The Next Generation of Microextrusion Technology

Microextrusion in combination with new and established manufacturing technologies offers opportunities for innovation.

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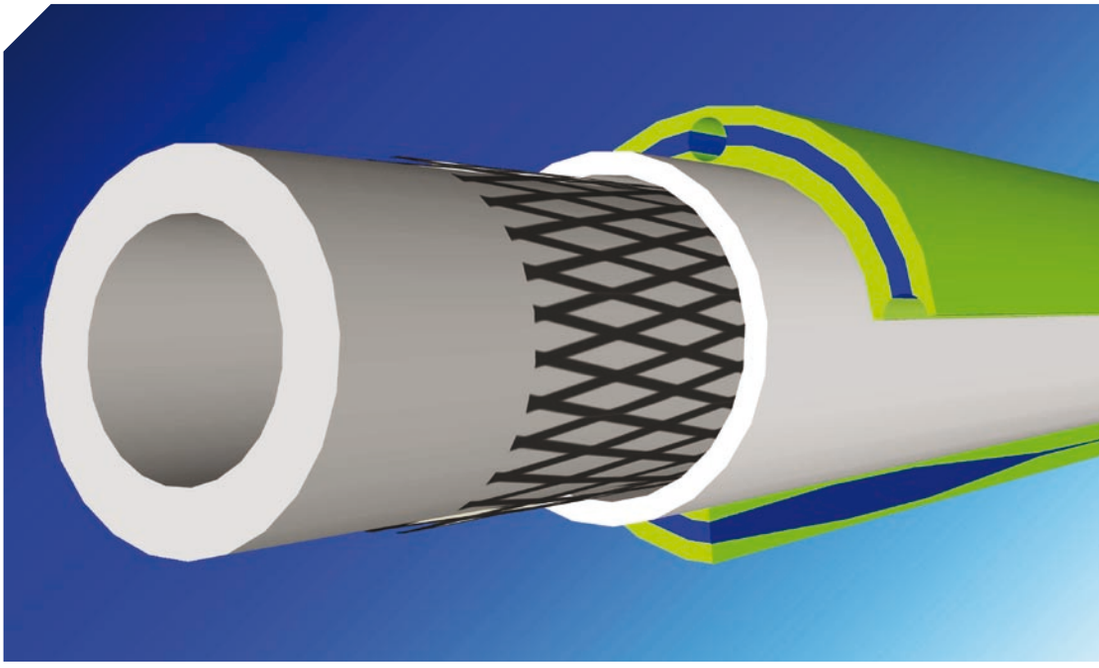
Introducing 2½-D extrusion

Microextrusion has enabled the development of new medical devices and led to advances in tissue engineering and minimally invasive surgery. Now, new technologies that combine extrusion and injection moulding principles are being introduced. They are a form of 2½-D, or intermittent, extrusion and include tapered and layered and totally intermittent extrusion processes.

These techniques reduce the number of catheter assembly operations and production costs whilst improving product quality and safety. The cumulative effect of these advances combined with technologies such as electrospinning and the application of conductive lines on catheter surfaces is providing new opportunities for innovation in hitherto unexplored areas. The objective of this article is to discuss the limits of polymer processing technology and to outline the capabilities of microextrusion to address evolving needs in the medical device and pharmaceuticals marketplace.

Many challenges arise during the development and commercialisation of medical devices, pharmaceuticals and tissue-engineering products: these include managing chemical interactions, process instability, validation and traceability requirements, and scale up from the prototype to full production stage. Materials and processing systems sometimes fall behind in meeting these evolving needs, resulting in delayed product introductions and unrealised scientific advances.



Intermittent extrusion produces tubing with multidurometer shafts.

Rheology and the effect of melting and pumping processes on specific raw materials are not universally understood, which has led to the production of thermally and mechanically compromised components that may hinder real performance potential. As a countermeasure, processes and products have been reengineered, adding costly inspection and sorting steps and compromising product design. Advances in polymer science have enabled the development of specialised drug-delivery and drug-elution devices. Manufacturing equipment must be optimised to process these materials; simply downscaling industrial designs to produce small volumes cannot provide the required performance. Customisable microextrusion systems are necessary to manufacture products that achieve the full potential made possible by advances in materials.

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Defining microextrusion

Microextrusion is an evolution in extrusion technology and not simply a scaled-down process. Well-engineered microextrusion equipment redefines melt pump technology. It eliminates the need for a gear pump, which is an extra part to clean and, by its very nature, is a source of process inconsistency and polymer degradation. Proper microextrusion equipment optimises material processing in terms of molecular weight, crystallinity, processing volume and system cleanability. The term microextrusion encompasses the following important aspects:

- dimensions of finished part (µm scale)
- measurement instrument (a microscope)
- quantities processed (grams as opposed to tons)
- microstructured properties (crystallinity, molecular weight, microscopic inclusions).

Microextrusion systems provide custom manufacturing solutions to fully leverage recent advances in materials.

Approximately a quarter century ago, the biomedical industry created a niche market around microextrusion technology, enabling previously unachievable results. It made possible the consistent precise production of small, complex extrusions. Tubing with multiple layers, lumens and stripes; various types of co-extrusions; and miniaturised products supported the development of advanced medical devices and pharmaceutical products.

Coextrusions mainly are used to distinguish one part from another or for imaging purposes. Coextrusion also can be applied to obtain radiopaque segments or electroconductive lines inside catheter walls. The technique can be used to add time-dependent drug-eluting sections.

Multilumen designs are generally used to introduce guides, optical fibres, tools or fluids. Sublumens also can be used as an actuating space for electro-active fibres or steering wires.

Multilayer cross-sections are mainly applied for radial mechanical functionalisation: to combine a weldable material with one that has certain performance properties, for example, or a material that has adhesive properties with a lubricious one. These constructions can increase burst strength or reduce overall material price because they allow for the use of specific materials only where they are needed. Other functionalities may include the addition of hydrophilic or drug-eluting layers.

Preventing the degradation of raw materials has benefited high-performance applications that require materials with optimised physical properties. Elimination of molecular weight degradation has led to the evolution of process modification–deriving properties, and crystallisation percourse allows the customisation of physical properties.

Microextrusion systems are now optimised for cleanroom environments, and offer the capability to dose fillers, mix

compounds and extrude biodegradable polymers, gels and pastes, drugs in the form of porous and nonporous composites, tubes, filaments, patches and tissue-engineering scaffolds in volumes of a few grams per hour.

Composition of a microextrusion system

A microextrusion system can be made up of several parts:

- Dehumidification system
- Polymer characterisation instruments
- Extruders
- Die heads
- Sizing units
- Cooling units
- Inline wall- and diameter-measuring devices
- Pullers
- Inspection devices
- Cutting systems
- Sorting systems

Parts of the process, such as dehumidification and polymer characterisation, are fundamental for achieving required quality, and functions such as automated inspection and sorting are important to constrain costs whilst increasing quality assurance. With that in mind, the system's core is essentially composed of the following parts:

- **Microextruder.** One or more microextruders deliver the molten polymer, but they perform many other functions. If the system functions correctly, it will produce a perfect melt sans bubbles, gels or nonmolten particles.
- **Die head.** Much has been written about the importance of rheology and surfaces and accuracy in flow shapes. However, each polymer at the molten state is a little different from a mechanical point of view, and it is impossible for a single die head to perfectly process every polymer.
- **Sizing unit.** This is typically considered to be a way to cool the product from the molten state without it collapsing, *if* it is considered at all. In fact, the sizing unit performs the dual function of conditioning the product's mechanical properties and, of course, its size.
- **Puller.** The importance of this part is often underestimated. The pulling speed determines the way in which the melt will draw down. Even a slight inconsistency can jeopardise the rest of the process and generate scrap; excessive force could damage the surface or affect its ovality.
- **Control unit.** The *brain* of the system, the control unit synchronises every component so that optimal performance is achieved even when resin characteristics change. A good system increases operator efficiency since the process conditions can be stored and repeated over time.

Processing challenges . . .

Processing polymers for the manufacture of implantable devices (especially for drug-eluting devices) is not a simple job. There are several challenges.

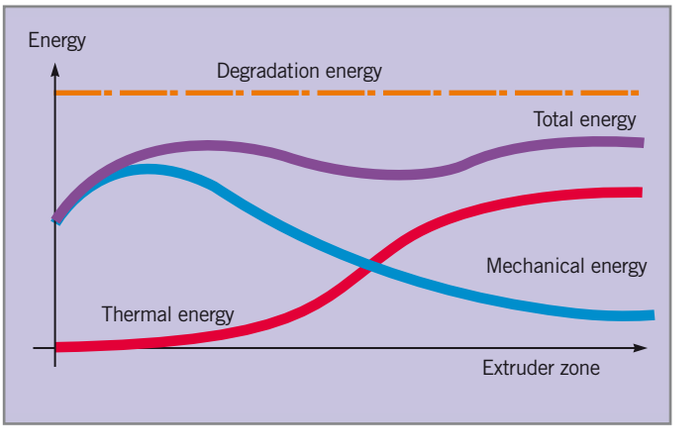
Manufacturers developing devices, especially those used in drug-delivery or critical high-performance applications, may need materials in prototype quantities. Custom materials can be very expensive, and it may not be cost effective to have pricey pellets ending up as scrap. Sometimes it is necessary to add drugs to the carrier resin, raising the cost of the compound by several hundred

euros per gram. At this rate, dead volume and overall performance issues become mission-critical items.

Manufacturers must be mindful that a long dwell time in the barrel can degrade a polymer. A reduction in the material's molecular weight can dramatically change the properties of the device and affect performance following implantation into the body. Extruding a high-molecular-weight biodegradable polymer in a standard machine will result, at best, in a 30% reduction of the molecular weight.

When a microcable coating as well as ultrathin-wall tubing or a submillimetric catheter is extruded, it's important to remember that flow rates can be as small as 1 ml/hr, especially in the start-up phase. Coupling and quality rules require tolerances from 10 to 20 µm in diameter and a few microns in wall thickness; ideally all tolerances should be between 3 and 5 µm.

FIGURE 1: Process energies in the extrusion process.



Also, everything must be easy to clean, and all materials that come in contact with the product must be carefully selected to comply with international standards and regulations.

. . . and processing solutions

Microextrusion technology solves each of the aforementioned problems by a specific approach.

To reduce stress on the polymer, the material is processed under optimal conditions of temperature, pressure and speed thanks to low dead volume, as well as screw and flow channel design. Mechanical and thermal energy is less than the degradation energy, thus preventing degradation of the material's molecular weight (Figure 1).

A microextruder's dead volume is about 10 cm^3, which is dramatically lower than a standard machine.

All of the main process control parameters are absolutely smaller and the relative percentage of error becomes smaller in absolute value.

Smaller smooth surfaces mean less friction and easier removal of material during the cleaning process.

Streamlined instrument design brings handles, buttons and any other process controls within easy reach of the operator. In fact, the core of a microextrusion plant is generally no longer than 3 metres.

Accurate engineering of the flow path—by avoiding edges or low-velocity pockets,

for example—can rapidly contribute to achieving remarkable results. Inadequate melt quality affects not only the visual quality of the product but also its mechanical performance. It should be stressed that rheology is not a simple matter and requires careful thought and the proper computational tools to be addressed effectively.

The impact of microextrusion on molecular weight

Preserving a polymer's molecular weight is one of the most important features of the microextrusion process, as shown in a study conducted by Dr. G. Perale.[1] In recent decades, interest has surged in the use of biodegradable polymers in everything from resorbable medical devices to environmentally friendly plastics.

Among commonly used polymers, polyesters and especially polylactide (PLA) play a key role. One of the first biodegradable synthetic polymers, PLA typically is used for surgical sutures. The material exists in the DL form at various rates, usually 50/50, and in separate D and L forms.

Despite the macroscopic effects of polymer degradation, associated kinetics and device properties are well known and have been widely investigated. Manufacturing processes, on the other hand, have not benefited from the same scrutiny.

PLA polymers are mainly used in fibre form, and wet spinning is the conventional processing method. The wet spinning process causes minimal polymer degradation, but because it is based on solvent dissolution instead of heat-melt technology, the occasional presence of residual solvent does not meet strict requirements for use in implantable tissue engineering applications, for example.

Modern approaches have been studied for the fabrication of micro- and nanoscale drug-delivery systems, but there are significant limitations. Extrusion, for example, carries an inherent risk of degrading the polymer through heat or pressure. It should be mentioned that a growing interest in thin-film methods has been observed in recent years. Since polymer degradation is a key factor that must be kept under control, the case study referenced below aims to test the efficiency of the microextrusion process, evaluating degradation of PLA after processing. The main risk resides in the possibility of significant reduction in the material's mean molecular weight (Mw), with a noticeable worsening of the polymer's mechanical characteristics and a reduction in degradation mean time as well as potential pyrogenic degradation.

PLA is one of the most readily available biodegradable polymers. For the purposes

TABLE I: Resin data sheet.

Physico-chemical properties (provided by producer)	
Intrinsic viscosity	ca. 1.5 dl/g[1]
Molecular weight (Mw)	ca. 265,000[2]
Residual monomer	< 0.5%
Solvents	< 0.1% (acetone)
Heavy metals	< 10 ppm
Tin (catalyst)	< 50 ppm
Water	< 0.5%
Fusion temperature	170°–180°C
Aspect	flocky powder
Colour	white
Odour	none
Mechanical properties for a PLDLA, Mw 250 KDa	
Glass transition (Tg)	ca. 52°C
Melting temperature (Tm)	ca. 170°C
Elastic linear module (E Young)	ca. 2 GPa
Elastic flexural module (G)	ca. 2 GPa
Tensile strength (R)	ca. 30 MPa
Elongation (yield) (DLy)	ca. 3.7%
Elongation (break) (DLb)	ca. 5.5%

1. In chloroform at 0.1% and at 25°C.

2. Mw evaluation may be affected by 5% mean error.

TABLE II: GPC procedure.

Chromatograph	Waters, Styragel columns HR3, HR4, HR5, precolumn
Eluent	DMF +0.05% LiBr
Solvent	DMF +0.05% LiBr
Calibration	Standard mono-dispersed PMMA
Sensor	Refraction index

TABLE III: Viscosimetry procedure.

Viscosimeter	Desreux-Bischoff
Solvent	Chloroform
Temperature	+25°C
Sample conditions	Atmosphere: vacuum Temperature: +4°C

TABLE IV: GPC results.

T2	Mw [Da]	Std	Mn [Da]	Std	D
Flock	269,000	8367	134,000	4183	2007
Granule	262,000	8573	130,000	5099	2015
Fibre	255,000	7906	126,000	4637	2024

of our trial, we chose a "worst-case" commercial-grade PLA characterised by a high mean molecular weight that has been approved for medical use on human patients. The main data are reported in Table I. The chemical and physical properties are provided by the supplier; the mechanical data are deduced from the literature.

The material arrived as a flocky powder. To facilitate extrusion, a granulation process was applied, melting the material at 180°C at low pressure (12.5 MPa). Extrusion was followed by air cooling at room temperature (20°C) and then dicing the material into granules measuring approximately 4 × 4 × 4 mm^3. Vertical extrusion was performed with a three-zone microextruder using a 12-20 low volume screw and 1.00-mm die, all designed by Gimac. Temperature was set between 100° and 115°C in the five extrusion zones. Gel permeation chromatography (GPC) was applied to evaluate molecular weight distribution (Table II). Viscosity was evaluated to obtain confirmation data (Table III).

Molecular weight distribution was assessed for the powder (as provided by the producer), the granules and the extruded fibres. Analysis was carried out on five samples per type. The results are reported in Table IV, where mean molecular weight (Mw), mean numerical molecular weight (Mn) and dispersivity (D) are presented, together with weights relative to standard deviations. Table IV shows the GPC results, and Table V displays the viscosity results. Figures 2 and 3 show, respectively, flock powder viscosity and extruded fibre viscosity.

Mean molecular weight variation was on the order of 5%, within the range of instrumental tolerance; similarly, molecular weight distribution had a variation rate on the order of 6%. Variations in viscosity ranged between 3.5% and 8.5%.

Taking into account instrumental tolerance, the data show neither a significant molecular weight modification nor a correlation with potential polymer degradation ($p>0.05$ on t-test standard distribution).

Physicochemical analysis shows neither a significant difference in the molecular weight distribution nor a significant reduction in the mean molecular weight between PLA samples before and after extrusion. The viscosity evaluation supports the molecular weight analysis. All data remain within the tolerance of the analytical instruments.

It can be affirmed, therefore, that the extrusion technique used leaves the molecu-

lar weight distribution substantially unmodified and does not reduce mean molecular weight. The data confirm that the microextrusion process, as used in these trials, represents an effective and risk-free way to process high-molecular-weight PLA into nondegraded fibres. Furthermore, a variety of dies and heads can be used with the extrusion system to produce tubing in diameters ranging from microns to millimetres.

Revolutionary aspects of microextrusion

Using specific techniques, it is possible to compound specially modified polymers with drugs encapsulated in micro or nanospheres. Optimised compounding ensures preservation of the unique properties of the drug and the material. In the case of thermally sensitive drugs, it is now possible to eliminate multiple exposures to thermal conditions through a single process.

> Process consistency is obviously important, but even more critical **is ensuring that the finished product has consistent characteristics.**

It is currently possible to extrude a drug-eluting product in the shape of a filament, rod or tube with a cross section composed of more than one bioresorbable material, enabling adjustment of the time release and dosage properties of the device. Preservation of the material's molecular weight and its bioresorption properties will enable a precise prediction of how it will interact within the body.

The mechanical properties of a tube or filament, in general, are dependent on the raw material that is used. Nevertheless, modern technology allows us to program a broad range of performance properties into a single resin type. By combining certain process parameters, for example, it is possible to obtain a range of expansion and elongation properties and burst pressures with the same resin. In-depth knowledge of a microextrusion system and the ability to accurately control the process can enable the fabrication of a PA tube or an FEP sleeve with customisable elongation properties that vary between 200% and 600%. (The process is considered stable when the process does not need to be reconfigured each time, but can be loaded from a recipe.)

TABLE V: Viscosity results.

T3	V reduced [dl/g]	V inherent [dl/g]
Flock	1.3083	1.3606
Fibre	1.2627	1.2460

2½-D extrusion

As previously mentioned, microextrusion technology is based on an accurate understanding of results derived from a specific combination of process parameters.

Process consistency is obviously important, but even more critical is ensuring that the finished product has consistent characteristics. To achieve adequate product stability, the system must autonomously resolve issues stemming from variations in the quality of raw materials. If the viscosity changes, for example, the system has to adjust for the variation whilst maintaining a constant output or vary it in a desired manner without deviating from the specified gradient of variation. For this to be achievable, the opposite also must be possible. In other words, as one or more constants are introduced into the system, output is changed in a controlled way. A change in output could be characterised by a change in size or shape or by a variation in the polymeric compound. For example, the most popular way to produce multidurometer shafts is by lamination, which consists of passing different segments in varying hardnesses through a laminating die.

In addition to the difficulty of the process, which requires considerable

operator expertise, it is time consuming compared with a system that is capable of selective extrusion—changing the proportion of soft and hard polymers during the molten phase to alter the stiffness of the finished product.

This technology can vary the overall amount of material and change the cross section of the extrudate to obtain a tapered longitudinal section, which, combined with variations in stiffness, can become a soft-tip shaft or intermittently radiopaque shaft. The process offers a significant cost reduction and does not involve delamination or welding.

FIGURE 2: Flock powder viscosity.

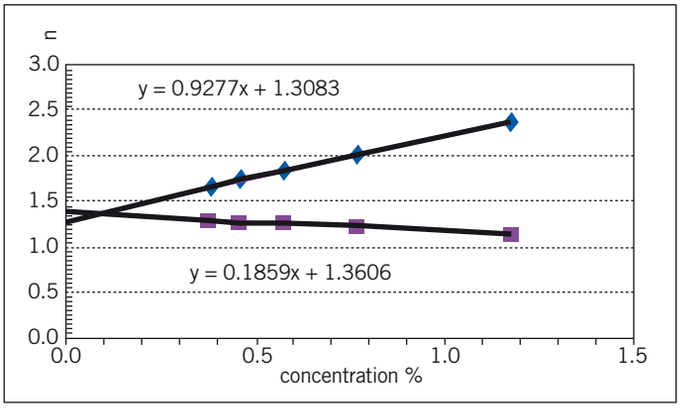
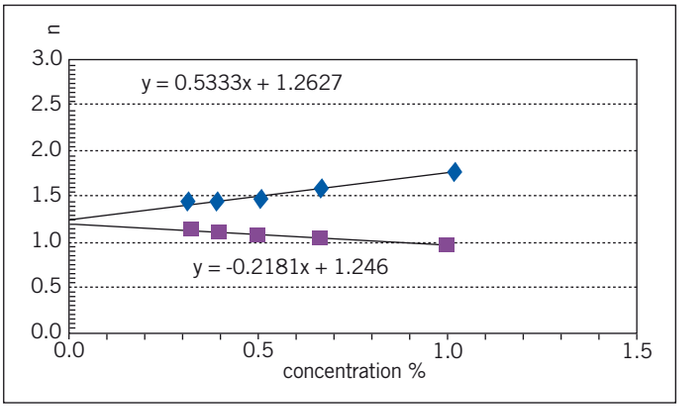


FIGURE 3: Extruded fibre viscosity.



A final example: consider how difficult and expensive it can be to maintain lumen integrity in a multilumen section with varying degrees of stiffness during the welding process. Clearly, the continuous extrusion of a multilumen part with varied stiffness or radiopacity is a simpler and more cost-effective way to achieve the same result.

Solvent-based processing

Solvent-based techniques are used in the device industry to process drug-eluting bioresorbable polymers. This process can be approached as melt extrusion, if melt extrusion is well controlled as is the case in microextrusion technology. Solvent-based extrusion is the only way to extrude polymers that contain highly heat-sensitive drugs, proteins or even cells, or any other kind of biologically active agent.

As noted earlier, microextrusion can be applied to materials that are heat-sensitive by using solvents or heat to liquefy the polymer and turn it into a carrier. The mixture is extruded in combination with special additives in the form of filaments, tubes or complex coextruded structures. With the right expertise, the process can produce hollow fibres with precisely calibrated porosity, regenerative medicine guides, drug-eluting fibres and related devices.

Spinning technologies

Although it is a relatively old technology, electrospinning is becoming popular because associated imaging and biological testing systems make it possible to analyse the resulting structure and biological activity in applications such as scaffolding, filtration and drug release. Electrospinning normally is not the best way to produce large quantities, but it is the best way to obtain nano-porous structures.

Other ways to successfully produce nano-fibres and nano-beads have been

developed recently. A combination of microcoextrusion, solvent-based microextrusion and nanospinning has the potential to produce next-generation materials or composites in the shape of stents and scaffolds that are able to interact with cells in completely new and different ways, either from a mechanical or biochemical perspective.

Conclusion

Microextrusion was developed by Gimac founder, Giorgio Maccagnan, a little more than 25 years ago. The technology revolutionised the use of extrusion in the medical device industry, and thanks to new developments, it is opening doors to yet more opportunities for innovation.

People often assume that the only difference between microextrusion and conventional extrusion is size, that one is just a scaled down version of the other. I hope this article has dispelled that notion and placed microextrusion in the proper context by shifting the point of view from the outside of the finished part to inside the molecule that composes it.

References

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