CONTINUOUS FLOW MANUFACTURING
A New Approach to Monomer Manufacturing for Ophthalmic Applications

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The manufacture of monomers for use in ophthalmic applications is driven by the need for higher purity, improved reliability of manufacturing supply, but ultimately by the need for the increased comfort, convenience, and safety of contact lens wearers. Daily wear contact lenses have the potential to fill this need for many customers; however, their widespread use is constrained by higher costs compared to weekly- or monthly-based lenses. New approaches that improve cost structure and result in higher quality raw materials are needed to help make contact lenses more affordable and accelerate growth of the contact lens market.

As consumers migrate to disposable daily-wear contacts and use more lenses, the demand for raw materials will increase. As a result, manufacturing methods must be adapted to provide a high-quality supply while meeting tight cost constraints. Monomers, a key component of contact lenses, are difficult to scale and frequently unstable. This means that to create a successful monomer supply chain for the ophthalmic industry, manufacturers must identify new approaches that incorporate lean manufacturing, efficient scaling, and innovation, while meeting price demands. To do this, manufacturing methods must be highly tuned for flexibility, batch failure minimization, and to produce optimized yields and purity.

Most of the monomer manufacturing for contact lens industry currently employs conventional batch manufacturing methods. The batch manufacturing process most often consists of the introduction and mixing of starting materials in a single vessel followed by a series of operations such as heating/cooling, reaction, distillation, crystallization, separation, and/or drying. The equipment is cleaned after each “batch” and the process is repeated. While batch manufacturing is a well-established method, it does not always offer the flexibility, scalability, and reliability required to meet the changing needs of the contact lens manufacturing industry. The limitations of batch manufacturing become particularly evident when one is confronted with reactions in which longer reaction times or lack of proper mixing result in less than desirable outcome or outright batch failure. In particular, as reactions are scaled up in batch reactors, protracted reaction times required to heat up or cool down reactants can cause unsatisfactory reaction performance. Continuous Flow Manufacturing (CFM) provides a practical solution where batch manufacturing falls short and expands the scope of potential reactions to include approaches that may have otherwise been impractical by batch process.

Benefits of Continuous Flow Manufacturing

- Improved cost efficiency
- Enhanced yields due to cleaner reactions and shorter reaction time
- Uniform mixing and excellent temperature control
- Real-time process monitoring
- Virtually eliminates large-batch failures
- Flexibility to precisely tailor batch size for lean manufacturing
- Improved operational safety

Components of a Continuous Flow Reactor

CFM takes advantage of miniaturization and reactor geometry to overcome limitations faced in certain batch processes. In its simplest form, CFM is performed using a miniature reactor set-up in a manner which allows intimate mixing and excellent temperature control, avoiding the need for long heat-up or cool downs. Further, the tiny reactor volume (typically a few ml) leads to short reaction time (often, seconds) and minimal side reactions. Besides offering a viable cost effective alternative to batch manufacturing, CFM offers excellent risk mitigation through precise process control and virtually eliminates risk of large batch failures.

CFM reactors are based on a system of long, narrow tubes that create a favorable ratio of volume to surface area. Efficient mixing in this geometry is usually achieved by a variety of means including small channels and static mixing. The narrow tubes that comprise the reactor are usually surrounded by a heat exchange fluid that circulates around each “reactor” to precisely control temperature. Pumps, feed mixing devices and collection/work-up devices complete the reaction set-up. Figures 1 and 2 illustrate this design for simple reactors employed in typical organic/polymer reactions.

CFM reactors can be readily customized for small-scale (up to a few kg per day) production through proper choice of material of construction and heating/cooling devices. Sigma-Aldrich has specifically designed and engineered equipment up to kilo-scale synthesis with a wide range of capabilities (Figures 3 and 4), including manufacturing processes designed specifically for the needs of the contact lens industry. One example is included in the next section.
Examples of Monomer Synthesis by Continuous Flow

Acryloyl chloride is an important building block for many directly derived acrylate polymers employed for ophthalmic and other applications. As shown in Figure 5, it is also a starting point for intermediate acrylate monomers that are ultimately converted to polymers used in contact lens manufacturing. Each of these materials can be efficiently produced using CFM. While Sigma-Aldrich has historically offered these monomers in small quantities in the Aldrich Catalog, the use of CFM now enables their supply in a manner that meets the scale, purity, and bulk pricing needs of industrial customers.

Typical Reactions Performed by CFM at Sigma-Aldrich

- Polymer Chemistry
  - Monomers for Biomedical Applications
  - Reagents for Polymer Synthesis (e.g. RAFT reagents)
- Pharmaceutical and Organic Chemistry
  - Pharmaceutical Intermediates (non-GMP)
  - Reagents and catalysts (e.g. chiral catalysts, fluorinating reagents)
- Materials Science
  - Nanoparticle Synthesis
- Specialized Reactions
  - Reactions involving hazardous species (e.g. azides, diazoacetates, cyanides)
  - Stenches

Characteristics of Reactions Suited for CFM

While CFM has many benefits, not every chemical reaction is ideally suited to realize these improvements. Characteristics of reactions that benefit from CFM include:

- Reactions requiring high temp or cryogenic conditions that limit scale in batch processes
- High volume products that require multiple plant runs
- Reactions involving sensitive/unsable species
- Reactions that involve hazardous

Sigma-Aldrich Continuous Flow Manufacturing Capabilities

- Materials of Construction: Hastelloy C-276, 316 Stainless Steel, Fluoropolymer (e.g. PFA)
- Temperature range: -80 to +175 °C, extendable to +300 °C
- Pressure range: 0 to 125 psi or 0 to 8 bars, extendable to 16 bars
- Residence time: 6 seconds to 10 minutes, longer times possible in special situations
- Throughput: Grams per day to 150 kg per day
- Upstream and Downstream batch processing access: up to 4000 gallon batch reactors
- Remote and local digitally controlled systems

For manufacturing needs that fall outside our typical capabilities, Sigma-Aldrich can work closely with customers to create customized CFM equipment that meets special needs. Sigma-Aldrich’s unique capabilities in CFM design and engineering can significantly accelerate project timelines, minimize up front capital investments, and result in excellent returns on invested capital.

Contact Us

Sigma-Aldrich offers customers a unique combination of breadth and depth of manufacturing expertise. Our dedication to supply chain and quality allows us to deliver solutions to meet your raw material sourcing and development needs. Our CFM groups in United States and Europe are backed by the excellence in Service, Quality and Innovation that Sigma-Aldrich represents. Contact us for more information on how our custom capabilities can exceed your expectations.

For more information or to request a quote, contact us at: sigma-aldrich.com/ophthalmic-monomers-contact