Extrusion Series | 2022
A Graham Engineering White Paper

Devil is in the Details: Medical and Pharma Processing Material Management

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For any extrusion process, the input materials will require some control method. It is crucial to develop the proper processes around the specific needs, from what is purchased to handling the components once they come off the extrusion line. In this white paper are the general steps in medical/pharma applications.

In each step, we attempt to walk through these and supply at least a modicum of information (not intended to be all-inclusive). In the end, what we all want to avoid is to "do no harm to the material."

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Material Specifications

The material specification is where it all starts. What is specified should be derived from objective data and not standard jargon from a table. Use rheological and thermal data as your tools whenever possible.

Is it a Natural Resin from the Manufacturer?

Does the vendor's specification work for you (not the TDS)? If so, have you tested/validated your process, factoring in the variation you might see from the vendor? While it may be impossible to test the entire range, the more variation you input into your process development and validation strategy, the better off you will be

Does the Supplier Offer Support for the Med/Pharma Industry?

Using "non-medical friendly" vendors should be avoided. At some point, you will need support. If you do require a narrower range for a specific attribute than what the vendor offers, the vendor will need to agree to supply you with it. A caveat to this will always be to make sure what you ask for is necessary. As an example, if the manufacturer's MFI range is 3 to 15 and your process data shows that you need something less, a supportive vendor will supply you with historical data. If their data shows that 75% of their lot distribution meets a 5-9 MFI, that fits what you need. You then know your risk level and can have a mitigation plan (inventory levels vs. use, etc.). Suppose their data shows that only 20% of their lots meet your needs. In that case, you might want to redevelop the process with a much more comprehensive range or rethink the material choice.

> "At some point, you will need support.

Is it a Compounded Resin?

Now there are three or more vendors nested and at least one process step/heat history? Have you tested and validated the possible range one is expected to see? Does your compounding partner have the proper controls in place for their vendors? Do they have the engineering bandwidth to institute the appropriate controls in their processes to deliver what you need regularly? Can they conduct the proper tests for the release of materials based on specification? Can they properly control the input materials? The goal is to use a compounding vendor that will minimize your risk. When it comes time for your vendor quality audit, consider conducting an engineering audit.

WE LIVE IN THE WORLD OUR QUESTIONS CREATE

- DAVID COOPERRIDER

Is it a High-Cost Resin?

Some natural resins are high cost. Bio-absorbables and implantable resins come to mind. The compounding of fillers, colorants, and APIs adds to the complexity. Compounded polymers with the usual radiopaque fillers are expensive and prevalent in the industry. Tantalum and Tungsten fill escalate those costs even further. What is specified for these materials will be important, and consistency will be one of the keys to success. Don't guess what you need. Test material limits as much as possible and determine what is best for the process and product. Testing is inexpensive when compared to scrapping high-cost materials. There is nothing worse than processing thousands of dollars per hour of scrap material on the extrusion floor. The price grows further up the manufacturing chain it goes and can be a disaster if it makes to the patient.

When putting together a material specification, one needs to weigh the balance of the higher cost and potential risk of supply issues. Test the range limits whenever possible, even off-spec materials, and you might be surprised when developing a "process window" for what can be accounted for.

Once the material is received, it will generally go through a receiving inspection process where all documents will be collected, verified, and stored. Part of what happens here is based on the specification. Samples may be sent to a lab for testing unless the vendor has been contracted to do so.

Incoming Inspection

When purchasing an off-the-shelf material in vacuum-sealed bags, please do not force your inspection team to measure pellets, mainly the hygroscopic resins. Most vendors usually control Pellet geometry well, and if they change their processes, they should notify you. Not that they can't be measured, but should they? Is it critical, or are we just looking for something to inspect? Hygroscopic resins will usually specify moisture content as packaged before vacuum sealing in a vapor block container. Once that container is breached, the moisture content will rise until it reaches an equilibrium with the new environment. This affects the amount of time needed to prepare the resin in manufacturing, which can often be overlooked (storage/material handling/staging and moisture still to come).

Trust but Confirm

When a material shipment arrives, a certification of analysis that the material complies with the manufacturer's specification should be included. They will have those test results listed (some still supply a CoC stating that the material meets requirements without data). If they agree to your specification, they should also provide their documentation with all the information you asked for – part, specification, PO, lot number, etc. The test results you've asked for should also be included.

Now the question is, do you verify their results by completing internal testing? Sure, there are ASTM and ISO standard tests that can be performed, so it should be straightforward. Just remember that you may come up with slightly different results based on the time function of polymer creation vs. your receipt and material type. You may even test for items not specified by or to the vendor (such as rheology information beyond MI, thermal analysis, Mw, etc.). Still, unless the vendor agrees to any part of the specification, it may be challenging to obtain an RMA based on these results.

Specialty Compunds, Compounds with APIs, and High-Cost Implantable Materials

The cost of compounded engineering resins increases by 2.5-5x, possibly more, depending on the filler/color. APIs bring them to another cost level. Implantable materials are even more costly before being compounded with additives or APIs.

Testing for Risk Mitigation

If your focus is on the patient, company finances, or both, the best way to mitigate risk is by conducting objective testing. Compounds and high cost implantable/ bioabsorbable materials should have at least rheology testing (even if it's not part of the specification) completed to build a historical database and thermal data/Mw depending on what is genuinely applicable to your process. This data can be correlated back to process parameters and will help your team to mitigate or minimize problems at some point.

Testing for Cost Savings

Think of it this way, if your organization buys a 2,000 lb. pallet of off-the-shelf (OTS) grade Pebax the cost is $16,000+. By spending an additional $1,200 for DSC, Mw, and capillary testing, you could reduce your scrap and be able to make another 100 lbs of product. The testing saves the material cost and the labor and overhead costs of producing scrap. Issues that make it to the downstream processes and fail create additional losses (balloon tubing, reflow processes, etc.).

Now think about applying that same formula to a 2,000 pound batch of Barium filled Carbothane, which costs $60,000-$80,000. You can also apply these numbers to many bio-absorbable resins, where a 5-kilo batch could cost more than 2,000 lbs. of Pebax.

What's Next?

Material specifications are complete, materials have been received, and gone through the inspection and testing processes (and the test results have been hopefully digitized and placed in a readily accessible location). The materials now need to be moved from the QC hold area and into storage. At this point, the company has already used capital and resources to obtain these assets. So what happens next?

What does the manufacturer recommend for storage? Based on your expected shelf life and your downstream processes, it may be good to conduct a gap analysis of minimum requirements vs. what you need.

You Have to Control the Environment

Almost every manufacturer will specify a controlled environment, minimal exposure to light, etc. Is your warehouse able to meet these specifications? Depending on the climate where you are located, is it hot and humid or cold and dry? While the area doesn't necessarily need an ISO clean room, it should be temperature- and RH-controlled, especially for high-cost slow-moving materials. 50lb. batches of compounds can last more than two years, even with frequent use for small and thin wall components.

Packaging Could be the Key?

Many high-cost bio-absorbable resins require low-temperature storage to maintain shelf life. These are usually supplied in low moisture vapor transmission rate (MVTR) packaging and should be returned to stores in the same vacuum resealed packaging. A vacuum sealer with MVTR packaging is not that expensive today compared to the material cost. It also makes economic sense to invest in the proper storage conditions for these costly materials to ensure maximum shelf life and processing characteristics. An industrial-grade refrigeration unit that offers redundancy is highly recommended.

Economics vs Risk

Other packaging options are less costly and can be considered depending on costs or criticality. Repacking systems offer low moisture transmission foil-lined and vacuum-sealed storage. More critical materials can be stored in light-blocking nitrogen purge container systems. It depends on what makes economic sense vs. the potential risks based on your inventory value or product lines, especially when one needs to balance price break quantities versus inventory turns.

How materials are issued to the floor can be critical. The higher the material cost, the more critical it becomes.

Moisture Equals Viscosity

How materials are issued to the floor and staged is important, the higher the material cost, the more important it becomes.

Remember, moisture = viscosity. One of the best ways to ensure that processes do not shift over time is to manage the material drying process.

Know Your Process

Things to consider to ensure minimal effect on material properties and process when drying hygroscopic resins:

- **What is the dryer capacity vs. the process's planned output (lb/hr)?**
- **Expected run time and planned material usage based on quantity of components required and calculated/ estimated yield factors?**
- **Maximum moisture content for the process?***
- **The longer the residence time, the lower the moisture content will need to be for many materials, yet too dry can also be a problem.**

***Note: not all methods are the same. Manufacturers' recommendations are based on process residence time in seconds, and many medical and pharma techniques can have extended residence times beyond the general recommendations.**

Know Your Material

Things to consider, continued:

- **How long and at what temperature do you need to dry the resin?**
- **Can you set back the temperature to maintain the moisture level, or do you have to continually refill the drying system?***
- **If you estimate that your run requires 5 lbs of material, do you fill a 50 lbs hopper with material and expose it to temperature for extended periods? It would be better to dry maybe 7 lbs. of material instead to avoid multiple drying heat histories to the resin.**

***Note: some PLC controlled units have features to minimize over-drying, but if you don't have these features available, it would be wise to understand that if it takes 4 hours to dry the resin, and your output is 5lbs/hr with a 10 lb hopper, you could run into trouble.**

Minimize Resin Esposure

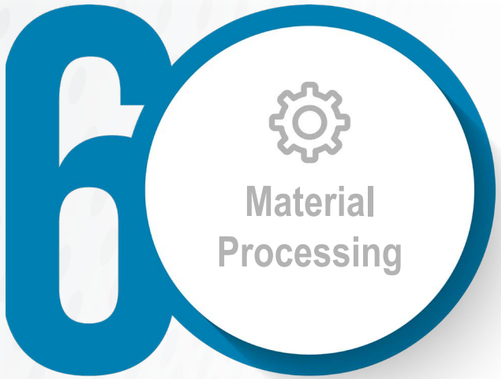
Things to consider, continued:

- Right size your drying systems whenever possible. In the above, a 7 lb batch of material will not dry efficiently (if at all) in a 50 lb capacity hopper.
- When the process is complete, remove the remaining material from heat exposure and package it adequately to return to storage.
- It is best to minimize resin exposure to drying temperature and is very important for resins where a small batch goes a long way. Knowing your processes, output rates, and yield factors is best and planning accordingly. These are usually well-known KPIs for the business end, so it shouldn't be too difficult to use for the operations to develop relevant best practices.

Test and Understand Moisture

Things to consider, continued:

- As well, many processors will verify moisture content before starting a process. Very few prove moisture content after processing has begun. Still, it would be good to trend moisture with process disruption throughout an extended process, especially when there are mismatches in drying system capacity and extruder output.
- Review how materials are returned to inventory to ensure they are correctly packaged, especially if you rely on time and temperature to properly dry materials without using a moisture analyzer.



This white paper is meant to be general enough to apply to any material based on what is essential to the material and/or device.

PERFECTION HAS TO DO WITH THE END PRODUCT, BUT EXCELLENCE HAS TO DO WITH THE PROCESS

- JERRY MORAN

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Component Handling & Storage

The final storage of parts and components is critical to future processes. By taking advantage of proper storage and storing techniques, you can set up future projects for success more effectively.

Is Component Storage the Secret Weapon?

How are your components stored? Are you practicing single-piece flow/JIT manufacturing? This is hard to do with extruded parts where the output rate is usually higher than what can be processed downstream, so batching product is prevalent.

Are parts stored in your cleanroom in PE wrap and left on tables? For how long? Remember, clean room lighting will have a much higher candle power at working levels than standard room lighting, and there is plenty of UV to go around unless you are equipped with non or low UV lighting. Most medical and pharma materials do not use UV inhibitors, so design your storage wisely.

Know Your Warehouse Inside and Out

The same thing goes for parts stored in separate climate-controlled rooms for extended periods. The top of the racking will be exposed to even higher levels of UV, so ensure to keep components in either UV block PE liners or bins whenever possible. Review your warehouse environment for components stored in the warehouse and use the same UV block packaging or containers.

More so than most other applications, there is a lot of time, effort, and money invested in processing medical and pharma extrusion processes because of GMP/ISO/Regulatory requirements that will create many control points and the critical nature of components. Not controlling the "bookends" of the process can lead to issues, especially with the effort invested in the process.

FDA 483 root cause investigation responses have changed how a company handles many processes, including materials procurement and use. Many issues can be avoided with proper planning, and no one wants to be on the wrong end of an FDA audit.

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