

Can Hot Melt Extrusion Displace Spray-Drying in Solubility Enhancement?



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ot melt extrusion (HME) is a well-established technology in the pharmaceutical industry, where it has been used since the 1980s. Applications include the preparation of controlled release dosage systems and other novel dosage forms, subcutaneous implants, taste masking, and as an alternative to the traditional solvent casting method in making orally dispersible films for patients who are unable or, in the case of children, unwilling to swallow tablets. It has also been used on a small scale in anti-tampering applications.

Solubility: The Perennial Issue

All that said, the original main driver and overwhelmingly the most important application for HME – by some estimates accounting for 90% of its use in pharma – lies in improving solubility and consequently bioavailability via the manufacture of amorphous solid dispersions (ASDs) for oral solid dosage (OSD) forms, mostly tablets and capsules. HME is also used as a continuous technology to produce these OSD forms as the pharmaceuticals industry slowly gets to grips with continuous manufacturing principles that have long since been accepted in many other industries.

The technology is really quite straightforward, according to Dirk Leister, who is technical marketing leader at Thermo Fisher Scientific, one of the major players in the field. "What is needed, beside the extruder itself, is a suitable polymer," he explains. "There are different grades and types of polymer, which becomes molten in the barrel of the extruder, and the API is distributed on a molecular level in the molten polymer. When it solidifies again, the polymer acts as a solubility enhancer. The API is then incorporated into the tablet, which helps the body to absorb it."

Similar principles are used in the preparation of novel dosage forms, particularly implants. In these cases, the APIs are typically loaded in small rods about ½ mm in diameter and about 2 mm long. These are administered subcutaneously and release the API in a controlled manner over a longer period of time.

When it comes to ASDs, HME mainly competes with spraydrying. Electrospinning and nanomilling are other options but these two account for the majority of current use in pharma. There is a perception



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minimal but at manufacturing scale, HME's advantages come more into play, according to Leister.

The extruder has an external heatable barrel to contain the dispersion. Inside this there are turning screws, which generate mechanical energy. "So at a certain point in time, when we have a steady state in the process, we don't need additional heating energy for the barrel; the mechanical energy that's been dispersed with the screws inside the polymer/API mixture is enough to do the mixing."

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in some parts of the industry that HME is dwarfed by spray-drying, but this is sometimes exaggerated. According to figures given by PharmCircle in 2020, HME accounted for 11 of the 48 of the amorphous dispersion processes used in marketed ASD products, whereas spray-drying accounted for 22.¹

Environmental Advantages Of HME

Given that about 50% of new molecular entities (NMEs) are poorly soluble and that drug solubility is widely, though not universally, perceived as the single most important technical problem the industry has, there should surely be scope for wider use of HME. So what are its key advantages and what has held back wider use?

There are also some key credentials of HME when it comes to the kind of environmental impact issues that the pharmaceutical industry is now having to address. Energy consumption is one. The differences between HME and spray-drying equipment at R&D scale is spray-drying. That makes HME the obvious choice for compounds that are unstable in solvents. More widely, the pharmaceutical industry consumes huge amounts of solvents, at least relative to the volumes of the final products it makes. This brings regulatory attention to the industry. In addition, the need to contain, recover and recycle these solvents costs substantial sums.

Energy costs and solvent use are the 'big two', in Leister's view but the list does not end there. HME equipment is intrinsically more versatile because the same machine can carry out multiple different applications. The footprint of HME equipment is also significantly smaller. The Thermo Scientific 24-mm extruder, for example, has a footprint of about 1.5 meters by 0.5.

"With spray-drying, you really have to have the big spray chambers and they are somewhat optimized for a certain amount of material you need, say 100, 200 or 300 kg," he says. "That's completely different with the extruder. When you run them, let's say at 25 kg per hour, you just make the processing time however long you need it to be to get your 300 or 400 kg. You don't need a bigger machine."

Scale is certainly not an issue for the use of HME outside the huge-volume generic products like aspirin or paracetamol, Leister says. HME is broadly applicable in both small volumes in R&D and formulation and in almost all the volumes the pharmaceutical industry needs, perhaps even more so now than before because the 'blockbuster' model is in decline and many more drugs are made in relatively small volumes.

Other than possibly in terms of feeding, scaling up is also not a major challenge for HME and there is plenty of data in the literature about it, Leister adds. "At the end of the day, it depends on the process. Each process is a bit different, but there are good technical and scientifical approaches to scale-up and the good thing is that, if you look at the process parameters you can control quite tightly within an extruder. There is not much volume in the barrel of the extruder, whereas if you have a big spray dryer, there might be areas where there's bad agitation."

Dr Thomas Quinten, principal scientist at The Janssen Pharmaceutical Companies, a subsidiary

of Johnson & Johnson, says that Janssen uses both HME and spray-drying extensively and the use of both is driven almost entirely by solubility and stability considerations. Where there is a choice to be made between them, this is determined by what works best.

"In the beginning of a project, we try to characterize our API extensively, in order to characterize the most important physchem properties. Sometimes we evaluate both technologies in parallel. We look at those



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concepts and perform extensive stability testing, and then we see for example which technology gives the most stable ASDs," he says.

Moreover, finding out which option works best for any given compound is as much an art as a science. It depends on the molecule and why one works better than the other in a specific product is sometimes hard to explain. This is why investigating both at the outset can pay dividends.

Temperature: A Roadblock?

The most commonly cited drawback for HME is the high temperatures intrinsic to the process. This is certainly the key factor holding back wider use in Quinten's view. Only a limited number of the polymers available allow compounding or processing at higher temperatures. Most have melting points of around 200°C, which raises issues of polymer degradation, the loss of functional groups, browning and/or charring. Those that can be processed at high temperature are not necessarily the most efficient in stabilizing any ASD. Spray-drying, meanwhile, typically takes place at temperatures well below 60°C.

"The melting point of an API is extremely important

because often the most stable solid form in the screening experiments also has a high melting point, so if we see that the melting point is 200°C or more, we know HME will be difficult, and we go to spraydrying. On the other hand, if we see that certain molecules or solvents are unstable, then of course HME can become important," he says.

"If there really are stable polymers out there that on the one hand allow for a stable HME process and on the other are capable of stabilizing the ASD - because the polymers do also have a function towards and stabilization of the ASD and the bioavailability because they have to be the spring-shoot mechanism - that could help to promote HME." More excipients that allow processing at higher temperatures would also "be a big pro" in Quinten's view.

Leister concedes that temperature "certainly is a challenge when you look at the pure figures." However, there are ways around the problem. The barrel of the extruder is segmented, so while a certain amount of time is needed for the polymer to travel from the inlet to the outlet, it is possible to insert the thermolabile components of the



"As Leister and Quinten agree, R&D people are willing to try out alternative technologies but there is a huge amount of inertia to overcome if these are to find their way to use at manufacturing scale." drying," Quinten says. Janssen itself, like others in the industry, is taking many environmental initiatives in different areas, but when it comes to ASDs, "it's the technology that provides the most stable ASD that often wins."

The need for downstream processing has been cited as another drawback of HME, though here too Quinten does not entirely agree. At worst, this is a minor detail and spray-drying can also require further processes, notably where spray-dried have poor flow or need compaction. "For HME, we can mill it quite well to the particle size that we desire. We can do it with a method that doesn't generate too much

formulation, such as the API, at a later point in time.

"In this way, we can cut down the time these APIs are exposed to the temperature. With a good process design, it can help to minimize or overcome the problem of a higher absolute temperature. You can use or design the process in a way that your API isn't exposed so long that it's really harmed, and that's something that we try to help our customers to do. We have demonstration labs, and application experts and expertise we can bring to the table when the customer is starting anew with HME and does not yet have the experience that we have."

Sometimes, in addition, the pharmaceutical industry is just not very green-minded. Solvents per se are not yet a main driver in its decision tree. "If, for example, spray-drying looks likely to give the most stable ASD despite the amount of organic solvent needed and the ecological footprint, we would still go for sprayshear or heat, then we can just basically apply direct compression to it. It's an extra step but not one that can kill a program."

Changing Industry Mindsets

Probably the single biggest factor that has held back wider adoption of HME is the intrinsic conservatism of the pharmaceutical industry, in terms of its mindset, the restrictions the filing system places on changes of process and an installed base of equipment. As Leister and Quinten agree, R&D people are willing to try out alternative technologies but there is a huge amount of inertia to overcome if these are to find their way to use at manufacturing scale.

"When we are talking about manufacturing and established production process qualified by the authorities, then there is very little or no chance that the technology being used will change," says Leister. "But when we talk about new projects and products being developed from the ground up, that's the point where the new technology can make its way from R&D to production in the end."

There is something of a chicken-and-egg issue with wider adoption of HME, Leister continues. Like many technologies, HME "needs a bit of expertise to make the best usage out of it." Where a large pharma company will have labs with HPLCs at all its sites, many standard procedures, and multiple experts in using it, when it comes to HME there will more typically be one or two labs throughout the organization and just a handful of experts.

"They bring the project to the instrument rather than having an instrument for each formulation scientist. That could change with a change in the ease of use of the instrument. So that's one point that we at Thermo Fisher Scientific are trying to emphasize with the development of all of our new extruders," he says.

Where HME is established in the production process or has been part of a project that transitioned successfully from R&D to pilot to manufacturing, Leister continues, users are much likelier to be willing to invest in a second project or different manufacturing capabilities

in hot melt. Getting a foot in the door is much harder where there is no experience of the technology. Help from a vendor with specialized knowledge in the field can be a major boon here.

"For customers who are new to the technology who would really like to work together with a CDMO, within the Thermo Fisher world our colleagues from Patheon are capable of running experiments on an extruder as well as spraydrying. They can really give the



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customers the chance to experience it first-hand and get data and results for their project."

Janssen, Quinten says, has many large spray-drying installations available in-house and more than 20 years' experience of the technique, as well as five or six commercial programs using it, whereas it has limited in-house HME capacity. Thus, there is always a strong commercial push towards spray-drying. However, he stresses, this is not a determining factor.

"We like HME technology; it's just that we don't have the commercial supply and that always plays a role. So, what's preventing us from using it more? Not really anything. For example, we have some initiatives and then although we don't really always have all the equipment, we can easily go to external partners. So that's a problem that can be solved."

Outlook

As well as improvements in technology related to polymers, Quinten sees the lack of third-party vendors in Europe as a brake on Janssen's wider use of HME at commercial scale. Currently, there are few other than Thermo Fisher and AbbVie, which is a competitor, who can offer compounding. Thus, European-based

> sponsors usually have to go to the US at when they would naturally prefer to work with European partners for the obvious reason of budgets, travel restrictions and time zones.

> Quinten does see an opportunity for HME as the industry moves towards continuous manufacturing. Where relatively large batches of 50-70 kg of ASD are needed, spray-drying has its limitations and HME could come into its own. At present, this option is simply not well enough

known and there needs to be more commercial HME partners available in the world to promote HME. Inertia will always be a factor, he adds, but still, HME has its promise because "if you go towards compression, a particle made by HME is denser than one made by spray-drying and it gives a better tableting process."

Leister is also seeing quite a number of customers exploring the HME process beyond the familiar areas of bioavailability for novel dosage forms and its suitability for continuous manufacturing. He is also seeing growing interest in some quarters about switching from spray-drying. A major customer recently tried Patheon's hot melt capabilities on a project in the R&D stage and ultimately made the switch to HME.

"One of the buzzwords might be 3D printing of personalized medicine," he says. "You can perfectly produce filament in the 3D printer that's loaded with API using an extruder - and there is also the nature of the instrument being a continuous and very stable process. This, I would say, are the two features over the long term that will help the adoption of extruders and HME."

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