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Hyaluronic Acid:
A wonder molecule for the cosmetic and pharma industries

By

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WHITE PAPER

Overview

Hyaluronic acid (HA) biopolymer is a naturally occurring material that helps retain moisture in the skin, eyes and lubricates the joints. However, with age, the body starts producing less and less of this material, resulting in conditions such as dry eyes, osteoarthritis, aging skin, and so on.

Pharma and cosmetic industries realized that this molecule produced by the body could be supplemented with material made in a factory to treat these conditions. Since then, due to the molecule's valuable physicochemical properties, it is being used in the treatment of various medical conditions. These include arthritis treatment (osteoarthritis), in contact lenses for dry eye syndrome, ocular surgery (ophthalmology), cosmetic space (skincare, plastic surgery), drug delivery, and more.

HA's crucial role in the wound-healing process presents a massive opportunity in regenerative medicine. Similarly, the chemical modification of HA could enable its application in new areas of medicine. Further, HA being a biodegradable material, it can be used without increasing carbon footprint or causing any environmental damage.

Read on to understand the many applications of HA and possibilities for the future.

About hyaluronic acid

Hyaluronic acid (HA) is a linear biodegradable polymer composed of repeating disaccharide units of b-1,3-N-acetyl glucosamine and b-1,4-glucuronic acid with a molecular weight of up to 6 million Daltons. HA is a highly hydrophilic polymer due to the presence of hydrophilic groups such as hydroxyl, carboxyl, and amide groups in it [1].

Currently, commercially available HA is polydisperse and is either isolated from rooster combs or produced through microbial fermentation [2].

The physiological and pharmacological functions of HA vary with their molecular weight. For example, inhaling high molecular weight HA has been applied to treat inflammation clinically, while low molecular weight HA exhibits proinflammatory characteristics [3]. Most commercial products top out around 4,000 kDa [4].

Additionally, absorption characteristics of intestinal epithelial cells are different for HA having different molecular weights. Certain diseases require optimal absorption of oral HA. Thus, the preparation of low polydispersity/or well-defined/monodisperse HA of appropriate molecular weight is highly desirable [2]

HA market analysis

HA, a natural component with therapeutic properties, commands a higher price than substitute products like collagen, omega-3, chondroitin sulfate, glucosamine, etc., that provide similar benefits.

Companies are marketing a wide range of products containing this molecule. This includes HA drugs for treating osteoarthritis and mouth ulcers, eye surgeries, lip filler, moisturizer and anti-aging products, skin serum, dry eye syndrome etc.

By Grade

- Cosmetic Grade
- Pharmaceutical Grade
- Food Grade

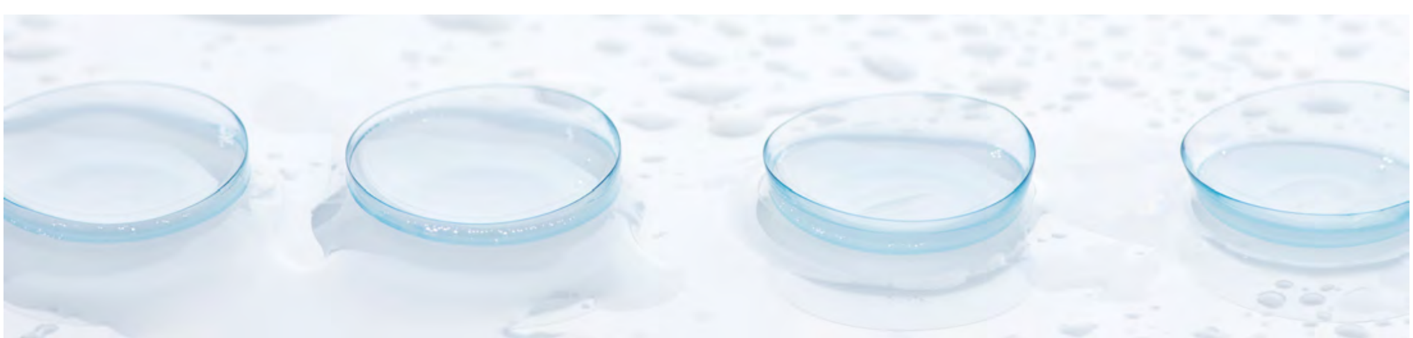
By Application

- Aesthetics
- Osteoarthritis
- Pharmaceutical API
- Cosmetics
- Dietary Supplements
- Ophthalmology
- Others

By End User

- Pharmaceutical Industry
- Dermatology Clinics & Cosmetic Surgery centers
- Food Industry
- Personal Care
- Others

[Source: Grand View Research, Inc]

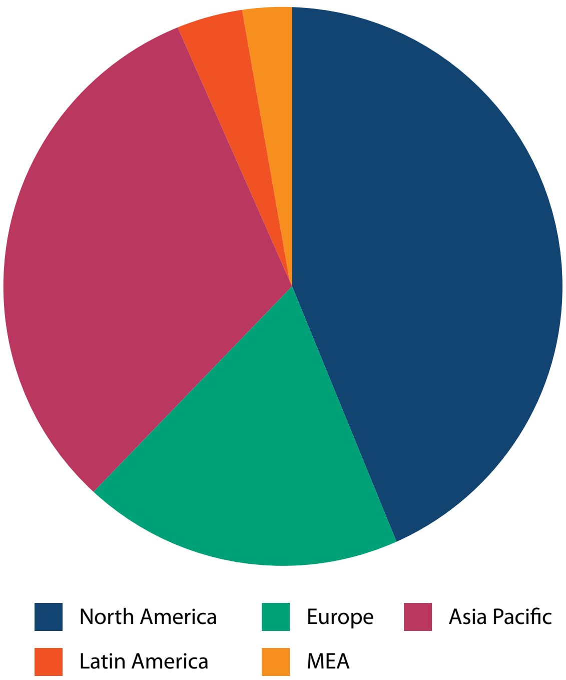


Global HA market

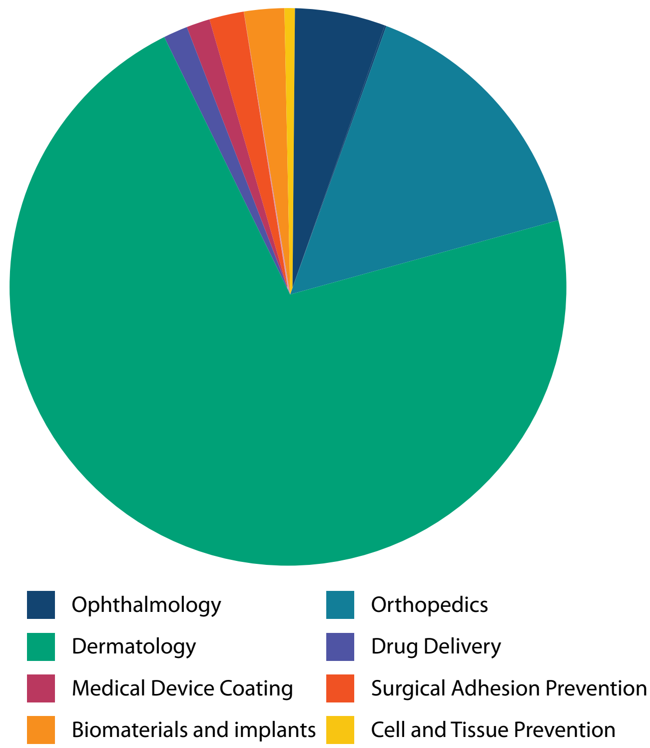
The HA market is projected to grow at 7.2% in terms of value to reach USD 15.48 billion by 2027 [5].

As per the pie chart below, North America accounted for the leading share in the global market for HA in 2019. The dermatology segment held the largest revenue share in 2015 due to various chronic wound cases in diabetic patients and the surge in demand for plastic surgeries requiring HA-based agents. Asia Pacific is anticipated to emerge as the fastest growing regional market in the forecast period due to growing elderly population in China and Japan – which provides a large customer base for anti-aging products and services.

Meanwhile, new HA products are continuing to emerge, with developers creating new applications based on functionality.



Global HA market share
by region, 2019 (%)
Source: Grand View Research, Inc.



Global HA raw material market volume
by application, 2015
(Thousand kgs)

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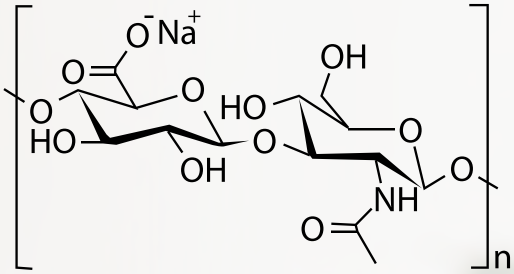
HA as a component of the human body



Structure of HA

In the human body, HA biopolymer occurs in the Sodium Hyaluronate form and is found in high concentrations in the umbilical cord, skin and vitreous humor of the eye.

HA is engaged in soft tissue hydration and structural scaffolding and provides viscoelasticity, which results in lubrication and shock absorbing functionalities.

HA contributes to variation of many biochemical processes such as cell proliferation and differentiation, cell adhesion and inflammation, wound healing and tissue repair etc.

- The molecular weights of HA from different sources are highly variable, ranging from 10^4 to10^8 Da
- Due to a variation in its molecular weight, its physical, chemical and biological properties are also different. As a result, HA derivatives can be utilized to make different formulations like fillers, creams, gels, and drops
- The average human body contains about 15 g of this disaccharide polymer
- Kinetics: The human body replaces about 30% of its HA every day (i.e., degraded and synthesized)

Source: Grand View Research, Mintel, companies

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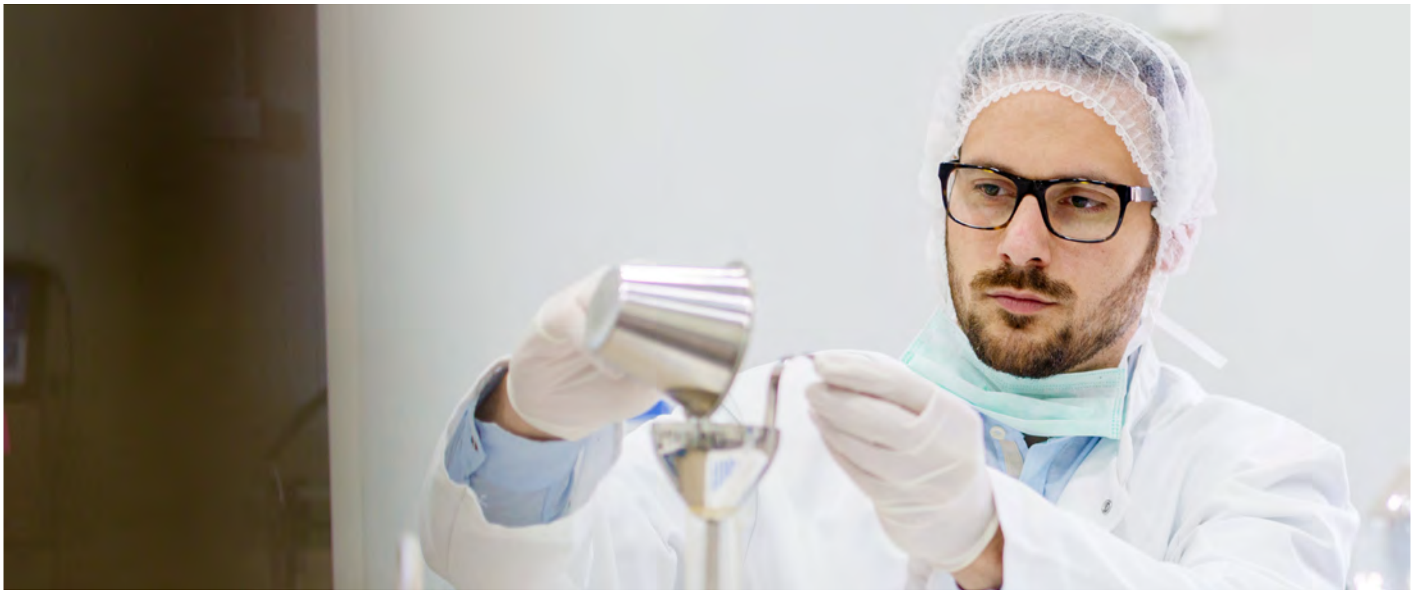


HA as a component of medical products

In Eye Drops and Contact lenses

Contact lenses have become an extensively used medical device, with HA commonly used as an additive for their surface coating, production material, and multipurpose solution [3]. The add-on of HA to specific contact lens solutions could be part of the reason why they work well for particular patients.

HA can also lower protein adhesion to contact lenses and improve hydrophilicity [6]. HA molecules in contact lenses will retain moisture to enhance the wearer's comfort. HA absorbed by contact lenses can also gradually release to the front of the eyes to heal dry eyes.

In the USA, as of 2015, more than 50 million people were suffering from dry eye syndrome [7]. Also, in more than 50% of the cases, people discontinued the use of contact lens due to dry eye and discomfort associated with it, particularly at the end of the day. A cure included the use of rewetting solutions, lubricants, comfort agents, or artificial tears via eye drops to stabilize the tear film. However, the main disadvantage of eye drops is their low residence time (less than 5 minutes) [8].

Extended-release of HA from hydrogel contact lenses to treat dry eye syndrome

A HA-loaded hydrogel contact lens has been successfully developed to treat dry eye syndrome. This form of contact lens can deliver HA within a therapeutic level for 10 days without affecting the optical and physical properties of the contact lens [9]. The HA-CD44 interaction allows retention of water in the ocular space due to its high-water binding capacity.

The HA entrapped in hydrogel sheets has shown sustained release probably due to crosslinked structure of lens matrix and high molecular weight of the long chain-like structure of HA. This compound resists degradation and adheres to the ocular surface for prolonged periods. Contact lenses as a drug delivery device have the potential to overcome the drawbacks of eye drops by providing extended delivery without blurring. The hydrogels appeared safe in a cytotoxicity study [10].

In Osteoarthritis

HA is approved for treating degenerative knee arthritis via intra-articular injections directly into the knee joint. It has resulted in the repair of the damaged tissue, thereby lessening pain and inflammation [11]. HA injections into joints can provide months-long relief from osteoarthritis.

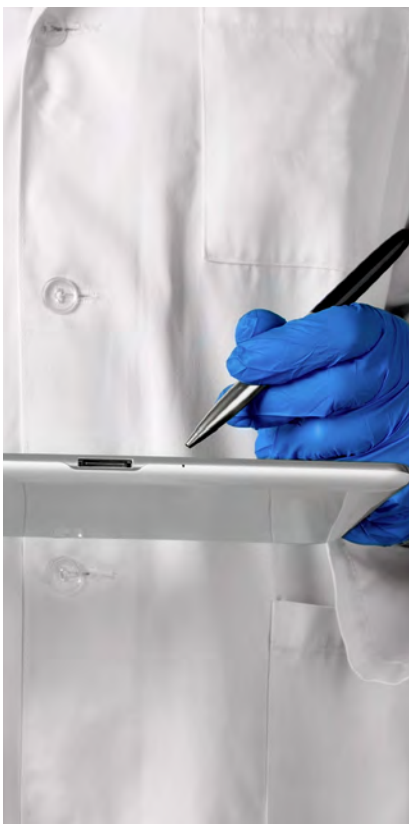
In Cosmetics

HA is a key molecule in skin aging, providing skin moisture by retaining water [12]. While the human body naturally produces HA and acts as 'nature's moisturizer,' cosmetology specialists say an extra drop a day can do wonders for skin tone, texture, and firmness.

HA is used as a dermal filler in cosmetic surgery. Many HA products mainly consist of beauty products, which provide essential moisture to maintain the skin's elasticity and smoothness. These include hyaluronic moisturizers, shampoos, creams, conditioners, and bath oils. A recently approved HA skin filler by the FDA binds to water when injected into the skin, providing volume to easily fill in the larger folds of the skin around the cheeks and mouth.

Today, HA is a workhorse of cosmetics that moisturize skin and reduces the prominence of wrinkles [13]. In medicine, plastic surgeons inject HA as a dermal filler to lift sunken areas in the face. It holds 1000 times its own weight in water. This property is being used in many cosmetic products that come with anti-aging and moisturizing benefits. HA can be used in skincare products or added to health food to reduce dry skin. Due to its high biocompatibility, HA can improve tissue growth to heal wounds when combined with receptors on the cell surface.

HA helps in the reduction of damage caused by scars, wounds, or lines. It is also used to improve the shape of the skin. Hence, it is used as a dermal filler, a major non-surgical procedure. Other key benefits include healing wounds and aiding in UV-damage repair. These special properties are driving sales of products with HA.



In biomedical application

HA is a versatile biomaterial that binds to specific cell receptor CD44 (frequently overexpressed on the tumor cell surface) and is useful in skin rejuvenation, drug delivery, tissue engineering, and molecular imaging. This is due to its biodegradable, non-toxic, biocompatible, non-immunogenic, and non-inflammatory characteristics. HA can be chemically modified by crosslinking, grafting, linking with hydrophobic substances and drugs, or through polyion complex formation with oppositely charged polysaccharides, proteins, or surfactants. Its interpenetrating network produces self-assembled aggregates, nanoparticles and gels etc. [14].

- Drug-HA conjugation enables cancer cell-specific targetting and onsite drug release
- Cleavable HA-drug conjugates have shown dramatic improvement in the absorption and efficacy of drugs [15]
- HA-based products are currently undergoing clinical trials catering to the treatment of various diseases. The use of implant technology can be viewed as a worthy prospect in the future. In situ gelling features of crosslinked HA have been tested for implantable and depot drug formulations [14]
- Sustained-release human growth hormone is yet another functional area using HA (Approval is still pending for this application [16]

HA is still one of the most impressive nanomaterials for constructing various drug delivery systems/ biomedical applications. HA-based nanomaterials show great promise for future biomedical applications in cancer therapy.

Challenges

- High hydrophilicity and enzymatic vulnerability of a native HA make it inferior, relative to commercially available synthetic polymers. This can be overcome through its mechanical enforcement, employing covalent and non-covalent approaches. In addition to improved stability and intrinsic properties, chemical modifications have been shown to dictate the biological fate of HA
- Many experiments show that HA-based nanomaterials can serve as a platform for targeted chemotherapy, gene therapy, immunotherapy, and combination therapy with good potential for future biomedical applications in cancer treatment
- The design and synthesis of structurally defined HA are vital to developing safer and more reliable drugs for a better understanding of structure-activity relationships. Although there is just one commercially available drug delivery product using HA, the molecule has been considered to have great potential as a novel drug carrier in the forms of conjugate and physically and chemically crosslinked hydrogel depot systems etc.
- It is necessary to obtain specially designated molecular weight or uniform size-defined HA to extend the applications of HA and make better HA-containing biomedical products. To achieve low polydispersity, we must know the regulatory mechanisms of initiation and elongation during the synthesis process of HA. The key mechanisms which control molecular weight during HA biotechnological synthesis should be clarified to develop methods to produce more uniform-size defined HA
- Additionally, progresses in metabolic engineering is necessary to improve HA yield and find biosynthetic strategies with good sustainability and acceptable production cost
- While various biological fields are developing, HA in the form of a useful formulation with desired properties such as robust stability, reduced dosage frequency, wide options for its delivery can be envisioned, which can improve its market in a broad sense
- Researchers have found that eating hyaluronic acid has several efficacies, including replenishing skin moisture, relieving osteoporosis, and restoring injured gastric mucosa. China granted hyaluronic acid as an ingredient for health food in 2008
- Rooster-comb HA is losing ground in the medical market. Despite the historical association with rooster combs today, only half of the major brands for knee injection products come from rooster comb. There is a need to find other ways of producing medical-grade HA

Syngene's capability in chemical modification of HA

For over 15 years, Syngene's Performance and Specialty Materials (PSM) group has been developing unique value-driven solutions to meet the innovation needs of its clients. Our capabilities include:

- Expertise in chemical modification of HA such as methacrylation, grafting, and crosslinking for various applications by improving and customizing its properties [15, 17, 18]. We have also developed a commercially viable downstream isolation process to produce high purity/ quality modified HA
- HA-based drug research has seen a recent surge mainly due to some properties like mucoadhesion, biocompatibility, and ease of chemical modification.
- Researchers have also been working on hydrogel contact lenses that can release HA at a controlled rate. Finally, exciting technologies on the horizon for eye care include crosslinked HA

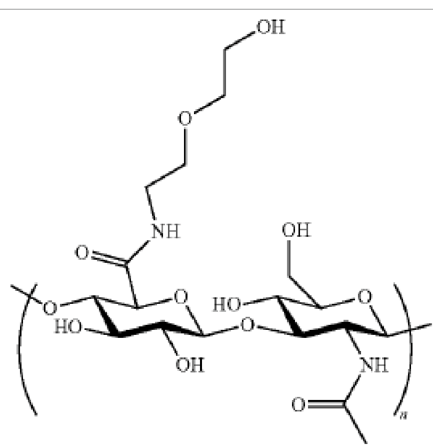
Synthesis of a PEGylated HA (1.2 MDa HA) using 2-(2 - aminoethoxy) ethanol, and a covalently crosslinked network of PEG - functionalized HA using BDDE was reported recently [18]. With the suitable chemical modification of HA (as an additive), Syngene's PSM can contribute to a biomedical device such as a contact lens that is highly comfortable for the wearer by improving wettability, lubriciousness etc. It is believed that the functionalized material has higher stability, longer shelf life due to less enzymatic, thermal, and oxidative degradation. It is also believed that these materials exhibit anti-biofouling, antimicrobial properties for prolonged contact with the body.

Native HA

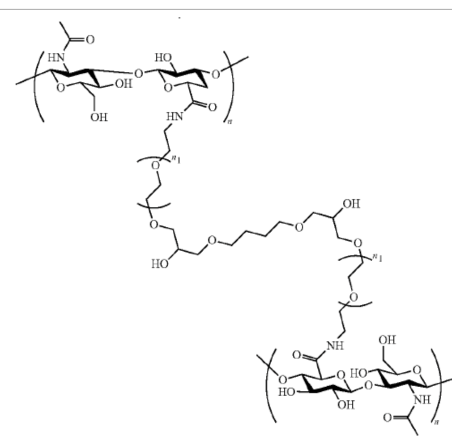
Grafted/Conjugated HA

Crosslinked HA

Chemical modifications of HA [18]



Grafting of HA



Crosslinking of HA

Future roadmap for HA

- Use of strategies like one-pot synthesis, chemo-selective synthesis, solvent-free methods, and 'click chemistry' approaches need to be employed for optimizing the synthesis of HA derivatives
- New chemical modifications of HA to make the cosmetic and medical ingredient even more common than it already is
- Functionalizing the amide and alcohol groups and studying how the modified HA behaves on the skin and in other biochemical environments
- Improving reproducibility of HA-derivatives during scale-up, their pharmacokinetic and pharmacodynamic properties to allow them to be successfully commercialized
- Developing HA-based next-generation products such as innovative crosslinked derivatives, polymer-drug conjugates, and delivery systems to enable high biocompatibility, prolonged half-life, and improved in situ permanence
- Developing economical approaches to make HA more feasible as a drug delivery agent or product. This is because lab synthesis of HA can be a laborious and time-consuming process. As a result, the final product can become very expensive when other costs such as the inclusion of nanocarriers, chemical conjugates, or any other biological agents are involved

Conclusion

HA has immense possibilities for application in the cosmetic and pharma industries. Apart from the chemical modification of HA by grafting and crosslinking, Syngene's performance and specialty materials (PSM) could contribute to creating new applications using 'click chemistry,' functionalization of the amide, and alcohol groups for preparation of HA derivatives, polymer-drug conjugate, delivery systems and so on.

Syngene's PSM unit has a strong legacy in this space, evidenced by robust and sustained growth from the last 15 years. We have clients across discovery, process development, and supply chain for various polymers of commercial importance. This includes polymers for the consumer industry for use in drug delivery (i.e., injectable, hydrogel), in personal care products (i.e., cosmetics, oral care, hair care), and so on.

By partnering with Syngene, you can accelerate your R&D programs in PSM to achieve faster go-to-market with high-quality products which are in tune with regulatory standards.

About the author

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Dr. Rudhramyna Gnaneshwar is a Group Leader-Performance and Specialty Materials (PSM) at Syngene International Ltd, Bengaluru. He has over 15 years of post-doctoral and industrial experience in synthetic polymer chemistry (Anionic/Cationic polymerization, controlled radical polymerization (ATRP, RAFT) for making various homo, random, block, star and comb polymers, ring-opening polymerization (ROP), functionalization of polymers, grafting of polymers, hydrogenation of polymers and so on).

Dr. Gnaneshwar has a M.Sc in Organic Chemistry and a M.Tech in Material Science. He earned a Ph.D. in polymer chemistry from National Chemical Laboratory, Pune. After 2.5 years of post-doctorate studies in New Synthesis Techniques and Application (NSTA) at the Institute of Chemical and Engineering Sciences (ICES), Singapore, and 1.5 years in Mitsui Chemicals Inc. at Sodegaura center, Chiba, Tokyo, Japan, he returned to India. He is currently working in Syngene for the last 11 years.

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