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INSPIRATIONAL NOTE

Inspirational chemistry of bioabsorbable long-acting injectables

Thomas Tice[1]

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Abstract
Long-acting injectables (LAIs) have made a tremendous impact on clinical medicine. As evidence, dozens of approved LAI products are on the market. These LAI successes, in a large part, came from the clever chemistry of their materials that control drug delivery performance. Beyond their materials, what innovations and technologies led to LAI success? What were the scientific progressions and who were the people and their stories behind LAI success? The answers to these questions are interesting to hear about, learn from, and be inspired by. Many people from many diverse fields contributed to the scientific advancement, product development, and product launches of long-acting injectables. Over 50 years ago, LAI pioneers envisioned a host of new drug delivery concepts and engaged their enthusiasm to reduce their concepts to practice. In doing so, they considered a variety of materials, dosage forms, routes of administration, and manufacturing processes, and they had to devise new tools to support product development. Because of the wide technology breadth of long-acting injectables, this publication focuses on bioabsorbable LAIs formulated with polymeric excipients such as lactide/glycolide functional excipients. Their historical progression of polymer chemistry and formulation development is shared. Successes are highlighted with some backstories.

Introduction — LAI interest surges

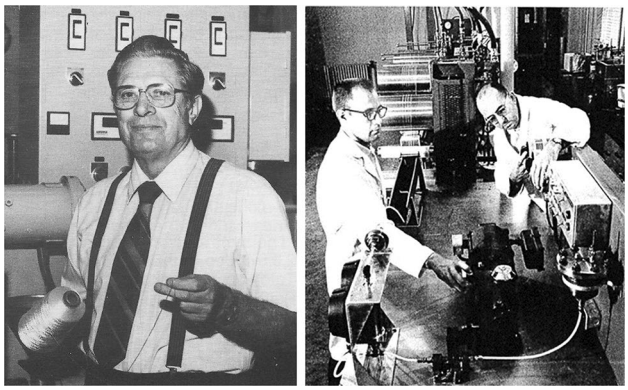
There is clearly a surge in LAI interest today, as substantiated by the number of LAI products in development and the multitude of LAI presentations given at conferences and webinars. This interest stems in part from LAI's potential to make today's new modalities a reality, such as long-acting, cytokine injectables to support immunotherapy, and the continued leveraging of already proven outcomes of LAIs such as better patient compliance, improved efficacy, and making local drug delivery possible. Key factors to address during LAI development have not changed over the years. These factors include drug potency, drug properties, drug stability, availability of a limited number of parenteral excipients, inherent biology hurdles, and manufacturing challenges particularly scale up. Drug potency drives injection volume and the duration of drug release, whereas the physical/chemical properties of both the drug and the polymeric excipient drive formulation compositions, product performance, and manufacturing boundaries. Today, more new chemical entities and a growing number of biological entities are being formulated as LAIs. This is a new trend, as most of the LAI products to date are reformulations of existing drugs, including drugs originally launched on the market as far back as the 1950s, e.g., dexamethasone (Ozurdex®) [1].

The beginning of long-acting injectables

Considering the polymeric excipient as the key component to LAI performance, perhaps the beginning of LAIs can be established as when their excipients were discovered. With this perspective, the beginning of bioabsorbable, polymeric LAIs would be the 1930s, when George Dorough from E.I. du Pont de Nemours issued a 3-page patent on the synthesis of polylactides (US Patent 1,995,970) [2]. Then, the next milestone for LAIs with lactide/glycolide polymers (LG polymers) is in the late 1960s when du Pont employees George Boswell and Richard Scribner were the first to combine LG polymers with drugs and achieved controlled-release drugs with these combinations. They foresaw the use of their discovery for small molecules and peptides (no mention of proteins), including drugs such as antipsychotic agents, natural and synthetic hormones, narcotic antagonists, vitamin B_{12}, and peptides such as polymyxin B sulfate. Their groundbreaking discoveries led to US Patent 3,773,919 issued in 1973, the first issued drug-delivery patent describing LG polymer/drug compositions for controlled release [3]. Interestingly, even with two insightful patents and du Pont being a chemical company, du Pont never manufactured commercial supplies of LG polymers for drug delivery applications.

✉ Thomas Tice
tom.tice@evonik.com

[1] Evonik Corporation, Birmingham, AL 35211, USA



Curtis Stoner (left photograph [4]) and RB Perkins (not shown) developed the first synthetic, resorbable suture in Southern Research Institute's fiber spinning laboratory [5] (right photograph c. 1961)

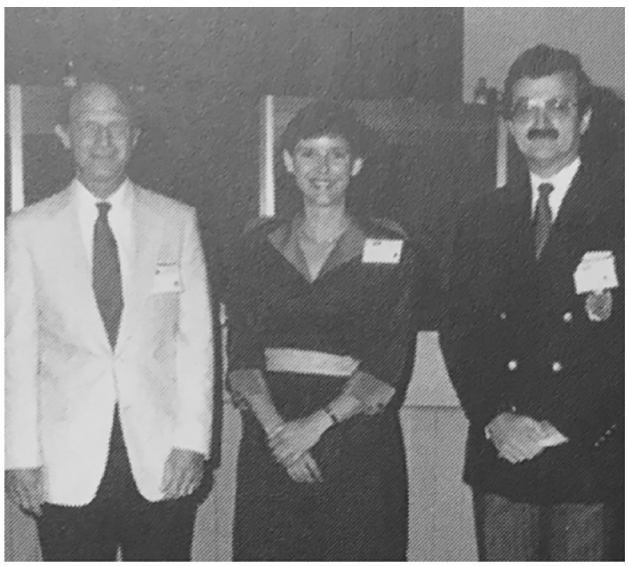
The beginning of LAIs for Southern Research Institute, a notable contributor to the field of controlled release, was when R.B. Perkins and Curtis Stoner developed the first synthetic suture. Although these researchers had no formal training in fiber work, they quickly demonstrated their technical entrepreneurship to the world with spinning fibers from materials that easily degraded during the fiber-spinning process. Curtis Stoner's education included Chemistry B.S. and Biology M.A., and he taught high school science for 4 years before joining Southern Research Institute. In 1966, R.P. Perkins' and Curtis Stoner's unique fiber-spinning capability and expertise in textile production was recognized by American Cyanamid, who needed polyglycolide fibers for sutures. With project success, American Cyanamid launched Dexon® surgical sutures in 1971, the first LG polymer product. This suture product and other medical devices to follow would show the safety of LG polymers in patients which supported their use in drug delivery products.

Manufacturing process innovation

From the suture project and interest in the diffusion of molecules through polymeric membranes, Southern Research Institute joined the emerging field of drug delivery. Like many others, their initial interest was contraceptive steroids with emphasis on using LG polymers for controlled-release excipients. In addition to steroids, Southern Research conducted a peptide contraception project funded by Syntex (1979). The peptide was nafarelin, an analog of luteinizing hormone-releasing hormone (LHRH). Because of nafarelin's good water solubility, it was difficult to microencapsulate nafarelin with LG polymers by using o/w emulsion solvent evaporation processes that were typically used for steroids. After a year of failures and just as the project was about to end, a process breakthrough happened. While reading paperback bound patents from the chemical industry (the internet did not exist at that time for patent searching!), I came across a patent that described a non-aqueous microencapsulation process using slow addition of liquid polybutadiene to cause phase separation of a polymer to form a microcapsule wall. I took this chemical process and translated it to LHRH microencapsulations. With a desire to use medical grade materials, I substituted silicone oil for polybutadiene, and the solvent and non-solvent for each processing step was selected based on the solubility profiles of LG polymer, silicone oil, and LHRH. The process is highly dependent on interfacial chemistry, where polymer-rich regions need to find and interact with LHRH peptide to create microparticles. The process worked almost immediately. In animals, the resultant nafarelin microparticles showed nafarelin release for several weeks, although nafarelin plasma levels were not optimum because of their biphasic off/on peptide release characteristics. The LHRH phase separation microencapsulation process was disclosed in US Patent 4,675,189. Examples in the patent specification included microencapsulation of nafarelin peptide and bovine growth hormone protein. Issued claims covered LHRH/LG polymer compositions but did not cover the phase-separation microencapsulation process.

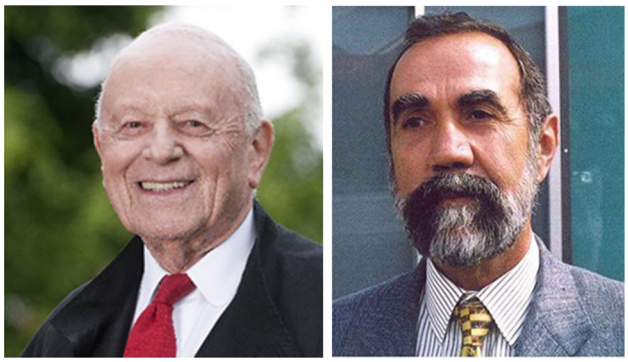
LHRH formulations lead product launches

Soon after Syntex (Lynda Sanders) presented these nafarelin microparticle results, Rolland-Yves Mauvernay and Pierro



Lynda Sanders (Syntex) was a member of the Syntex/Southern Research Institute team that first discovered how to release LHRH peptides from LG polymer microparticles. Shown are members of the Controlled Release Society's 1989 Executive Committee: Jorge Heller (President Elect, left), Lynda Sanders (President) and Nicholas Peppas (Past President, right). Jorge Heller dedicated much of his career to biodegradable polyorthoester polymers and their application for long-acting, parenteral drug delivery

Orsolini from Debiopharm visited Southern Research Institute. Debiopharm had a relationship with Andrew Shally (Tulane University) who won the 1977 Nobel Prize in Physiology or Medicine for his discovery of hypothalamic hormones, especially LHRH. In addition to understanding LHRH's role in reproduction, Dr. Shally found that certain tumors have receptors to LHRH that could be used to control certain cancers. Debiopharm licensed Tulane's LHRH analog triptorelin (D-Trp [6] LHRH) and saw the potential of a long-acting triptorelin microparticle product to treat prostate cancer, not achieve contraception.



A collaboration with the vision and financial support of Rolland-Yves Mauvernay (left) and Pierro Orsolini (right) from Debiopharm and the microencapsulation drug delivery technology of Southern Research Institute resulted in the launch of Decapeptyl® in 1986, which was the first long-acting, LG polymer microparticle on the market

A fast-moving product-development initiative led to the market launch of Decapeptyl® in 1986 in Europe. This product was the first commercial LG polymer injectable microparticle product on the market as well as the first injectable peptide-releasing LAI product on the market. Noteworthy, Decapeptyl® is still on the market today manufactured and distributed by Debiopharm's original licensees, Ipsen-Beaufour and Ferring.

The launch of Decapeptyl® would then be followed by nine other long-acting LHRH injectable products (several top-seller products) using LG polymers in the form of microparticles, implants, and in situ forming formulations. The durations of LHRH release of these products ranged from 1, 3, 4, and 6 months. These nine products are Lupron Depot® (leuprolide), Trelstar® Depot (triptorelin), Trelstar® LA (triptorelin), Suprecur MP (buserelin), Decapeptyl® SR (triptorelin), Zoladex (goserelin), Suprefact® Depot (buserelin), Eigard® (leuprolide), and Fensolvi® (leuprolide). Indications for these products included treatment of prostate cancer as well as breast cancer, endometriosis, and precocious puberty. Interestingly, Syntex's nafarelin analog (where it all started) was never developed as a LAI product with LG polymers.

The overwhelming success of these products relied on the development of new tools. For example, many different in vitro drug release methods to screen prototype formulations were developed for a variety of different dosage forms with a variety of durations of drug release (weeks and multiple months). In addition, discriminating, accelerated tests were developed to reduce performance testing to 14 days or less. At the time, only < 24-h dissolution testing for oral dosage forms was being practiced. Of note, the US and European pharmacopeias reference the 3-timepoint test for oral drug products to LAI in vitro release testing for product release.

Beyond LHRH

In addition to Decapaptyl®, Southern Research's phase-separation process was used to manufacture several other LAI products, e.g., Novartis' Sandostatin® LAR to treat acromegaly and carcinoid tumors, OraPharma's Arestin® to treat periodontal disease, and Amylin's Bydureon®/BCise® to treat type 2 diabetes.

Amylin's Bydureon's® exenatide peptide (GLP-1 peptide) microparticle is a unique product in of itself. The target product profile was a 1-week formulation to treat type 2 diabetes. From the beginning of its development, the formulation faced a significant drug burst release. Drug burst would cause serious side effects, like nausea. The Amylin team came up with a unique solution. They lowered the peptide content of the microparticles to lower the burst and moved peptide release out to 6–7 weeks. Amylin then used weekly injections, where each weekly injection added on to the peptide plasma levels from previous injections until peptide plasma levels reached efficacious levels at 6–7 weeks. Thereafter, each weekly injection replaced a previous injection of microparticles with all their drug spent. For life cycle, the same Bydureon® microparticles were suspended in medium triglycerides, an oil-based vehicle. Unlike suspending microparticle powder with aqueous vehicle prior to administration, the new formulation was a ready-to-use suspension of microparticles, that required less shaking before administration, 15 shakes instead of 80 shakes. Bydureon® microparticles were rebranded BCise® and is the only human LAI microparticle product using an oil-based vehicle.

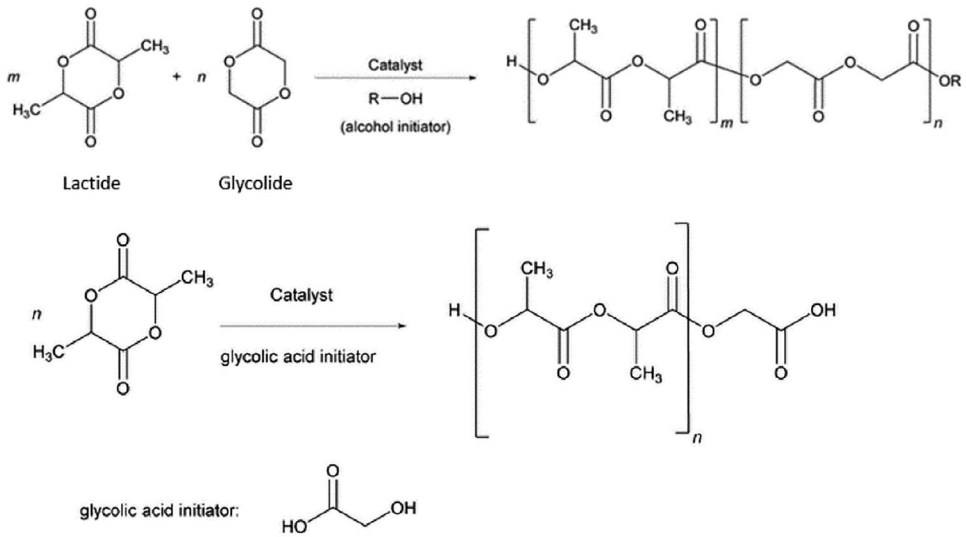
Excipient innovations

Tom Kissel and his colleagues at Sandoz early on in the field of drug delivery were interested in LAIs for peptides and developed a star LG polymer that are used in LAI microparticle products

In the 1970s, Thomas Kissel, David Bodmer, Jones Fong, Jane Pearson, Hawkins Maulding, and coworkers at Sandoz, now Novartis, were also very active in LAI development with LG polymers. They launched Parlodel LA® bromocriptine/LG polymer microparticles in Switzerland 1 month just after Decapeptyl® was launched. At the time, Sandoz was one of few industry groups interested in LAIs for peptide delivery. Sandoz funded a study to measure the resorption of ^{14}C radiolabeled 50:50 LG polymer from lypressin microparticles, and they studied the behavior of LG microparticles in vivo [6].

Also, Sandoz synthesized and developed a star LG polymer for Sandostatin® LAR to improve the hydrolysis rate of LG polymer and overcome the undesired biphasic drug release seen with earlier LHRH microparticles [7, 8]. This star polymer was also used to shorten the duration of Parlodel® LA bromocriptine release from 6 months to 1 month resulting in the launch of Parlodel® LAR [9]. To obtain a star or branched polymer, Sandoz's 50:50 LG polymer was synthesized by a glucose-initiated, ring-opening polymerization of lactide and glycolide monomers. Glucose's multiple alcohol groups enabled formation of the LG polymer branches. Novartis later launched a third LAI product, Signifor® LAR, using a blend of LG polymers. Blending of LG polymers in addition to LG polymer synthesis tuning to modulate drug release is a strategy now used in other LAIs, e.g., Ozurdex® and Durysta® ocular implants.

Another LG polymer synthesis twist came from Atrix Laboratories scientists (Richard Dunn and coinventors) where they cleverly used 1,6-hexanediol to initiate ring-opening of their LG polymer. With this initiator, polymer chain growth occurred in two directions instead of multiple directions as was the case for Sandoz's star LG polymer. A linear polymer resulted with the diol initiator incorporated as an ester in the center of the polymer. This linear polymer synthesis was different from the more normal ring-opening synthesis using a single alcohol, like lauryl alcohol



Ring-opening polymerization with lactide and glycolide monomers. LG polymers that are synthesized with alcohol initiators have an ester end group at one end of their polymer chains based on the chemistry of the initiator, e.g., poly(lactide-co-glycolide) copolymer shown in the top of this figure. LG polymers that are synthesized with acids have an acid end group at one end of their polymer chains, e.g., polylactide homopolymer shown in the bottom of this figure

that incorporates as an ester only at one end of the polymer chain. Atrix's diol-initiated LG polymer added patent protection to its Eligard® product, which was the first LAI in situ forming product on the market [10]. Eligard® releases leuprolide, an LHRH agonist, for the treatment of prostate cancer. Interestingly, Atrix's in situ forming technology (Atrigel technology) began as a dental product idea (without drug) for guided tissue regeneration of periodontal tissue. This dental product development was funded by Vipont Pharmaceuticals before becoming Atrix Laboratories.

Commercially available LG polymers appeared on the market in the 1980s and years thereafter improved in quality and consistency with increasing batch sizes as compared to polymers used in the earlier years. LG polymer solubility improved with better manufacturing procedures to control of glycolate block length and block-length distribution. Fit-for-purpose polymer purity is now offered with respect to residual monomer and tin catalyst. PEG-LG diblock copolymers are now available and are typically used for nanoparticles with conjugated proteins on their surface or for solubilization of poorly soluble drugs. LG polymer powders (print powders) are also available today for 3D printing of implantable medical devices and orthopedic scaffolds with osteoconductive properties.

Formulation understandings

Terry Tsong-Pin Hsu and Robert Langer published an important paper in 1985, unfortunately probably forgotten today, showing the effect of molecular weight of poly(ethylene–vinyl acetate) (EVA) copolymers on drug release [11]. As EVA does not degrade, this paper demonstrated that the rate of drug release is clearly dependent on polymer molecular weight. Formulations with low-molecular-weight EVA display faster drug release because they have less strength to withstand osmotic pressure as water enters the formulation. Drug release from LG polymer formulations also depends on polymer molecular weight. But unlike EVA, LG polymer molecular weight continually decreases over time as the LG polymer hydrolyzes in bulk once placed in the patient. Consequently, when describing the mechanism of drug release as diffusional release followed by release due to LG biodegradation, it is important to keep in mind that decreasing LG polymer molecular weight is occurring with decreasing polymer strength which facilitates drug release well before the LG polymer substantially reduces in molecular weight enough to leave the site of administration.

Another backstory

Early on at Southern Research Institute when we still had a lot to learn about LG polymers, our polymer synthesis team was making LG polymers with various lactide/glycolide ratios and molecular weights. As a result, we found ourselves formulating LAIs with many different LG polymer physical chemistry properties without knowing how all these polymers would release drugs in vivo. As a result, to better organize our learning, we strategically decided to focus on polymers with lactide/glycolide monomer mole ratios of 50:50, 65:35, 75:25, 85:15, and 100:0. This strategy is reflected in Southern Research publications and the standard polymers that are sold today by polymer suppliers [12, 13].

Excipient biocompatibility

Jim Anderson and his group at Case Western Reserve University taught the drug delivery community the importance of appreciating cellular and tissue responses to drug delivery materials. His publications are an excellent source of information on the biocompatibility of LG polymers. Jim Anderson's education includes Chemistry BS, Physical Organic Chemistry Ph.D., and graduation from Case Western Reserve Medical School all leading up to building an expertise in multiple subjects ranging from pathology to biomedical polymer synthesis.

Jim Anderson at Case Western Reserve University School of Medicine taught the drug delivery community the importance of appreciating cellular and tissue responses to drug delivery materials

Yes, LG polymers are hydrophobic and typically cause a minimal inflammatory response. But LG polymer hydrophobicity is essential to achieve drug release for many months. Leveraging the synthesis of LG polymers, tunable hydrophobicity via the lactide/glycolide ratio is used to control the ingress of water into LG polymer formulations, which throttles drug release as well as polymer bioabsorption through hydrolysis [14–16]. Understanding biocompatibility and tissue/material interactions continues to be important today as we navigate inherent biology hurdles such as those seen in ocular drug delivery where LG polymer cylindrical implants seem to be more compatible in the vitreous of the eye as compared to the same mass of LG microparticles [17].

Concluding remarks

From a materials perspective, the beneficial inherent properties, broad tunability, better solubility, and polymer purity options of LG polymers and the physical properties of potent drugs played a central role in the development of long-acting LG polymer injectables. With these materials, many academic scientists and company product developers contributed to building the foundation of drug delivery science and reached out to other fields to find ideas and technical solutions. They invented tools to facilitate development activities, and they navigated the boundaries of parenteral formulations, inherent biological hurdles, sterile manufacturing processing, and regulatory requirements.

The development of lipid nanoparticles for delivery of mRNA for COVID-19 vaccines followed a similar innovation process. Physics reached out to chemistry (Pieter Cullis is the example). High throughput tools were devised to synthesize and screen hundreds of ionizable lipids (Bob Langer and team). Mixing technologies from other applications were applied. Amino acid substitutions locked in antigen structure to prevent antibody-dependent enhancement. Additionally, improved Corning glass for vials made it possible to double the rate of fill/finish operations without generating undesirable glass particles.

In addition to learning from LAI stories and LAI technical advancements, we should look outside of the pharmaceutical industry for inspiration whether it is technical inspiration or creative thinking inspiration. Take for example the basic principles of innovation used by the Wright Brothers who were the first to achieve controlled flight [18]. Their success resulted from more than their passion and dedication to their flying machine. They invented tools, e.g., invented the wind tunnel, to aid their technology development. They translated ideas from existing technologies, e.g., boat propellers existed but there were no air propellers. They also leveraged the properties of the materials available to them at the time and developed manufacturing techniques to solve critical technical challenges. For instance, they had to revert to building their own lightweight engine which marked the first use of aluminum in aircraft construction. From experimentation, they selected a specific wood species and developed a method for making their propellers. And they used double-layered muslin cloth with a specific twill that was covered the wings with a 45-degree weave orientation to improve strength.

A few thoughts to the future

LAIs have clearly established themselves as one of the proven, here-to-stay drug delivery approaches. LAIs will continue to grow because of their historical success, technical flexibility, and ability to deliver drugs systemically and locally from a variety of dosage forms like microparticles and implants. LAI products will continue to provide solutions for unmet medical needs like treatments for ocular and rare diseases, neurological diseases, and cancers. To stay ahead, one should be curious of advancements in other fields and follow the new modalities, particularly those leveraging immunology, molecular biology, and medical discoveries. LAIs of the future will be driven by the drugs identified or specifically designed for the new modalities. LAI technology will advance and adapt to the physical/chemical and labile properties of proteins. The emergence of new therapeutic peptides, nucleic acids, and highly potent drugs will be a part of future of LAI products as well. Lastly and already happening, the knowledge base of LAIs, their parenteral functional excipients, and manufacturing processes are being applied to polymeric nanoparticles. These nanoparticles, for instance, are made with LG polymers and diblock polymers comprising PEG and various LG polymers. As examples, polymeric nanoparticles are being decorated with one or more moieties like antibodies and peptides to stimulate immune cells, and they are being used to solubilize poorly water-soluble drugs.

In closing, although this article covered only a very small part of the many, many contributions made to the success of long-acting injectables, hopefully, it brought forth some interesting insights that were inspirational. Hopefully others will be moved to share their stories and science so they can also inspire others to create new ideas that can be transformed into practical solutions and new treatments for patients.

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Thomas Tice Dr. Tice has 43 years' experience developing complex parenterals and long-acting injectables. His primary expertise includes long-acting, injectable microparticle formulations, bioabsorbable lactide/glycolide polymers, and microencapsulation processes. His educational background includes Chemistry BS, Biophysics PhD (polymer science) and Microbiology postdoctoral fellowship. He is presently affiliated with Evonik Corporation.