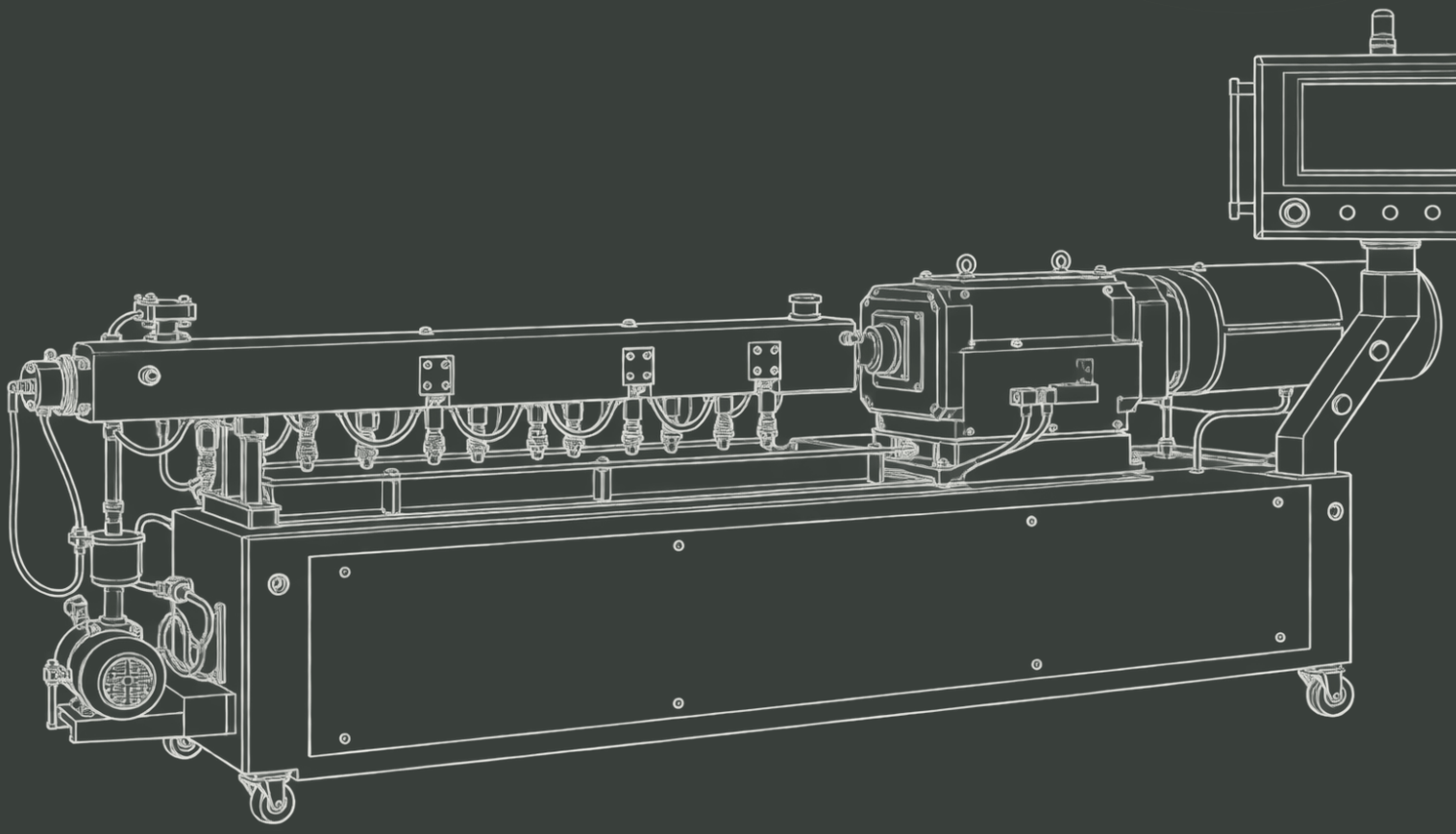
Forma

PERSPECTIVE · AMORPHOUS SOLID DISPERSIONS

Are we choosing the right ASD technology, or just the familiar one?

Hot-melt extrusion has a perception problem. And the industry may be leaving significant value on the table because of it.



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Hot-melt extrusion has a perception problem

And I believe the pharmaceutical industry is leaving significant value on the table because of it.

Between 2012 and 2023, the FDA approved 48 drug products containing amorphous solid dispersions (ASDs). Spray drying (SDD) accounted for approximately two-thirds of these approvals, with hot-melt extrusion (HME) representing most of the remainder.

48	~⅔
FDA-approved drug products containing ASDs, 2012–2023	of those approvals used spray drying; HME made up most of the remainder

That imbalance is interesting, particularly when we consider the commercial advantages HME can offer: continuous processing, smaller manufacturing footprints, solvent-free operations, and potentially lower manufacturing costs.

So why isn't HME used more frequently?

Having worked extensively with both technologies, from early formulation development through scale-up and commercialization, I don't believe the answer is that spray drying is inherently superior.

I believe we have become too comfortable selecting SDD early in development, often before fully evaluating whether HME could deliver an equally effective, and potentially more commercially attractive, product.

And that decision can have consequences well beyond formulation development.

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We need to stop equating API melting point with HME feasibility

One of the first questions asked when evaluating an API for HME is its melting point.

If the API melts above 180–200°C, HME is often dismissed because of concerns about thermal degradation.

I think this is an oversimplification.

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> The objective of HME is not necessarily to melt the API. It is to achieve a molecularly dispersed drug within a suitable polymer matrix.

Those are two very different requirements.

The API's crystalline melting point does not dictate the temperature at which an amorphous dispersion can be manufactured. Drug-polymer miscibility, polymer viscosity, plasticization, and processing conditions all influence the temperature required to achieve a homogeneous dispersion.

Consider polymers such as Soluplus and Eudragit EPO. Their relatively low glass transition temperatures, combined with appropriate plasticizers or surfactants, can create processing windows substantially below the melting point of the API.

A recent study by Benson et al. (2026) demonstrated this principle using encorafenib, an API with a melting point of approximately 189°C. By combining computational modeling with material-sparing experiments, the researchers identified formulations exhibiting substantial melting-point depression, including a 25% drug-loaded Soluplus system with a measured melting transition around 157°C.

189°C	~157°C	<1 g
Encorafenib melting point	Melting transition in a 25% drug-loaded Soluplus system	API needed for a meaningful HME feasibility assessment

What interests me most about this study is not simply the temperature reduction.

It is the development strategy.

The researchers demonstrated that meaningful HME feasibility assessments could be conducted using less than 1 gram of API.

For early-stage programs, where API availability can be severely constrained, that changes the conversation.

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> We should be using predictive tools and targeted experimentation to determine whether HME is feasible, rather than using melting point as a reason not to investigate it.

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Thermal degradation is a function of temperature and time

The second misconception is that exposing an API to elevated temperatures automatically makes HME unsuitable.

Thermal degradation is fundamentally a kinetic process.

An API exposed to 170°C for two minutes may behave very differently from the same API exposed to that temperature for thirty minutes. Some compounds degrade rapidly, while others remain sufficiently stable over the short processing times associated with extrusion.

This is why I believe conventional thermal screening, while necessary, is insufficient for making HME technology-selection decisions.

We need to understand the actual degradation kinetics under relevant processing conditions.

And we need to recognize that the barrel temperature displayed on an extruder is not necessarily the temperature experienced by the material.

Screw configuration, shear, viscous dissipation, melt viscosity, throughput, and residence-time distribution all influence the thermal and mechanical history of the formulation.

These are engineering variables that can be studied and optimized.

A formulation that fails at 180°C with a five-minute residence time might perform acceptably at 150°C with a shorter residence time, provided the lower-temperature process still achieves the required drug-polymer mixing and amorphization.

This does not mean every thermally sensitive API can be processed using HME.

It means we should establish the actual processing window before concluding that it cannot.

The often-cited albendazole comparison by Hengsawas Surasarang et al. demonstrated severe degradation during HME, while spray drying successfully produced an ASD.

That is a legitimate limitation of HME under the conditions evaluated.

But I would argue that the appropriate conclusion is not that high-melting-point APIs are unsuitable for extrusion. It is that the formulation and processing window must be established before committing to the technology.

There are also successful commercial examples that challenge the conventional temperature argument.

Nilotinib, for example, has a reported crystalline free-base melting point of approximately 235°C. Yet patents associated with the development of Danziten describe HME processing using HPMCAS at substantially lower temperatures, around 120–160°C.

~235°C

Nilotinib crystalline free-base melting point

120–160°C

HME processing range with HPMCAS described in Danziten-related patents

The important takeaway is not that HME works for every high-melting-point compound.

It is that melting point alone is a poor basis for excluding it.

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The real question: can both technologies deliver the same product performance?

There is another assumption worth challenging.

Even when HME is technically feasible, SDD is frequently perceived as the better option for achieving dissolution enhancement.

That may be true for some molecules. But it is certainly not a universal rule.

A 2024 study by Trenkenschuh et al. compared ternary ASDs manufactured using HME and SDD with HPMCAS as the polymer carrier.

By incorporating TPGS as a surfactant and plasticizer, the researchers were able to reduce melt viscosity and manufacture extruded dispersions with solid-state characteristics comparable to those produced by spray drying.

More importantly, adjusting the particle size of the extruded material enabled comparable dissolution performance.

This is particularly relevant from a manufacturing perspective.

In SDD, particle size, morphology, residual solvent, drying kinetics, and formulation characteristics can be interdependent. Changing one process parameter can affect multiple critical quality attributes.

HME offers a different manufacturing approach.

Once the dispersion is established, downstream milling and particle-size engineering can provide additional flexibility to optimize the material for its intended dosage form.

Of course, milling introduces its own challenges, including heat generation, particle-size variability, and downstream flow or compaction behavior.

But the broader point remains:

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> If two technologies can deliver comparable physical stability, dissolution, bioavailability, and product quality, why wouldn't we seriously evaluate the one with the more attractive commercial manufacturing profile?

That should be a fundamental part of technology selection.

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We spend too much time optimizing formulations and too little time thinking about commercialization

This is where I believe the industry needs to change its approach.

In early development, technology selection is understandably driven by feasibility, API availability, speed, and the ability to generate clinical material.

But the process that gets a molecule into Phase 1 is not necessarily the process we would choose to manufacture that product commercially.

And by the time a program reaches late-stage development, changing the manufacturing technology becomes increasingly difficult.

Consider what commercial spray drying requires.

Beyond the spray dryer itself, depending on the process and solvent system, a commercial operation may need substantial solvent-handling infrastructure, explosion protection, solvent recovery systems, secondary drying, environmental controls, and significant facility capacity.

None of this makes SDD a poor technology. It is an extremely capable and commercially proven platform.

But it does create manufacturing complexity and capital requirements that should be considered early.

Commercial spray-drying capacity can also become a constraint, particularly when multiple programs compete for specialized equipment and qualified manufacturing infrastructure.

HME offers potential advantages that deserve greater consideration.

It is continuous, generally requires a smaller equipment footprint, avoids organic solvents in conventional melt extrusion, and can provide an attractive route to higher-volume manufacturing.

COMMERCIAL SDD MAY NEED	HME CAN OFFER
Solvent-handling infrastructure	Continuous processing
Explosion protection	A smaller equipment footprint
Solvent recovery systems	No organic solvents in conventional melt extrusion
Secondary drying	An attractive route to higher-volume manufacturing
Environmental controls and significant facility capacity	

Scale-up is not automatic. Screw geometry, specific mechanical energy, residence-time distribution, heat transfer, and melt rheology must be understood and controlled.

But these are manageable engineering challenges when the process is developed with scale-up in mind.

And in some cases, the commercial economics can be compelling.

> A formulation that is marginally faster to develop but substantially more expensive or difficult to manufacture may not be the best long-term choice.

We need to evaluate both.

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Technology selection should be a development decision, not a default

I am not advocating for HME over SDD.

There are molecules for which spray drying will clearly be the better technology, particularly when thermal sensitivity, drug-polymer compatibility, high drug loading, or other formulation constraints make extrusion impractical.

What I am advocating for is a more disciplined approach to making that decision.

At Forma, our approach to ASD development starts with understanding the molecule and its intended product profile, rather than committing prematurely to a manufacturing technology.

That means evaluating thermodynamic miscibility, solubility parameters, thermal behavior, degradation kinetics, polymer selection, melt rheology, and the critical quality attributes that will ultimately determine product performance.

It also means using computational tools, material-sparing screening, and appropriately designed experiments to evaluate competing technologies before significant development resources have been committed.

And importantly, it means considering commercialization from the beginning.

QUESTIONS THAT SHOULD SHAPE TECHNOLOGY SELECTION

1. Can the process achieve the target drug loading?
2. Will the ASD remain physically stable throughout the intended shelf life?
3. Can we consistently manufacture the required particle attributes?
4. What happens when batch requirements increase from a few kilograms to hundreds of kilograms?
5. What will the manufacturing cost, capacity requirements, and supply-chain risks look like at commercial scale?

These questions should influence the technology-selection decision, not become problems to solve years later.

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Are we leaving opportunities on the table?

I suspect a meaningful proportion of programs that default to spray drying could also be successfully developed using HME.

Would that number be 10%? 20%? Perhaps more?

We do not have sufficient comparative data to establish that percentage, but I believe the opportunity is substantial enough to justify a different development mindset.

Not every HME-feasible formulation will outperform an SDD formulation. And not every process that looks attractive at laboratory scale will deliver the expected commercial advantages.

But we cannot identify those opportunities if we eliminate HME before properly evaluating it.

The industry has invested heavily in improving the science of amorphous solid dispersions. We have better polymers, more sophisticated predictive models, improved processing equipment, and a much stronger understanding of drug-polymer interactions than we did a decade ago.

Our technology-selection strategies should evolve accordingly.

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> The goal is not to manufacture an amorphous solid dispersion. The goal is to develop a robust, scalable, commercially viable medicine.

And sometimes, the technology we overlook early in development may be the one that makes the most sense on a commercial scale.

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Technology selection should be a development decision, not a default.

Forma evaluates HME and spray drying side by side, starting from the molecule and its commercial future.

ASD SELECT

Your HME vs. SDD answer in two weeks

A fixed-price screen: in-silico modeling, characterization, MicroEvap triage and feasibility, using up to 1.2 g of API.

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