend towards low solubility will see the market for solubility enhancement excipients grow at a compound annual growth rate of nearly 13% in the period from 2014 to 2024.1 And the overall pharmaceutical excipients market is expected to be valued at $8.43 billion by 2019, up from $5.76 billion in 2013.[2]

Various techniques are being followed to achieve increased solubility of the drug compounds depending upon active pharmaceutical ingredients (API) characteristics, formulator's capabilities, and relative cost effectiveness of the strategies. Among advanced solubility enhancement technologies, the most important ones are solid dispersions and lipid solubilization. In fact, lipid excipients are the largest category of solubility enhancement excipients because of their large levels of use in drug formulations and their ability to increase the solubility of lipophilic active ingredients. Polymers come in second due to the increasing use of solid dispersion technologies.

In addition to solving solubility challenges, other issues driving the excipient market are an increasing demand for new excipients in drug manufacturing procedures, technological advancement in drug delivery systems, and the emergence of innovative drugs for the treatment of chronic diseases. Moreover, the growing generics market has increased the demand of excipients.[3]

In this exclusive *Drug Development & Delivery* report, excipient manufacturers share their insights about the role excipients play in formulating and manufacturing drugs for improved bioavailability, solubility, and delivery.

Controlled drug delivery based on EUDRAGIT® from Evonik.



Hang-glider effect for controlled release of a poorly soluble drug (Ashland Specialty Ingredients).

Ashland Specialty Ingredients—Bringing Bioavailability Enhancement to a Broader Range of APIs

It is well known that the majority of active pharmaceutical ingredients (APIs) currently in development are poorly soluble. Amorphous solid-dispersion technology has tremendous potential to increase bioavailability and absorption for APIs with poor solubility because it offers improved solubility with limited or no impact on permeability. Over the last decade, Ashland has made significant investments in understanding and developing this technology, particularly through hot-melt extrusion and spray drying.

Vivian Bi, Technical Director, Solubilization and Contract Services at Ashland explains: "A key component of a solid dispersion is the polymer system. Polymeric excipients stabilize the amorphous API in solid state then maintain its supersaturation in aqueous media. Excipients can also be used to control the release once the API is solubilized."

Ashland has experience with solid-dispersion polymers, such as copovidone and hypromellose acetate succinate, as part of a broad range of cellulose and vinyl pyrrolidone polymers. Over the years, Ashland has developed and characterized hundreds of amorphous solid dispersions. In more than 90% of the studies, a prototype with desirable stability and increased solubility was achieved.

"No one polymer system is a solution for all APIs," says Dr. Bi. "Ashland provides know-how on polymer selection and expertise to support R&D programs focused on improving solubility. In our Wilmington, Delaware, Center of Excellence, resources are available to conduct proof-of-concept studies to assess solid dispersions and determine if solid dispersion is the right approach for increasing API solubility and bioavailability."

Initial studies can be conducted with small amounts of API (~10 g) to develop several formulations and select an effective combination of drug and polymer. The study can then be expanded with a design-of-experiments model to optimize the drug load and polymer level. Once the optimum formulation is selected, Ashland scientists can provide scale-up, process development, final dosage form development, and non-GMP manufacturing services for animal toxicology or additional studies.

To demonstrate how controlled release of a poorly water-soluble drug can be achieved with solid-dispersion technology, Ashland performed a study with nifedipine. As with any formulation involving an insoluble drug, the primary challenge was to achieve enhanced bioavailability through solubility improvement, says Dr. Bi. However, in this case there was the additional challenge of sustaining that solubility for 6 hours or more. An amorphous solid dispersion (ASD) of nifedipine in pellet form was developed, resulting in extended release over 8 hours by combining copovidone and typical controlled-release grades of hydroxy-propylmethylcellulose (HPMC). This combination was processed with nifedipine in a hot-melt extruder.

Copovidone has excellent extrudability due to its thermoplasticity and HPMC is known for its ability as a crystallinity inhibitor, as well as a controlled-release polymer, Dr. Bi says.

"The aim for this type of formulation is to achieve a hang-glider effect, where the drug is not only solubilized in the immediate term, but also achieves continued release and sustained supersaturation for an extended time," explains Dr. Bi. "Stable ASDs were achieved at 20% drug loads. In the next phase of the case study, nifedipine release rate was effectively controlled while maintaining supersaturation by varying the HPMC molecular weight."

BASF—A Focus on Highly-Functional Excipients

BASF offers a range of excipients for immediate and modified release, polymers and solubilizers, as well as excipients and solvents for skin delivery applications. Examples of immediate-release excipients include binders and disintegrants (e.g. water soluble Povidones or Kollidon® grades), water insoluble Crospovidone or Kollidon® CL grades and Copovidone or Kollidon® VA64 and VA64 Fine), and the Kollicoat® IR-based coating systems. Modified-release excipients are derived from a range of chemistries and properties such as Kollicoat® SR30 and Kollidon® SR for controlled release, Kollicoat® MAE30DP/100P for enteric, and Kollicoat® Smartseal for taste-masking as coating polymers for matrix tablets, granules and soft gel capsules, and mannitol-based Ludiflash® for orally dispersive tablets.

Solubilizers are also derived from a range of structures with some having the lipophilic hydrophilic balance (HLB) values 12 or higher. For example, Soluplus® with HLB value of 14 is derived from PEG, which is grafted with vinylcaprolactame and vinylacetate, while Kollidon VA64 (HLB 0) is a random copolymer comprised of vinylpyrrolidone and vinylacetate (60:40). Both these excipients are used as solubilizers for poorly soluble compounds offering unique advantages over many existing polymers in solid dispersions.

"Excipients play an important role in the formulation and manufacturing of pharmaceutical dosages, functionally required either as fillers, binders, coatings, or solubilizers to improve the solubility and enhance the bioavailability of drugs," says Shaukat Ali, PhD, Technical Support Manager, BASF.

Several excipients have "high functional" roles, meaning if used as binders, they could also be used as solubilizers or vice versa. For instance, Copovidone (Kollidon VA64), which is used as a wet/dry binder, can also be used as a solubilizer for poorly soluble compounds in solid dispersions. "These unique interchangeable characteristics are critical in selecting the appropriate excipients to design and develop the desired formulations to alleviate API-excipient interactions and enhance shelf life while maintaining the integrity and efficacy of pharmaceutical dosages."

The use of BASF excipients can be best demonstrated in a marketed HIV drug, comprised of two individual APIs, Lopinavir and Ritonavir (Kaletra®). Both are poorly soluble drugs and are marketed in soft-gel capsules and tablets. The patients have to take 6 capsules per day while the solid dispersion formulation requires only 4 tablets per day. Consequently, the pill burden on a patient is less with tablets than soft-gel capsules. Kaletra contains Polyoxyl 35 castor oil in soft gel as self-emulsifying system (SEDDS) while the tablet formulation contains Copovidone as solid dispersion/solution. Another example is Norvir® soft gel, which contains Polyoxyl 35 castor oil, while the tablet contains Copovidone.

"These examples demonstrate the applicability of two high functional excipients as good solubilizers not only in tableting but also in soft-gel formulations," says Dr. Ali.

Colorcon—Creating Economical, Low Friability Tablets for Film Coating & Packaging

In solid oral dose development, API compatibility will drive the selection of the excipient. Tablets are still the most common solid oral dosage form for many reasons, including ease of manufacturing, convenience for the patient, accurate dose administration, and good stability.

Excipient choices for a formulation are typically driven by functionality requirements and compatibility with the API. For more

than 50 years, Starch 1500® partially pre-gelatinized maize starch has had marketed product success in innovator, generic, and OTC market segments across more than 80 countries. When used as secondary excipient, typically alongside microcrystalline cellulose (MCC), Starch 1500 delivers low-moisture activity with good tablet hardness and low friability, which are critical for film coating and packaging of the final tablet, says Deborah Taylor, Global Market Communications, Colorcon.

Film coating of tablets provides benefits for both product development and manufacturing. For the formulator, film coating is included to improve product stability and final product quality, while attaining in-use shelf life. For the manufacturer, film coating strengthens the dosage form, enables improved packaging efficiency, and prevents cross contamination. For the patient, a film coating improves compliance through enhanced swallowability and palatability, and allows for better product differentiation and minimizes medication errors through color and appearance.

"Starch 1500 is manufactured exclusively for the global pharmaceutical industry and provides the formulator with an economical binder and disintegrant option for direct compression, stability for moisture-sensitive drugs through low-water activity, effectiveness for low-dose drugs, and process flexibility for granulation, says Ms. Taylor.

SIDEBAR

NSF International—A New Standard for Pharmaceutical Excipients

NSF International recently published the first American National Standard for pharmaceutical excipients: NSF/IPEC/ANSI 363 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients. This consensus-based standard incorporates multiple regulatory and industry requirements into a single, rigorous standard for the manufacturing and distribution of pharmaceutical excipients. The new standard is designed to help pharmaceutical companies verify GMP compliance and strengthen safety and quality throughout the supply chain.

"It's an important advancement for an industry that once virtually ignored excipients, even though they typically make up 70 to 90% of the volume of most pharmaceutical formulations," says Maxine Fritz, Executive Vice President of Pharma Biotech, NSF Health Sciences.

The new standard raises the bar for excipient manufacturers. Pharmaceutical manufacturers should now require all of their excipient manufacturers to meet or exceed the NSF/IPEC/ANSI 363 standard. Manufacturers of finished pharmaceutical products can do this by auditing their individual excipient manufacturers annually – a daunting task when you consider the number of excipients used in any given formulation. It should be noted that auditing is equally challenging for excipient manufacturers, who may need to host hundreds of audit teams a year.

Auditing excipient manufacturers presents a special challenge because most excipients are manufactured in bulk and sold to many industries, not just the pharmaceutical industry. The pharmaceutical industry will need to work closely with its excipient manufacturers to ensure they are manufacturing ingredients with the appropriate GMPs in mind.

Fortunately, there is a better way, says Ms. Fritz. In addition to collaborating on the development of the new standard, NSF International developed an excipient certification program. Instead of hosting hundreds of audits a year, excipient manufacturers can now apply for certification from NSF International. Manufacturers certified to the NSF/IPEC/ANSI 363 standard demonstrate that their excipients are manufactured to the appropriate GMPs for pharmaceutical use. "We believe certification will become a competitive advantage for excipient manufacturers and should help eliminate the nearly continuous audit process many excipient manufacturers endure annually."

"This will be an interesting development for excipient manufacturers," says Christopher Wilcox, PhD, Vice President, Sales & Marketing, Pfanstiehl, Inc. "It can only be good for pharma in the long term, as higher quality standards will inevitably translate to safer products for patients. Pfanstiehl has been manufacturing cGMP, injectable-grade excipients for decades in an ICH Q7 compliant environment. We have expected and prepared for these changes for many years and see the industry moving towards treating excipients more and more like APIs, as they should be. The days of sourcing food-grade excipients for pharma applications is coming to an end."

And Shaukat Ali, PhD, Technical Support Manager, BASF, says: "Implementation of recent NSF international guidelines means more empowerment of regulatory authorities and drug manufacturers. The NSF international guidelines also provide increased transparency with excipient manufacturers while minimizing adverse health effects and protect human health, and safety of the drug products worldwide. BASF is committed to adherence to stringent controlled policy by the regulators and other auditing agencies by implementing the validated method standards and protocols to test and qualify the excipients to meet current monographs and follow the guidelines concurrent with the changes in monographs."

Pharmaceutical companies purchasing excipients certified to the NSF/IPEC/ANSI 363 standard can elect to purchase Certification Audit reports. The NSF Excipient Certification Program offers the report purchaser the benefit of initial GMP certification and annual surveillance by expert auditors against the NSF/IPEC/ANSI 363. "Certification combined with an independent audit report provides additional assurance of excipient quality," says Ms. Fritz.

Evonik—Software Screens Polymers to Identify the Best

Partly due to the use of high-throughput screening methods in the drug discovery stage, there has been a recent surge in the number of poorly water-soluble drug substances under evaluation (more than 70% of newly discovered actives). As a result, pharmaceutical formulation development scientists have adopted hot-melt extrusion (HME) and spray-dried dispersion (SDD) techniques in combination with polymeric excipients as the main approaches to improve the aqueous solubility of these APIs. HME and SDD techniques break the strong crystal lattices of poorly soluble drugs under high temperature/shear or through solvation of the API in a highly polar solvent, respectively. The amorphous active is then stabilized in the glassy polymeric excipient matrix through polar, dispersive, and/or ionic interactions, as well as possible hydrogen bonding between the functional groups on the polymer and the active.

When selecting excipients for solubility enhancement through amorphous solid dispersion stabilization, the desired strong interaction between the polymer and the active is often undermined by the random mixing of these components.

Solubility parameters have been used since the early 1900s to identify good solvents for small solutes and polymers. When forming solid dispersions, the solvent and solute roles are inversed as the smaller solute molecule (API) is dissolved in the larger macromolecular polymeric solvent. It is essential to build selection quality into the polymeric excipient-drug combination screening studies by considering the individual molecular structures and potential interactions. Similar to crystalline molecules like table salt and sugar that dissolve in water through ionic interactions and hydrogen bonds, when polymer and active are capable of such bonds, the formation and stabilization of amorphous solid dispersions are enhanced. Hence, pharmaceutical-grade excipient polymers like poly(meth)acrylates (EUDRAGIT®), cellulosics (HPMC, HPC, HPMCAS, HPMCP), vinylpyrolydones (povidones and copovidones) and others should be included in the initial screening studies.

Evonik has been manufacturing EUDRAGIT poly(meth)acrylate polymers (anionic, cationic and neutral) for more than 60 years. This family of polymers has been used extensively in thousands of pharmaceutical product formulations for controlled-release coatings or in matrix applications.

"In addition to hydrogen bonding, polar attraction, and dispersive force potential, EUDRAGIT polymers offer ionic interactions with free-base and free-acid drugs or salts, allowing unique possibilities for solubility enhancement of poorly water soluble actives," explains Dr. Firouz Asgarzadeh, Director Technical Services, Pharma Polymers and Services, Health Care Business Line, Evonik.

Evonik has developed a platform called Melt Extrusion Modeling and Formulation Information System (MemFis™) that uses solubility parameter calculations and hydrogen bond formation probabilities to screen 30 different excipient polymers to identify the best 2-3 first experiments for developing solid dispersions.

Evonik has applied MemFis to numerous customer projects. In one recent case study, the customer initiated the screening studies with random mixing of polymers and the active with no success in improving the solubility of a poorly soluble active. The contract research organization that the customer was using referred the client to Evonik to evaluate the MemFis tool. The results from MemFis identified a cationic polymer that was overlooked in the initial random mixture study. The use of the identified polymer resulted in the successful enhancement of API solubility. "The strength of this platform is the unbiased screening of all commercial polymers and not just Evonik polymers," says Dr. Asgarzadeh.

Fuji Health Science, Inc.—Developing Unique Excipients to Overcome New Challenges

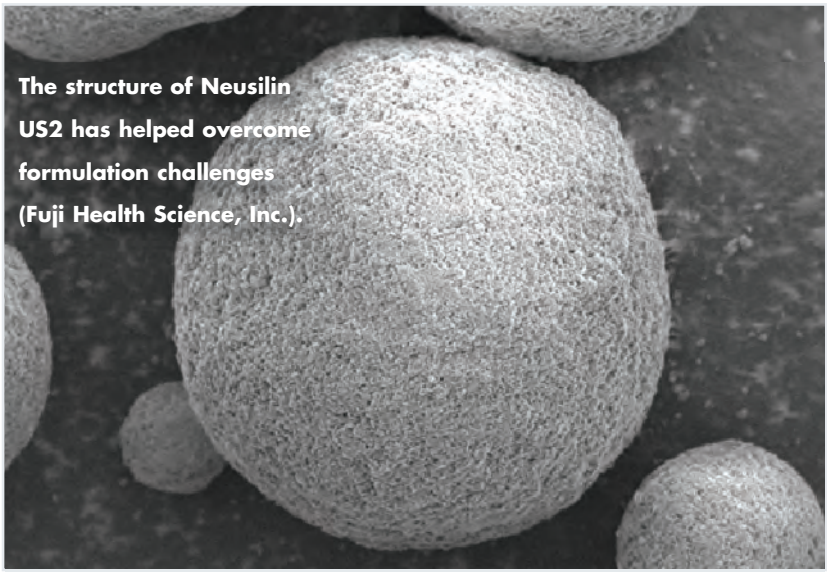
In light of recent solubility and bioavailability challenges, formulators are turning away from conventional fillers or binders and utilizing novel and unique excipients that offer enhanced functionality. A lipid-based

delivery system, such as self-micro emulsifying drug delivery systems (SMEDDS), is a promising approach to enhance bioavailability of poorly water-soluble drugs, says Xi Han, PhD, Technical Sales and Support, Excipients, Fuji Health Science, Inc.

One challenge in commercializing this delivery system, however, is that it requires the product to be in a liquid form, such as a liquid-filled capsule or solution. This limitation could result in poor patient compliance or, in the case of liquid-filled capsules, the potential for incompatibilities between the active and the capsule shell.

There is a need for inert carriers to solidize lipid-based delivery systems or convert them to a powder and ultimately tablet form. Two of Fuji's specialty excipients, Neusilin® and Fujicalin®, are made through a proprietary powdering technology, resulting in a high specific surface area with a mesoporous structure. This unique structure provides a high oil adsorption capacity and can convert the lipid-based delivery system into a freely flowing and compressible powder that maintains enhanced bioavailability.

In one example, explains Dr. Han, a customer was looking for an alternate dosage form for a lipid-based delivery system. Their initial trials with a liquid-filled soft gel had stability failures due to an incompatibility between the drug and capsule shell. Various carriers were evaluated to solidize the lipid and Neusilin was determined to offer the best performance in terms of drug loading, dissolution, and tablet hardness without the need for additional binders.



The structure of Neusilin US2 has helped overcome formulation challenges (Fuji Health Science, Inc.).

Gattefossé USA— Lipid Excipients for Oral Bioavailability Enhancement

Among the fast-developing approaches that address the challenges presented by the vast number of existing and emerging drug entities is lipid-based drug delivery (LBDD). The field surrounds novel excipients and formulation technologies based primarily on the function of fatty acids, fatty acid esters, and their assemblies. In recent years, the field has witnessed significant development of methods and predictive tools resulting from industry/academia-wide collaborations that help the design, characterization, and evaluation of LBDD systems in ways that may not have seemed possible a decade ago.

Successful design of LBDD systems requires a clear understanding of two sets of factors: the properties and challenges unique to the drug candidate; and the physico-chemical and bio-pharmaceutical role of lipids in the formulation, says Jasmine Musakhanian, Scientific & Marketing Director, Pharmaceutical Division of Gattefossé USA.

Lipid excipients are generally considered for their ability to solubilize/disperse the drug molecule in the dose, but more importantly for their impact on the processes that follow *in-vivo*. The primary mechanism for lipid formulation is micellization in the gut milieu by self-emulsification of surface-active lipids and or by digestion of the oily components by bile salts and pancreatic enzymes.

The micellization process leads to formation of lamellar/multi-lamellar micelles with even greater solubilizing properties preventing the active drug from falling out of solution; ameliorating the drug's affinity for the

Liquid formulation of solubilization in aqueous media (Gattefossé).

aqueous monolayer lining the intestinal enterocytes; and facilitating the subsequent passage across the lumen due to enhanced membrane fluidity.

Examples of Gattefossé self-emulsifying excipients are Labrasol®, Labrafil® M1944, and Gelucire® 44/14, which form fine dispersions (20-300 nm) once in contact with aqueous media. "A key aspect of excipients like Labrasol and Gelucire 44/14 is their ability to solubilize/disperse the active in the GI milieu and to improve drug permeability by inhibiting/saturating the enterocyte-based transporters," says Ms. Musakhanian. "This is particularly useful for drugs that have permeability issues."

Other products like Gelucire® 50/13 and 48/16, due to their solid-state characteristics, are suitable for preparation of solid dispersions by melt extrusion or spray atomization for preparation of self-emulsifying solid dosage forms.

Another important bioavailability enhancing mechanism associated with lipid formulations pertains to the biopharmaceutical role of excipients comprised of long-chain fatty acids (LCFA) like oleate and linoleate. The latter associate themselves with chylomichron synthesis and lipoprotein transport via the lymph, and therefore, are helpful for promoting lymphatic absorption of highly lipophilic drugs that would otherwise be eliminated pre-systemically in the liver. The approach is most effective for delivery of drug actives with log P>5 and solubility of >50 mg/L in triglycerides. Examples of Gattefossé excipients with LCFA's are Maisine™ and Peceol™.

As excipient choices are often linked to a processing technology, Gattefossé supports its products with application data and guidelines, including direct compression, spray atomization, melt-granulation, fluidized bed coating, and melt-extrusion processes.

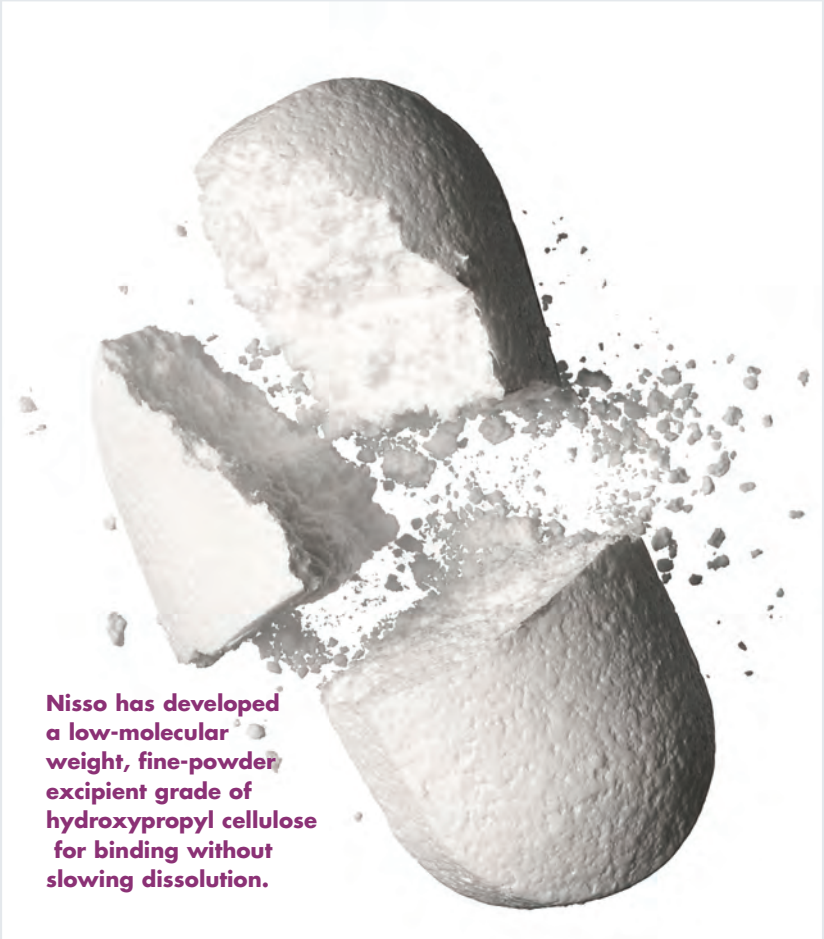
Nisso—Manufacturing a Unique Grade of HPC

Nisso has recently announced completion of a hydroxypropyl cellulose (HPC) manufacturing capacity expansion at its facility in Nihongi, Japan. The expansion was completed to respond to the growth in worldwide demand for NISSO HPC. The production facility has multiple lines that operate independently to provide increased supply security.

"Customers appreciate the 5-year shelf life and low lot-to-lot variability of NISSO HPC, while a robust global warehouse and distribution network provides responsive supply to customers with short lead times," says Mr. Kenji Sugisawa, Global Manager of NISSO HPC.

NISSO HPC is a highly efficient excipient, traditionally used as a tablet binder in pharmaceutical and nutraceutical products, but with growing application in spray drying, hot-melt extrusion, and film formation.

A particular focus of the



Nisso has developed a low-molecular weight, fine-powder excipient grade of hydroxypropyl cellulose for binding without slowing dissolution.

expansion was to support growth of the new grade called NISSO HPC SSL-SFP, which stands for Super Special Low viscosity, Super Fine Powder hydroxypropyl cellulose. "This grade is unique in the market, as Nisso technology was developed to create the lowest molecular weight of HPC (approximately 40,000 Daltons) for binding without slowing dissolution," explains Mr. Sugisawa.

The SFP grinding technology is also used to produce an extremely fine powder (d50 approximately 20 microns) for high binding efficiency, while maintaining adequate power flow. SSL-SFP utilizes this combination of low molecular weight and super fine powder to create a new level of performance in HPC.

One customer recently reported using SSL-SFP to rescue a product launch. They found capping problems on scale up and adding 1% SSL-SFP to the formulation resolved this issue without costly and lengthy reformulation," says Mr. Sugisawa. "Other customers have reported using SSL-SFP to reduce tablet size for reformulation projects by replacing 15% MCC with 3% HPC."

A harmonized standard for hydroxypropyl cellulose has been formally approved by the USP Monographs, European Pharmacopeia, and the Japanese Pharmacopeia on December 1, 2014. NISSO HPC produced after that date will conform to the harmonized standard and will make it easier for customers to develop a single product formulation that meets global regulatory requirements, he says.

Pfansthiehl—Carbohydrate-Based Excipients Stabilize & Protect the API

Carbohydrate-based excipients such as trehalose, sucrose, and mannitol enable formulation scientists to stabilize large and small molecule injectable therapeutics that would otherwise not make it to the clinic due to low solubility and/or bioavailability. The majority of commercialized injectable drugs depend on this class of excipients as stabilizers, tonicifying agents, or bulking agents.

Complex large molecules and cells are often prone to aggregation, denaturation, and/or oxidation. A key function of carbohydrate-based excipients is to stabilize and protect the active ingredient to make sure it reaches the patient, having the same molecular conformation, the same bioavailability, and the same potency every time. In injectable formulations, this means that the manufacturing process used to produce these critical excipients must be exceptionally robust, free of contaminants, low in elemental impurities, and strictly monitored and controlled. High-quality excipients are essential for consistent formulations, as they are almost always present at much higher

Pfanstiehl's Class 100,000 cGMP drying/packaging area.

concentrations than the active itself.

Pfanstiehl manufactures parenteral-grade excipients such as trehalose, sucrose, mannitol, sorbitol, and maltose for use in liquid and lyophilized applications where high quality, cGMP-produced components are required. "Trehalose is particularly effective as a stabilizer for complex molecules and cells under the high stress conditions that most formulations must endure," explains Christopher Wilcox, PhD, Vice President, Sales & Marketing, Pfanstiehl, Inc.

Trehalose and sucrose are each widely used in commercial monoclonal antibody (mAb) formulations and have also proved beneficial for ADCs, vaccines, and cell therapy applications. Mannitol is widely used as a lyoprotectant and bulking agent in injectable applications. Sorbitol has unique properties that make it an interesting choice for protein and vaccine stabilization.

For one client, an ADC formulation was stabilized best with sorbitol. However, the impurity profile and lot-to-lot inconsistency of the sorbitol excipients available were not suitable for the injectable application. Therefore, the team was going to have to completely reformulate the product or put the program on hold. "We assured the client that this would not be an issue with a cGMP-produced sorbitol excipient, which will be delivered to the client shortly," says Dr. Wilcox.

Another client was having difficulty developing a platform formulation for stabilizing a range of monoclonal antibodies. Dr. Wilcox says: "As soon as the formulation team became familiar with Pfanstiehl's cGMP-produced trehalose excipient, they were able to use it across the board as a stabilizer of choice, and gained great peace of mind after seeing their quality issues decrease as a result." ◆

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Drug Development
EXECUTIVE

Franco Negron
Senior VP, Drug Product Services, North America
Patheon

Patheon
Performance the World Over®

Patheon: Comprehensive Development & Manufacturing Solutions for the Entire Drug Development Cycle

Patheon delivers a combination of unrivaled quality, reliability, and compliance, with a reputation for scientific and technical excellence to customers in the pharmaceutical and biopharma industries. With more than 8,000 employees worldwide, Patheon has a comprehensive set of solutions to help customers of all sizes satisfy complex development and manufacturing needs at any stage of the pharmaceutical development cycle. Armed with the best scientific minds, a reputation for operational excellence, and innovative solutions like the Patheon OneSource™ supply chain offering, Patheon has become a trusted partner to its customers, helping solve their complex development and manufacturing challenges. *Drug Development & Delivery* recently caught up with Franco Negron, Patheon's Senior Vice President of Drug Product Services in North America, to discuss his company's business strategy, two recent acquisitions and integration plans, the role biosimilars play in Patheon's business, and significant trends driving the pharmaceutical industry over the next few years.

"We have had a series of multiple mergers and acquisitions, bringing five companies into the Patheon network in the past 3 years. The first was in 2013 with the acquisition of Banner Pharmacaps, followed by our merger with DSM Pharmaceutical Products and the acquisition of Gallus Biopharmaceuticals in 2014, and most recently, the IRIX and Agere deals in March 2015."

Q: What is Patheon's current business strategy?

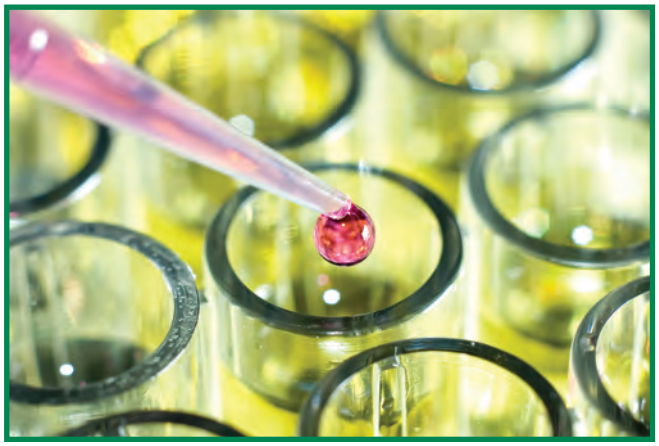
A: Patheon's success and position as a global industry leader is built on a four-pronged business strategy: to strengthen core operations, sell the business differently, enter logical adjacencies, and drive industry consolidation. From top leadership down to line employees, the business is focused on performing well for customers, as measured by the customers. Products must be delivered right the first time and on time. Throughout the Patheon organization, there is a remarkable focus on providing value to customers, who increasingly demand simplified supply chains and a wide range of services. Patheon's ability to stay on top of customer needs and industry trends has led to multiple mergers and acquisitions that have expanded the company's breadth of services and capabilities, while also more than doubling its top-line in less than 2 years, making it the industry leader with a reputation for high quality.

Q: Patheon recently announced two acquisitions within a week of each other. Can you tell our readers more about these deals?

A: The acquisitions of IRIX and Agere align with Patheon's strategy to enter into logical adjacencies. As customers increasingly seek a more simplified supply chain, the logical business model is to build a breadth of services through the full life cycle of a product, from development to commercialization. The company is always looking to add scale and expand its product portfolio while maintaining a focus on quality.

The acquisitions of IRIX and Agere further reinforce our leading position because we are now armed with integrated solutions to meet customers' most complex challenges. Through these deals, we can offer more advanced formulation services, strengthen the company's number one Product Development Services position, gain comprehensive API development services, amplify our North American presence, and enhance the Patheon OneSource offering.

Patheon OneSource focuses on driving value through simplicity, speed, and expertise. Patheon's range of capabilities bridges the gap between product development and commercialization, giving us the ability to take customers through the entire life cycle of a product and every piece of the value chain. Patheon engages in partnerships and acquisitions that support business strategy through both organic and inorganic growth opportunities.



Q: How do you manage integrating two companies into the Patheon network at one time?

A: We have had a series of multiple mergers and acquisitions, bringing five companies into the Patheon network in the past 3 years. The first was in 2013 with the acquisition of Banner Pharmacaps, followed by our merger with DSM Pharmaceutical Products and the acquisition of Gallus Biopharmaceuticals in 2014, and most recently, the IRIX and Agere deals in March 2015.

Patheon has arrived at an integration formula that is robust, repeatable, and highly structured, allowing for seamless transitions for employees, customers, and suppliers. Experienced teams lead the integration process, with a strong focus on keeping employees informed and tuned in to the company's commitments to a unified culture. Our culture has five key aspects: 1) provide industry-leading customer experience; 2) be the highest quality, most efficient, and flexible provider; 3) deliver the best technical and scientific solutions to enhance product value; 4) create a culture of engagement, accountability, and a commitment to excellence in all that we do; and 5) operate our business in a compliant, safe, disciplined, responsible, and ethical fashion. This hands-on culture has been adopted by each acquired company and more than 8,000 global employees, and we are replicating this success with our IRIX and Agere colleagues.

Q: What role do/will biosimilars play in Patheon's future?

A: Biosimilars are part of the industry's future. We foresee a series of large market biosimilars being approved in the next few years. Cell culture manufacturing processes are more productive now than they were 15 to 20 years ago, and the scale and capacity required to manufacture these has decreased significantly. While biosimilars were historically manufactured in-house, outsourcing is now increasingly gaining favor. Patheon has accumulated expertise and experience working with innovator products for the past 10 years, as well as biosimilars in the past few years, so we are extremely well-positioned to take advantage of this opportunity with biosimilars.

Q: What trends do you see driving the pharmaceutical manufacturing industry in the next few years?

A: Outsourcing and consolidation will continue to influence the CDMO industry in the coming years. Customers seek reliable partners with broad capabilities, scalability, and excellent quality track records. As a result, the CDMO industry will likely see the same consolidation and outsourcing that contract research organizations experienced years ago. The market is moving more and more toward consolidation, and only the best performers will become long-term partners to the pharma industry.

Outsourcing was historically done for pricing reasons. However, now the decision to outsource, whether by big or small or emerging pharma companies, is considered a more strategic proposition to add value through seeking smart business solutions and partners to gain access to new technologies, faster cycle times, and enhanced performance.◆

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CLINICAL TRIALS

Accelerating the Clinical Trials Process

By: Tom Johnson

INTRODUCTION

The drug research and development process is a marathon. The journey from concept to FDA approval to availability typically takes upward of a decade and can cost somewhere in the neighborhood of a billion dollars. Pharmaceutical organizations are faced with time and cost complexities throughout the process, including Phase I through Phase IV clinical trials.

Reducing the time and cost of the R&D process as a whole, and of clinical trials in particular, is of paramount importance. Why is this so critical? The more companies must invest, the greater their financial exposure and risk. The longer the process takes, the greater the odds the company making the investment loses its competitive advantage. At a minimum, the window between product market introduction and patent cliff is narrowed, limiting the revenue stream before other manufacturers can enter with generics. Collectively, we should be encouraging the development of new life-altering and life-saving drugs and therapies. Instead, the clinical trials experience may discourage industry players from achieving that noble objective.

IDENTIFYING & UNDERSTANDING CLINICAL TRIALS CHALLENGES

None of this is news to pharmaceutical companies. In fact, since the turn of the century, they have executed several initiatives to cut cost and schedule. Organizations have reduced headcount, focused on process efficiency, and implemented internal collaboration portals to slash operating expenditures without sacrificing quality or compliance. They also have embraced a new business model. Rather than conducting the R&D process in-house, pharmaceutical companies are teaming with external partners to leverage their expertise and accelerate the process.

Clinical trials are a natural fit for the external partner business model, allowing companies to take advantage of the strengths of contract research organizations, laboratories, investigators, vendors, trial sites, and others. Working with these partners requires a robust collaborative operating environment. Organizations have tried extending their internal collaboration portals to address this need, with little success. The gap between internal and external collaboration is wide. As a consequence, these organizations have assumed responsibility for administrative activities and functional implementations that must be managed by IT and business owners – resulting in an increase in the very expenditures they were looking to avoid.

Organizations should take an alternate track in order to put an efficient and effective external partner collaborative environment in place. Understanding and identifying the collaborative challenges that accompany external partner-based clinical trials helps organizations recognize how to proceed to overcome those challenges.

FINDING THE RIGHT PARTNERS, INCLUDING VENDORS, SITES & PARTICIPANTS

Before a clinical trial can get off the ground, pharmaceutical companies must determine which partners and patients are qualified candidates for consideration. Viability can be a function of experience, certifications, location, financial status, compliance record, stage of illness, and other factors. Rather than conduct this background investigation before every trial, organizations need an updated registry they can access to kick-start their due diligence for partner and patient evaluation and invitation.

SELECTING & SECURING PARTNERS

The bid and proposal process, regulatory and legal requirements, and execution of master service agreements and statements of work mean the effort to bring partners into the fold can take months. In addition, convincing CROs, investigators, or sites to participate in a clinical trial is not a given because these resources possess expertise that is in demand. Successfully closing deals with partners requires making the negotiation as painless as possible. One way to do so is to make it easy for potential partners to share and sign documents throughout the negotiation. Standardized and streamlined documents, processes, and applications, along with the incorporation of new technologies like electronic data capture, also are valuable tools that minimize the administrative burden and convince prospective partners that their time can be optimized.

ON-BOARDING ORGANIZATIONS & INDIVIDUALS

Clinical trials activities necessitate the sharing of assets (applications, documents, and data) amongst pharmaceutical companies and their external partners and trial participants. Establishing "connections" that create communications paths between parties is a precursor to collaboration. How these connections are implemented directly affects the level of effort and cost required to build and maintain them. This consideration becomes particularly important as the number of partner organizations rises.

In addition, individuals must be provisioned so that they receive user accounts that allow them to access the assets of partners. Organizations have several important decisions they must make in this regard. Does each asset owner maintain its own directory of external users, or is there a central repository for all users across the clinical trial community? Are user accounts provisioned on request, or does an identity proofing event have to precede provisioning? What kind of credentials must users present in order to access assets? Is username/password sufficient, or is a stronger credential, such as a common access card or one-time password token, appropriate? The answers to these questions significantly impact on-boarding time and asset security.

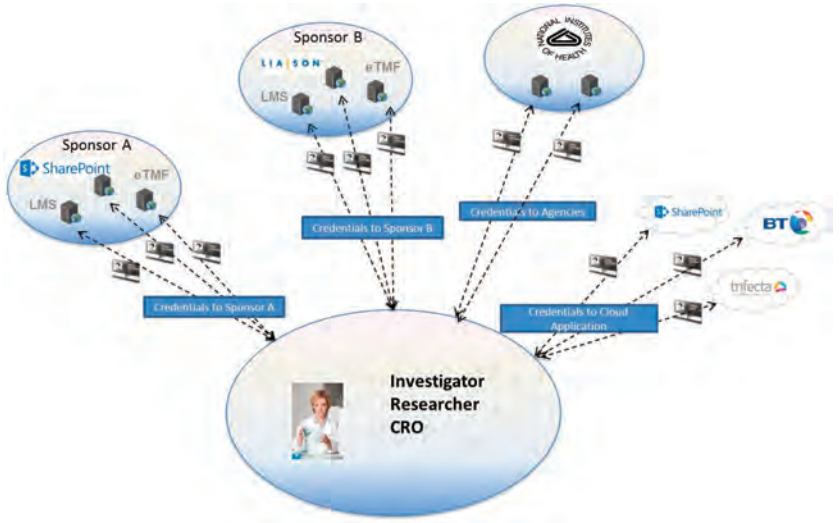
CONTROLLING ACCESS

Before individuals can collaborate with their clinical trials peers by accessing assets, they must be authenticated to help verify their identities and prevent unauthorized intrusion. Asset owners need a mechanism for assigning privileges and permissions, validating credentials, and enforcing access rules, which may need to change over time as an individual's role and responsibilities evolve on current and future clinical trials.

DEVELOPING & EXECUTING PROTOCOLS

Defining the protocols that dictate how clinical trials will be run affects decisions spanning everything from on-boarding/access and patient reporting to documentation and process standards and collaboration tools/technologies. Reaching consensus mandates a high level of internal and external coordination amongst discovery teams, regulatory and health authorities, medical and clinical personnel, and others. Organizations must look for ways to shorten what has traditionally been a lengthy process. Options include dynamically created and deleted team

FIGURE 1



Multiple Trials, Multiple Credentials

sites for temporal information sharing and implementation of electronic or digital signatures to replace printing, ink signing, and mailing of hardcopy documents.

ACCOUNTING FOR GROWTH

Scalability is a key consideration pharmaceutical companies must consider with respect to clinical trial time and cost. Growth is multi-faceted. The number of partners and individuals involved in a clinical trial can become quite large, making on-boarding and controlling access to assets increasingly difficult. Meanwhile, companies, their partners, and individuals all may be participating in multiple trials simultaneously. In this instance, investigators and patients may have to maintain several credentials and master different technologies, applications, and processes, as depicted in Figure 1. Collectively, these circumstances raise risk and slow efficiency. Organizations must look for ways to effectively accommodate growth without impacting performance.

BALANCING SECURITY & PRODUCTIVITY

Clinical trials require participants to share sensitive information with one another. These transactions must occur in compliance with government, industry, and corporate standards, regulations, and policies – without compromising the intellectual property that is integral to the R&D process. At the same time, collaboration cannot be so onerous that partners balk at joining the trial or individuals lose productivity. Organizations must strive for a collaborative operating environment that allows partners to connect quickly, empowers asset owners to control access, provides a simple yet compelling user experience, and accounts for the growth and dynamic needs of the community supporting clinical trials.

FACILITATING EXTERNAL PARTNER COLLABORATION WITH AN IDENTITY HUB

Clearly, building and maintaining a collaborative operating environment that addresses the challenges that accompany the conduct of clinical trials is a significant undertaking. Establishing connections, provisioning organizations and individuals, controlling access, and sharing applications, documents, and data require investments of IT resources, capital expenditures, and operating expenditures. If pharmaceutical companies and their partners attempt to create the necessary infrastructure and systems on-premises to complete these and other tasks to conduct clinical trials in a secure, seamless collaborative environment, the time and budget commitments are reminiscent of the legacy do-everything-yourself business model.

Instead, companies should look to the cloud, where they can eliminate redundancies and promote community. A hybrid cloud offers the openness and scalability of a public cloud, along with the security and control of a private cloud. A hybrid cloud-based identity hub can serve as the centerpiece for the clinical trials community of pharmaceutical companies, external partners, patients, and other participants.

The concept of the identity hub is straightforward. Rather than spending time and money putting point-to-point connections in place with all external partners with whom they must communicate (an endeavor that scales horribly), organizations simply connect once to the identity hub, which provides the communications path to all partners.

"If pharmaceutical companies and their partners attempt to create the necessary infrastructure and systems on-premises to complete these and other tasks to conduct clinical trials in a secure, seamless collaborative environment, the time and budget commitments are reminiscent of the legacy do-everything-yourself business model. Instead, companies should look to the cloud, where they can eliminate redundancies and promote community. A hybrid cloud offers the openness and scalability of a public cloud, along with the security and control of a private cloud."

Likewise, organizations connect their relevant applications to the identity hub one time, rather than relying on multiple portals or other connection strategies.

The identity hub, in conjunction with portal service partners, also can host a registry that includes connected organizations, applications, and individuals, as well as information about vendors, sites, and patients that may not yet have participated in a clinical trial but are part of the larger scientific/R&D community. The registry contains attributes for each entity, which can span everything from certifications and geographic location to privileges and permissions for application and information access. Thus, the identity hub is perfectly positioned to work with asset owners to enforce the rules that govern access to the community's assets by individuals involved in clinical trials.

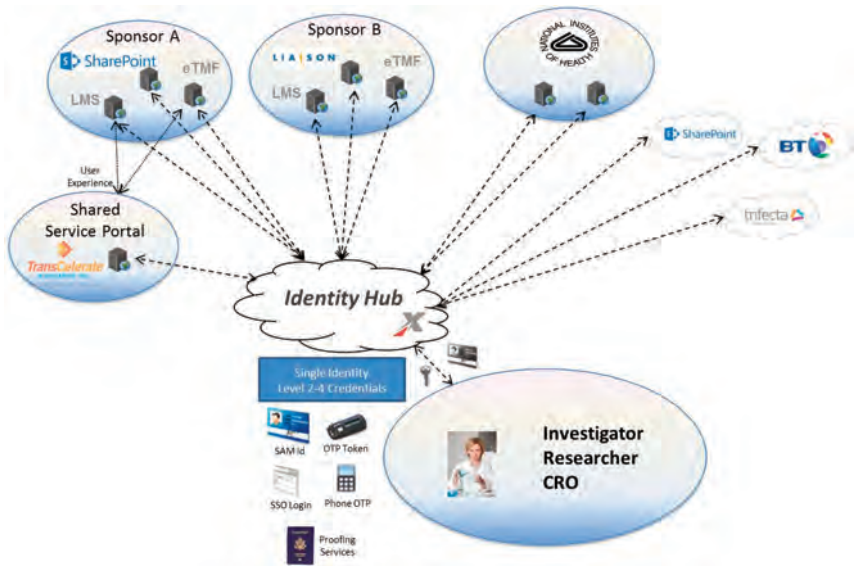
WHO OWNS THE IDENTITY HUB?

Because the identity hub resides in the cloud rather than on-premises, pharmaceutical companies need not assume the responsibility for implementing and operating it. A viable option is to turn to an identity hub provider, who can deliver the solution as-a-Service. As a result, the identity hub provider takes the lead on establishing partner connections, provisioning organizations and individuals, and maintaining the registry or central repository that plays a key role in vendor and site selection, as well as application and information access throughout a clinical trial.

To ensure that the identity hub is aligned with regulatory and business requirements, organizations utilizing the hub service should participate in its governance. Through a delegated administration process, asset owners configure the identity hub with the privileges and permissions they wish to assign to clinical trial participants. The identity hub service encapsulates these governance rules and enforces them when individuals request access to these assets. Access requests occur when individuals present credentials to validate their identities. These credentials have been issued to individuals by an identity provider, which could be a member organization of the community, a trusted third-party connected to the identity hub, or the identity hub provider itself. The identity hub provider authenticates credentials, where the accepted types of credentials are defined by the community.

Given the nature of documentation and information shared during clinical trials, identity providers should be issuing strong credentials that align with the National Institute of Standards and Technology's 800-63 regulations. These credentials only are provided to individuals with an existing business relationship with an inviting partner, or

FIGURE 2



Multiple Trials, Single Credential Via Identity Hub

after the completion of an identity-proofing event, which can be conducted either in-person or remotely via webcam or an independent party like Experian. During these events, individuals confirm their identity by accurately answering personal questions and/or presenting an official government document like a passport or birth certificate. To ensure credentials meet regulatory compliance and are appropriate for use in conjunction with clinical trials, the identity provider should be certified as a Credential Service Provider by the SAFE-BioPharma Association.

Once individuals receive their credential, they can use it to conduct all clinical trials business through the identity hub, as illustrated in Figure 2. One credential significantly lessens the likelihood of loss or compromise and provides an avenue for audit of access history. It also allows for a single sign-on user experience. After the identity hub provider authenticates the presented credential, a portal service can display a dashboard for the individual that shows which applications are approved for access, which clinical trials the individual is working, and other relevant information. In fact, as use cases evolve and an individual's role and level of security requirements change, the identity hub provider can take advantage of the dashboard to assist individuals through an automated step-up process to upgrade their one credential. By making engagement easier on individuals such as investigator site personnel, clinical trials productivity is enhanced.

The identity hub provider can deliver additional value to the community by connecting its own or trusted third-party applications to the identity hub and making them available to organizations and individuals conducting clinical trials. These applications can raise security and efficiency throughout the clinical trials process. For example, collaboration solutions offer encryption at-rest and in-transit, document version control, dynamically created team sites, and credential-controlled access to real-time audio/video conferences. The identity hub provider can leverage credentials to provide SAFE-BioPharma-compliant electronic signature functionality that empowers clinical trials participants to automate the exchange of reports, assessments, and other documents that require signatures. This capability improves security by creating a clear audit trail while simultaneously keeping trials moving by eliminating the need to print, sign, and send documents.

FROM CONCEPT TO ADOPTION

The identity hub is not a theoretical construct; it is being used today by pharmaceutical companies to help conduct clinical trials and ultimately speed new drugs to market. Merck has connected its EngageZone portal to a hybrid cloud-based identity hub hosted as-a-Service by an identity hub provider. Merck's CRO, academic, investigator, and laboratory partners reach EngageZone by connecting to the same identity hub themselves. By embracing this approach, Merck has reduced on-boarding times for external partners from weeks or months to just days. When Merck needs to execute specific collaborative efforts with its partners, it now can create dynamic team sites in a matter of hours instead of days.

TransCelerate BioPharma, the consortium of 19 pharmaceutical companies formed to improve efficiency and productivity in clinical development, is incorporating an identity hub into its collaboration-focused solution. Access to TransCelerate's electronic portal through which all 19 companies communicate with investigators globally will be controlled by

an identity hub. The identity hub gives the pharmaceutical companies the level of security they demand to ensure their intellectual property is protected while they work with competitors to standardize industry processes and procedures that will improve clinical trials execution. Investigators will use a single credential to reach the portal and navigate a dashboard to access the applications, documents, and data associated with the clinical trials being run by each TransCelerate member with whom they work.

PUTTING IT ALL TOGETHER

Pharmaceutical companies continue to search for ways to reduce the cost and duration of the drug R&D process. That means they will stay the course on their transition to an external partner business model, playing to the strengths of CROs, laboratories, investigators, academic institutions, and others. In other words, collaboration beyond enterprise boundaries is here to stay. The demand for secure, seamless collaboration will manifest itself most acutely in the execution of clinical trials.

Making collaboration secure and seamless, while containing cost and schedule, is a challenge. Taking the wrong approach to deploying a collaborative operating environment can exacerbate the challenge, putting pharmaceutical companies and their external partners at risk. Hybrid cloud-based identity hubs, delivered as-a-Service, are proving to be an effective option for achieving all collaboration objectives. Identity hubs that serve as the foundation of the collaborative environment allow organizations to engage more quickly, while minimizing redundant infrastructure and capital expenditures. Identity hub providers ease the burden on IT and accelerate the on-boarding, identity proofing/credentialing, and authentication activities that lead to greater productivity by clinical trials teams.

By improving the collaborative experience without sacrificing control or security of sensitive information or intellectual property, identity hubs and their providers help pharmaceutical companies minimize the time and cost of clinical trials and the drug R&D process as a whole. As a result, pharmaceutical companies will be better positioned to maximize new drug revenue streams, and that means more life-altering and life-saving new drugs and therapies will be available to all consumers. ◆

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BIOGRAPHY

Tom Johnson has over 25 years of experience guiding process improvement, managing technology deployment, and directing program teams in the Life Science, Healthcare, and Aerospace and Defense industries. He currently serves as Senior Director of Healthcare and Life Science Solutions at Exostar. In this role, Mr. Johnson leads the company's Healthcare and Life Science secure business collaboration program, directing all development and implementation efforts for solutions for application and information access and protection. Exostar's Life Sciences Identity Hub brings together over 15,000 individuals in more than 700 manufacturing, contract research organization, laboratory, and academic organizations worldwide. Mr. Johnson has a BS in Industrial Engineering from Georgia Tech University.

Technology & Services Showcase

Analytical Support Services

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As a parenterals specialist with over 80 years of expertise, **Baxter's BioPharma Solutions** business offers unique drug delivery systems and a variety of sterile contract manufacturing form/fill/finish services and solutions for injectables, designed to meet complex and traditional sterile manufacturing challenges. A leader in pharmaceutical contract manufacturing for more than 30 years, BioPharma Solutions' esteemed scientists provide a wealth of industry experience in biologics, small molecules, vaccines, and cytotoxics (including ADCs). Offering resources to help you solve the high-stakes challenges you face in today's complex parenteral marketplace, we know that the work we do is ultimately vital to the patients you serve. For more information, visit **www.baxterbiopharmasolutions.com** or contact Baxter BioPharma Solutions at (800) 4-BAXTER.

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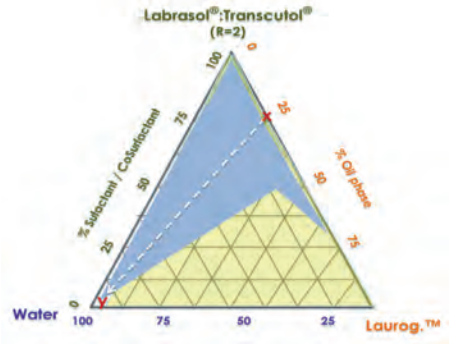

Ternary diagramming is an indispensable tool for developing microemulsions and SMEDDS for topical or oral delivery of poorly soluble drugs. In this example, the blue zone represents unlimited number of formulations possible by simply varying combinations of three excipients. Point "X" for instance is SMEDDS containing 25% Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact **jmusakhanian@gattefossecorp.com**

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THERAPEUTIC FOCUS

Direct Effects™ Diabetic Neuropathy Therapy: Treating Symptoms & Modifying Disease

By: Ronald Aung-Din, MD

INTRODUCTION

Peripheral neuropathy is the most common neurological manifestation of diabetes. Symptoms of diabetic peripheral neuropathy (DPN) often manifest before diagnosis of diabetes. Most common symptoms are numbness of feet with tingling, burning, and aching sensations. As it progresses, fingers and hands become affected in symmetric fashion. DPN may affect 50% to 90% of diabetics, depending on criteria used. With obesity in epidemic proportion, insulin resistance with incidence of diabetes has significantly increased.

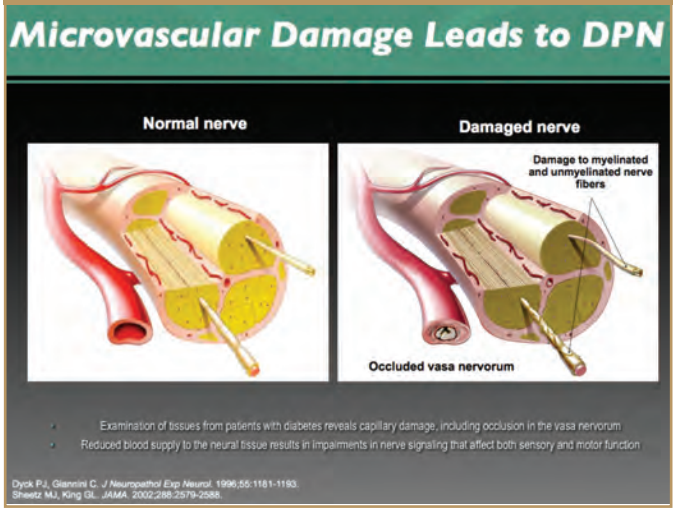
In addition to persistent neuropathic symptoms affecting sleep, wearing shoes and socks, and walking; most significant is loss of protective sensation in feet. As sensation is lost, minor injuries are undetected and not addressed early; leading to ulcerations, infection, and potential amputation. Between 60% to 70% of foot ulcers are preceded by neuropathy. And 85% of diabetes-related lower limb amputations are preceded by foot ulcer. Three of 10 undergoing lower limb amputation will lose another leg within 3 years, with over half dying within 5 years of first amputation. With such grim statistics, it makes sense to treat DPN when detected to modify disease and control symptoms.

THE ETIOLOGY OF DPN & TREATMENT CONSIDERATIONS

The cause of nerve damage in DPN is loss of blood flow to small peripheral nerves and cutaneous nerve-endings, result of blockage of small capillaries (vaso nervorum) by metabolic process of diabetes (Figure 1). Ultimately, as diabetes progresses, other blood vessels, such as to heart and brain, are affected, leading to heart attacks and strokes.

As blood flow and nutrients are lost, nerves are unable to function properly or die, causing loss of sensation with neuropathic symptoms of tingling, burning, sharp pain, electric-like sensations, and pain to touching clothes and bed sheets (allodynia). Part of pathologic process is loss of myelin

FIGURE 1

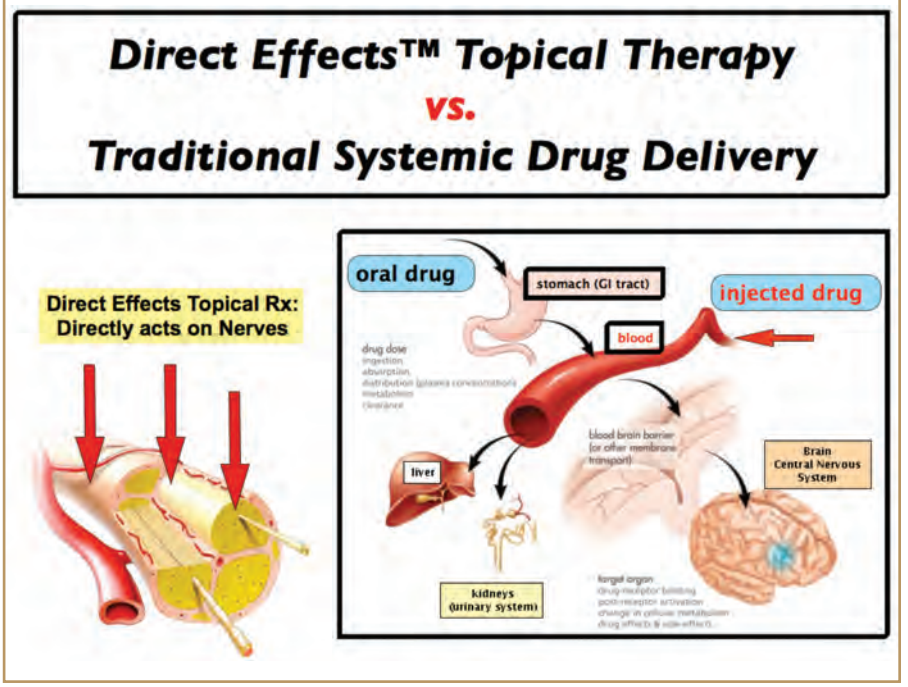


(demyelination) of peripheral nerves that prevents proper nerve conduction and results in neural "short-circuiting and cross-talk," causing neuropathic symptoms. Demyelinated nerves leak potassium, further affecting conduction. Accordingly, drugs that block potassium channels, such as 4-amino pyridine (4-AP), can improve conduction in damaged nerves. One such oral extended-release preparation, Ampyra (Acorda Therapeutics) is indicated for improving nerve conduction in multiple sclerosis (MS), an immune-based central demyelinating process.

Systemic treatment for peripheral demyelinating neuropathic process, such as DPN, must consider coexisting peripheral vascular disease, limiting drug access to damaged nerves. In this regard, it makes sense to use topical preparations of drug compounded to allow penetration to the level of cutaneous nerve endings, an area of pathologic process in DPN. Additional issues of systemic therapy complicating drug delivery to peripheral nerves include the following (Figure 2):

- GI transit and absorption
- Hepatic first-pass metabolism
- Cardiac and hemodynamic factors affecting drug delivery and blood levels
- Drug interactions with concomitant medications
- Side effects from drug action at unintended areas

FIGURE 2



NEUROTROPHIC SUPPORT TO ENHANCE BLOOD FLOW & IMPROVE PERIPHERAL NERVE FUNCTION

In addition to control of blood sugar levels through medications, diet, and exercise, specific nutritional agents help heal damaged nerves in DPN. One product is METANX® (Pam Labs), a combination of L-Methylfolate 3 mg, Methylcobalamin 2 mg, and Pyridoxal 5'–phosphate 35 mg. It is considered "Medical Food" and regulated by the FDA with prescription requirement. Metanx addresses underlying conditions

FIGURE 3

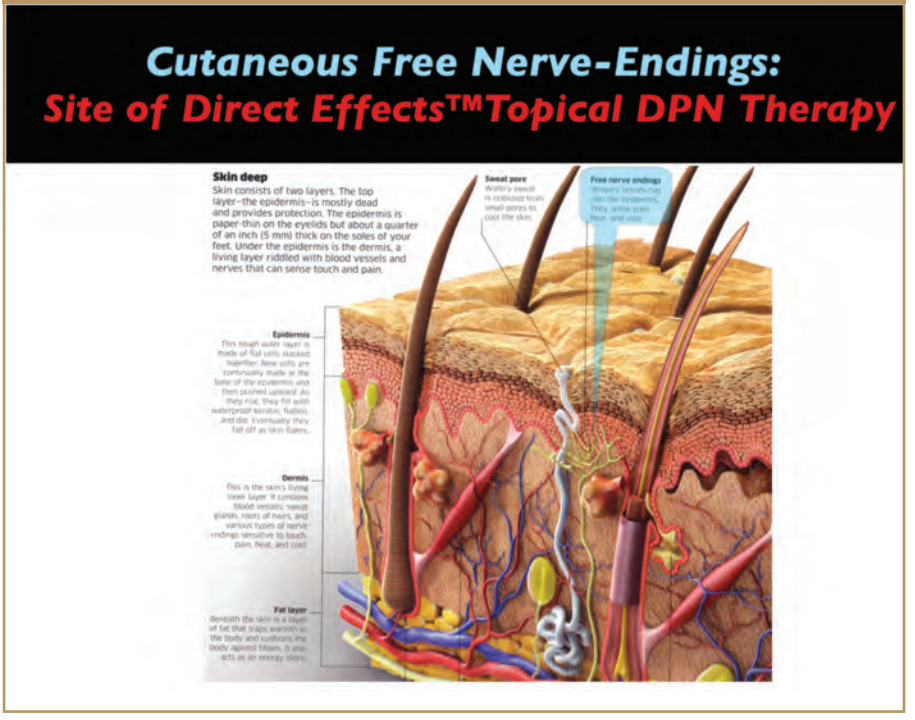
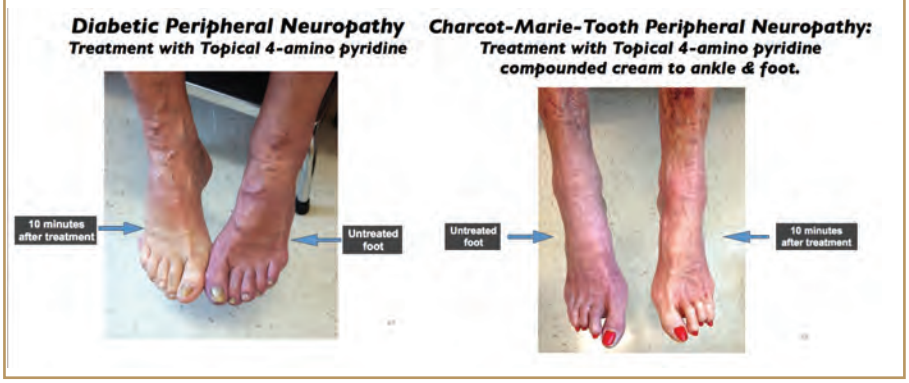


FIGURE 4



of endothelial dysfunction in blood vessels to small nerves (vaso nervorum) that leads to DPN.

L-methyl folate increases nitric oxide synthesis, which improves blood flow to cutaneous nerves. Metanx is prescribed as a twice-daily tablet.

Studies with oral L-Methylfolate, Methylcobalamin (Me-Cbl), and Pyridoxal 5'–phosphate (P-5-P) in DPN indicate improvement of cutaneous sensation at feet of affected patients compared to baseline at 6 months and 1-year therapy.

A preliminary study also suggests L-Methylfolate, Me-Cbl, and P-5-P are associated with increased intraepidermal nerve fibers density (IENFD) in patients with DPN. The increased epidermal nerve fiber density may be associated with diminished symptoms of pain, anesthesia, paresthesia, and dysesthesia observed with therapy.

A skin biopsy is performed to measure IENFD in lower extremities of patients with DPN. Loss of nerve fibers is associated with increased neuropathic pain. Small Fiber Neuropathy (SFN) is a major cause of painful burning, numbness, and tingling in feet and hands of DPN and other neuropathic conditions. SFN often precedes diagnosis of diabetes and has been termed "impaired glucose tolerance neuropathy."

Diagnostic efficiency of skin biopsy is ≈ 88%, making it useful in diagnosing SFN associated with diabetes. The test is invasive, but enables direct study of small nerve fibers. Often in patients with DPN who still only have SFN, routine nerve conduction studies and electromyography are typically normal as these only measure large nerve fiber function (Figure 3).

SYMPTOMATIC PHARMACOLOGICAL TREATMENTS FOR DPN & OTHER NEUROPATHIES

There exist numerous drugs to treat symptoms of DPN but which do not affect underlying condition causing peripheral nerve dysfunction. They do not disease modify or repair nerves. Among symptomatic therapies for DPN and other peripheral neuropathies are:

- "Pain pills," such as narcotics, NSAIDs, and acetaminophen
- Tricyclic antidepressants, such as amitriptylene (Elavil)
- SNRIs, such as venlafaxine (Effexor), duloxetine (Cymbalta), and milnacipran (Savella)
- Anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica)
- Topical products lidocaine cream and patch anesthetize skin to provide neuropathic pain relief but make affected areas more numb
- Capsaicin cream causes initial increased burning sensation followed by temporary relief

UNMET NEED IN DPN & TOPICAL COMPOUNDED CREAMS AS "LOGICAL POLYPHARMACY"

There exists a void in treatment of DPN. As SFN and DPN are primarily conditions affecting cutaneous (skin) nerves and free nerve-endings, the author has developed a topical therapy for treating DPN and other neuropathies that manifest similar peripheral nerve dysfunction. Compounded combination cream is rubbed into the dorsum and soles or palms (top and bottom) of affected feet and hands two to three times/day (Figure 4).

Compounded cream consists of generic drugs commonly used to treat neuropathic pain in combination with L-methyl folate, methyl cobalamin, and 5-pyridoxal phosphate. Additionally, 4-amino pyridine (4-AP) and apomorphine (Apo) are added to improve conduction of damaged nerves and enhance treatment of neuropathic symptoms. Other compounds and vitamins are added according to need, as discussed further.

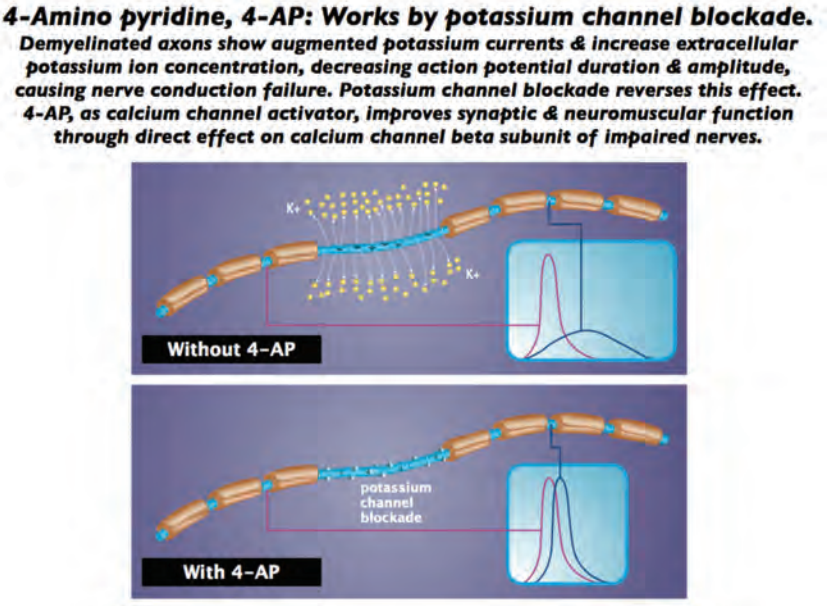
4-Amino Pyridine (4-AP)

4-Amino pyridine, 4-AP (fampridine, dalfampridine) is an organic compound with the chemical formula C5H4N–NH2. 4-AP extended-release tablet, name brand AMPYRA (dalfampridine), was granted orphan drug status in 2010 to improve walking in patients with multiple sclerosis, MS. 4-AP is a potassium channel blocker demonstrated to increase walking speed in MS, which has also been shown to improve visual function, enhance motor skills, and relieve fatigue in MS. Common 4-AP side effects include dizziness, nervousness, nausea, and other GI symptoms. Overdoses can cause paresthesias, seizures, and heart rhythm disturbances such as atrial fibrillation. 4-AP works through potassium channel blockade. Electrophysiologic studies of demyelinated axons show augmented potassium currents increase extracellular potassium ion concentration, decreasing action potential duration and amplitude. This may cause nerve conduction failure. Potassium channel blockade apparently reverses this effect. Studies have shown 4-AP, as a potent calcium channel activator, can improve synaptic and neuromuscular function through direct effect on calcium channel beta subunit of impaired nerves. Although it improves MS symptoms caused by damaged poorly conducting nerves, 4-AP does not prevent MS disease progression.

Spinal cord injury patients have also been observed to improve with 4-AP therapy. These include improved sensory, motor, and pulmonary functions as well as decreased spasticity and pain.

Based on the aforementioned and and author's experience with topical 4-AP, improvement in neurological function in MS, stroke, and cerebral palsy patients was seen when applied to back of the neck at hairline (BONATH), nuchal region. It was tried and found useful in treating nerve dysfunction associated with DPN, SFN, and other peripheral neuropathies (Figure 5).

FIGURE 5



Apomorphine (Apo) & Other Compounds

Apomorphine is used as injection to treat symptoms of Parkinson's disease (PD). The author has extensive experience (USPTO No. 8,592,424,B2, granted November 26, 2013) with it as topical preparation in Parkinson's, tremor, spasticity, erectile dysfunction, and neuropathic pain. Applied to

FIGURE 6

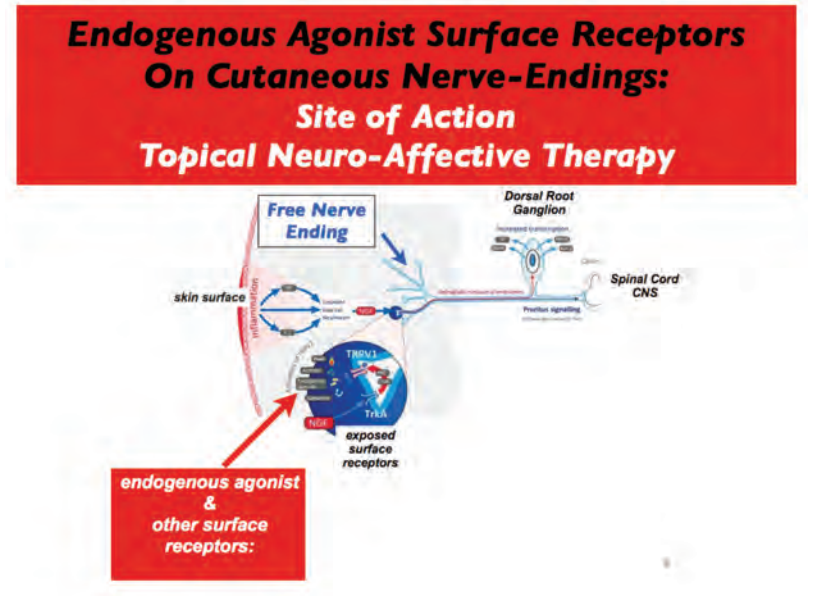


FIGURE 7

TREATMENT OF PERIPHERAL NEUROPATHY WITH TOPICAL DRUG AND NEUROTROPHIC* COMBINATION CREAMS

Patient	Diagnosis	Duration of symptoms	Treatment	Results
M.M. 67y/o female	Idiopathic peripheral neuropathy: ? thyroid disease	3 years of numbness, pain, and tingling. 50% decreased sensation bilateral feet.	topical 4-AP, apomorphine, and MFP to left foot.	Left foot sensation improved to 10% decrease from normal in 15 min.
J.M. 69y/o female	peripheral neuropathy, chemotherapy post-lumber laminectomy.	pain, numbness, and weakness x 2007, worse after chemotherapy for breast cancer 2009.	4-AP, apomorphine, tramadol topical cream with oral MFP	peripheral neuropathic symptoms stable with improvement of numbness from chemotherapy.
C.M. 75y/o female	Diabetic peripheral neuropathy	3-4 years bilateral foot numbness, tingling, and pain:L>R.	4-amino pyridine and apomorphine topical cream.	50% reduction in tingling with improved sensation in 10-15 minutes.
M.A. 90y/o female	familial peripheral neuropathy and failed back syndrome	peripheral neuropathy diagnosed at Mayo Clinic 1995 with EMG/NCV.	2+ years (7/2011) of daily Rx with apomorphine and tramadol cream 2x/d.	With oral tramadol and topical neuropathy cream, able to function normally.
A.M. 72y/o male	Diabetic peripheral neuropathy	several years numbness and burning pain with insomnia. Treated with other topical preparations in evening.	combination topical 4-AP, apomorphine, and MFP both feet.	In 5 minutes, improved sensation and pain reduction in both feet. Now using regularly.
R.H. 85y/o male	acute metabolic neuropathy superimposed on hereditary CMT neuropathy	Life-long with recent worsening to extent could not ambulate without walker	6 weeks Rx of topical 4-AP, apomorphine, gabapentin, lidocaine, prilocaine, and MFP* 3x/day.	Pain, numbness and weakness improved. Ambulating without walker or assistance
P.D. 87y/o female	Charcot-Marie-Tooth with recent increased symptoms	3 years of increasing pain, numbness, and weakness with gait difficulties.	3 weeks of Rx of above combination 2x/day.	20% improvement in baseline pinprick and temperature; no change in vibratory sensation.
K.M. 64y/o male	diabetic/metabolic peripheral neuropathy with superimposed lumbar radiculopathy	2 years of numbness, tingling, aching feet with restless legs and sleep disturbance	2 weeks of above topical Rx nightly.	80% relief of pain with 20-30% improvement in sensation within 5-8 minutes of each application. Improved sleep.
C.A. 70y/o male	peripheral neuropathy with entrapment neuropathy of feet	4 years of bilateral foot paresthesias with EMG/NCV documented peripheral neuropathy. Hx of spinal and lower extremity injuries from severe auto accident with coma from head injury.	1 week of above topical Rx continuing.	Immediate significant pain relief with improved sensation in the feet.

*MFP neurotrophic support: methylcobalamin, methyl folate, and pyridoxal phosphate

BONATH in PD, motor as well as "non-motor" PD symptoms were alleviated. Through action at dopamine, serotonin, and norepinephrine receptors, significant pain relieving and muscle relaxant effects are also noted when topically applied to spine and peripheral areas of nerve dysfunction. Adding Apo provides added therapeutic benefit to topical DPN treatment.

Gabapentin and pregabalin are used to treat neuropathic pain of various etiologies, including DPN, post-herpetic neuralgia, spinal radiculopathy, and post-laminectomy syndrome. Local anesthetics, such as lidocaine and prilocaine, are useful as topical treatments in reducing nerve pain, but increase numbness associated with DPN.

Capsaicin, tizanidine, and tramadol are other compounds effective in combination neuropathic creams, depending on patient need. Capsaicin deactivates pain producing free nerve-endings through action on TRPV1 receptors on the surface of nerve endings; but can cause significant initial burning. Tizanidine acts as both pain modulating agent and muscle relaxant. Tramadol, a non-narcotic opioid agonist, provides greater degree of pain relief when needed.

Neuro-Affective Effect of Topical Drugs on Cutaneous Nerve Endings

Finally, topical therapy not only allows active drug to easily and directly reach targeted cutaneous nerve endings without requiring circuitous compromised blood flow, but receptors on nerve endings provide direct neural therapeutic avenue for topically applied neuro-active drugs.

Cutaneous nerve endings are peripheral end-components of dorsal root ganglia with extracellular surface receptors conducive to binding by topically applied drugs. The neurochemical effects of topical agonist and antagonist compounds on endogenous surface receptors may modulate afferent input to dorsal root ganglia, influencing nerve signal processing to brain. Therapeutic benefit appears to be achieved through attenuation of central nervous system (CNS) efferents, as reduction in clinical symptoms. Among cell surface receptors on cutaneous nerve endings are those to TRPV1, NGF (nerve growth factor), opioids/endorphins; and to endogenous agonists serotonin, dopamine, norepinephrine, and others. It is believed these receptors are affected by topical compounds possessing agonist and antagonist properties, thereby providing therapeutic benefit. CNS and skin are derived from the same embryological tissue, neuroectoderm. Receptors in CNS are therefore represented on skin nerve endings, allowing the two entities to process and share neural information as a closed-loop system (Figure 6).

CONCLUSION

Using the aforementioned methodology, symptomatic and neural restorative therapies treat DPN in preparations applied directly to areas of pathology. The epidermal nerve fiber layer is the target site. As high concentrations of drugs and neurotrophic agents are achieved at places of nerve and blood vessel dysfunction, therapeutic benefit is obtained in much shorter time than through blood flow.

Relief of pain and neuropathic symptoms is typically noted within 5 to 8 minutes of topical drug application. Visible trophic changes in skin occurs within 15 minutes as nerve function is improved and blood flow is redirected in skin and subcutaneous tissue. Improved sensation from pretreatment baseline follows within 30 minutes.

Figure 7 gives examples of results in patients treated with various combinations of drugs and neurotrophic agents. DPN is the most common condition treated but other neuropathies also responded to topical therapy: hereditary neuropathy (Charcot Marie Tooth, chemotherapy related neuropathy, post-traumatic and compression neuropathy, radiculopathy, and metabolic neuropathies.

Longest continuous treatment period using topical creams for a neuropathic process is more than 3 years. Patient achieved benefit with daily use, symptoms exacerbating when treatment is interrupted. Many peripheral neuropathies are progressive and not curable. In these, treatment relieves symptoms and improves aspects of nerve and vascular function, but rarely normalizes the condition. After diabetes, thyroid disease, B12 deficiency, gammopathies, and other potential causes of peripheral neuropathy are ruled out, 60% to 70% peripheral neuropathies remain idiopathic, of unknown etiology.◆

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BIOGRAPHY

Dr. Ronald Aung-Din practices General Neurology and Neuropsychiatry in Sarasota, FL. Through affiliation with Lovelace Research Institute, Albuquerque, NM, he functioned as Principal Investigator in over 60 clinical trials, helping bring to market drugs in Epilepsy, Multiple Sclerosis, Neuropathic Pain, and Parkinson's Disease. In May 2008, Dr. Aung-Din founded AfGin Pharma, LLC, a research and development biotech company dedicated to Direct Effects Topical Neuro-Affective Therapy, a novel non-systemic delivery of neuro-active compounds he discovered useful in treating neurological and neuropsychiatric conditions. The therapy is unique in that rapid (within 10-30 mins) therapeutic results are achieved without usual systemic side effects and drug interactions. Dr. Aung-Din has been granted 4 patents relating to the technology in EU and by USPTO.

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External Delivery

Perfuming the Pig

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

My apologies to the swine lovers of the world for the title to my column this month. I like pigs. They're cute, smart, have a nose way more sensitive than a bloodhound's, and help the environment by eating garbage. Then we eat the pig. I'm a little confused by that. So that you do not think of me as discriminating against pigs, here are a few more animal terms that are used in everyday English.

Cash cow	Bull in a china shop	A little squirrely
Snake in the grass	For the birds	Sounds fishy
That's a real dog	The cat's meow	He's a real stud
Pony up the money	Horsing around	Monkey on my back
Tiger by the tail	Lionized by his men	Elephant in the room

Because I turn companies around and buy and sell them for a living, I have often heard the term *Perfuming the Pig*. The expression pertains to both the buy and sell sides. When I am on the buy side, throughout negotiations, I will generally make the point that the company is overpriced and not nearly as good as the sellers want us to believe it is. In order not to insult the sellers and get into a heated debate, I will always state that it appears that they have been Perfuming the Pig. I say it in a kidding manner with a smile, but the sellers also know where I am coming from. I have never seen the people on the other side of the table not smile when I have said that.

When I am on the sell side, I will also use the same expression. In this case, when I am negotiating the sale price, at the proper time, I will assure the buyers that I have not *Perfumed the Pig* and that the asking price is fair for the company. Again, I have always seen the people on the other side of the table smile when I use that expression.

Ann Richards, the former Governor of Texas, had a memorable use of the expression by stating that, "You can put lipstick and earrings on a hog and call it Monique, but it's still a pig."

Perfuming the Pig is also used extensively in marketing. The Chief Marketing Officer (CMO) in any company has one of the least secure jobs amongst all employees. The executive recruiting firm, Spencer Stuart, states that a CMO should only expect to be in the position for 23 months before being terminated. This is because senior management in most companies look at the CMO as the Chief Perfumer of the Pig (CPP rather than CMO). Oftentimes, management is expecting the CMO to take a retail product or retail product line that is not selling and apply marketing perfume to it so that it will sell.

Unfortunately, unless the CPP/CMO puts a massive amount of perfume on the pig(s), a retail product that no one wants to buy will remain a retail product that no one wants to buy. In this case, unlike buying and selling companies where you have plenty of time for your due diligence investigation, perfuming up a retail product that no one really wants or needs is very misleading in my opinion. This is because the retail dud product looks like a great buy, it being all perfumed up, and is now an impulse purchase. Once you get it home and the perfume has worn off, you realize that it really is a dud. Want to bet that the receipt states "all sales final" and no returns?" Also, the expression, buyer beware is certainly a good thing to keep in mind in the land of the perfumed pig. So keep in mind that if it looks like a pig, goes oink oink, and smells like Armani cologne, then it may be a perfumed pig. ◆

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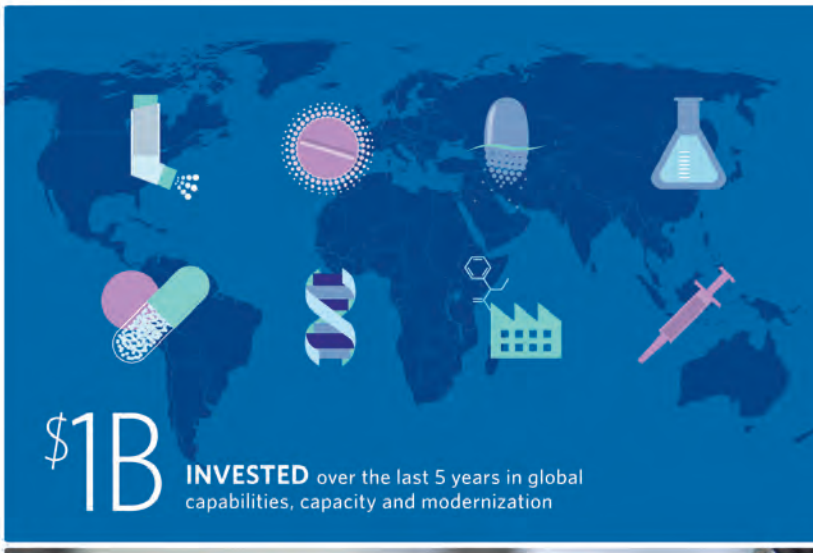

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