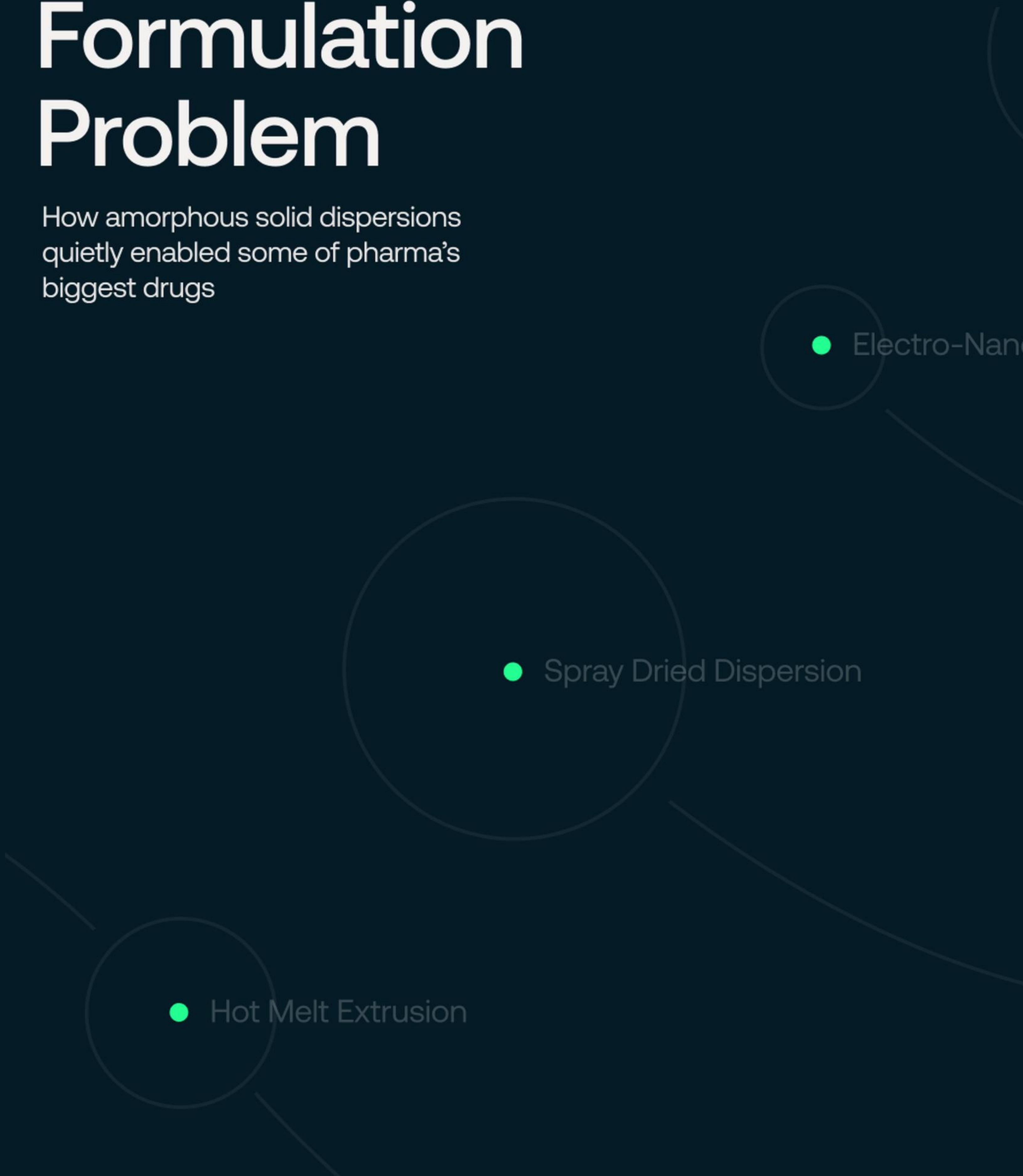
The $50B Formulation Problem

How amorphous solid dispersions quietly enabled some of pharma's biggest drugs



The Value of Solubility

How amorphous solid dispersions quietly enabled some of pharma's biggest drugs

For much of the pharmaceutical industry's history, the central challenge of drug development was biological: identifying the right target and designing a molecule capable of modulating it.

Today, that challenge increasingly looks different. Many modern drug candidates successfully hit their targets but struggle with something more fundamental: they do not dissolve.

Over the past two decades, medicinal chemistry has steadily pushed molecules toward greater potency and specificity. The result has been a generation of compounds that are often highly lipophilic, structurally complex, and difficult to solubilize. While these properties can improve binding to difficult targets, they frequently create molecules whose oral absorption is limited by dissolution rather than permeability.

This shift has elevated the importance of formulation science in a way that would have been difficult to imagine a generation ago. Technologies that improve the solubility and dissolution behavior of drug molecules have become essential tools for translating promising compounds into viable therapies.

Among these technologies, amorphous solid dispersions have emerged as one of the most important.

The Value Unlocked

A review of leading oral small-molecule drugs launched over the past decade reveals how central ASD technologies have become.

Many of the industry's most commercially successful therapies rely on either spray-dried dispersions or hot melt extrusion to achieve clinically viable exposure. The drugs shown in the table collectively represent nearly $50 billion in estimated peak annual sales.

Among the most prominent examples are:

- **Trikafta (~$10B peak sales) –** *spray dried dispersion* enabling a transformative cystic fibrosis therapy
- **Lynparza (~$5B) –** *hot melt extrusion* formulation supporting one of the leading PARP inhibitors in oncology
- **Sotyktu (~$4B) –** *spray dried dispersion* used to deliver the TYK2 inhibitor for psoriasis
- **Erleada (~$3.5B) –** *spray dried dispersion* enabling oral exposure of the androgen receptor inhibitor used in prostate cancer
- **Venclexta (~$3B) –** *hot melt extrusion* dispersion stabilizing the poorly soluble BCL-2 inhibitor used in hematologic malignancies

Of the five largest drugs in this group, three rely on spray-dried dispersions and two rely on hot melt extrusion—an illustration of how central these technologies have become to the commercialization of modern small molecules.

These are not niche products. They are foundational medicines across multiple therapeutic areas, including oncology, hepatology, immunology, infectious disease, and rare disease.

The pattern is clear: formulation technologies have become key enablers of modern small-molecule blockbusters.

ASDs are no longer an exotic formulation option used only in exceptional cases. They are increasingly part of the standard toolkit used to unlock difficult molecules.

The Molecules ASD Solves

The growing importance of ASDs reflects a broader shift in the physicochemical profile of drug candidates entering development.

Many contemporary small molecules share several characteristics:

- **High lipophilicity,** which improves target binding but reduces aqueous solubility
- **Large molecular weight and structural complexity,** often associated with modern kinase inhibitors and targeted therapies
- **Strong crystal lattice energies,** which make dissolution from crystalline form slow and unpredictable

As a result, a large proportion of drug candidates fall into the region commonly described as BCS Class II, where permeability is adequate but dissolution becomes the primary limitation on oral absorption.

In crystalline form, these drugs may dissolve too slowly in gastrointestinal fluids to generate therapeutic plasma exposure. Even when absorption occurs, it can be highly sensitive to physiological variability, including:

- gastrointestinal pH
- gastric emptying rates
- intestinal fluid volumes

Amorphous solid dispersions address this challenge by shifting the drug from its crystalline state into a higher-energy amorphous form embedded within a polymer matrix.

This change fundamentally alters dissolution behavior. Instead of slowly dissolving from a crystal surface, the drug can generate a rapid burst of supersaturation in solution.

Formulators often describe this behavior through the “spring and parachute” model:

- the amorphous drug creates the spring, producing rapid supersaturation
- the polymer matrix provides the parachute, slowing nucleation and crystallization

When properly designed, this system maintains elevated drug concentrations in solution long enough to enable efficient absorption.

Table 1 – Recently Launched Drug Products Leveraging ASD Technology

Brand	Launch Year	ASD Technique	Manufacturer	Therapeutic Area	Est. Peak Sales ($B)
Trikafta	2019	Spray Drying	Vertex	Cystic Fibrosis	**$10B**
Lynparza	2018	Melt Extrusion	AstraZeneca	Oncology (PARP)	**$5B**
Sotyktu	2022	Spray Drying	BMS	Immunology (Pso)	**$4B**
Erleada	2018	Spray Drying	Janssen	Oncology (Prostate)	**$3.5B**
Venclexta	2016	Melt Extrusion	AbbVie	Oncology (CLL/AML)	**$3B**
Alyftrek	2024	Spray Drying	Vertex	Cystic Fibrosis	**$3B**
Epclusa	2016	Spray Drying	Gilead	Hepatology (HCV)	**$2.5B**
Rezdiffra	2024	Melt Extrusion	Madrigal	Hepatology (MASH)	**$2.5B**
Mavyret	2017	Melt Extrusion	AbbVie	Hepatology (HCV)	**$2B**
Sunlenca	2022	Spray Drying	Gilead	Infectious Dis. (HIV)	**$1.5B**
Journavx	2025	Spray Drying	Vertex	Pain Management	**$1.5B**
Jaypirca	2023	Spray Drying	Eli Lilly	Oncology (MCL/CLL)	**$1.2B**
Orkambi	2016	Spray Drying	Vertex	Cystic Fibrosis	**$1.1B**
Symdeko	2019	Spray Drying	Vertex	Cystic Fibrosis	**$1B**
Qulipta	2021	Melt Extrusion	AbbVie	Neurology (Migraine)	**$1B**
Braftovi	2020	Melt Extrusion	Pfizer	Oncology (Melanoma)	**$0.8B**
Zepatier	2016	Spray Drying	Merck	Hepatology (HCV)	**$0.5B**
Phyrago	2023	Electrospraying	Handa	Oncology (CML)	**$0.3B**
Alvaiz	2023	Melt Extrusion	Teva	Hematology (ITP)	**$0.2B**
Oriahnn	2020	Melt Extrusion	AbbVie	Women's Health	**$0.1B**

The Technologies Behind Modern ASDs

Two manufacturing technologies dominate the commercial production of amorphous solid dispersions.

Spray Drying

Spray drying has become the most widely used ASD technology in modern drug development.

In this process, a drug and polymer are dissolved in a solvent system and atomized into fine droplets that rapidly dry in a heated chamber. As solvent evaporates, the drug becomes immobilized within the polymer matrix in an amorphous state.

Spray drying offers several advantages:

- precise control over particle morphology
- broad polymer compatibility
- flexible formulation screening during development
- scalable manufacturing processes

These characteristics have made spray-dried dispersions the technology behind several recent blockbuster drugs.

Hot Melt Extrusion

Hot melt extrusion represents the second major ASD platform.

Instead of solvent evaporation, HME relies on thermal and mechanical energy to disperse the drug within a molten polymer matrix. The mixture is processed through an extruder where shear forces distribute the drug uniformly before the material solidifies into an amorphous dispersion.

Key advantages of this approach include:

- solvent-free processing
- compatibility with continuous manufacturing
- robust polymer-drug mixing

Both technologies have proven capable of supporting large-scale commercial production and remain the backbone of industrial ASD manufacturing.

The Challenges Behind the Technology

Despite their commercial success, amorphous solid dispersions remain one of the most technically demanding formulation strategies in oral drug development.

The primary challenge is the inherent instability of the amorphous state. Because amorphous drugs exist at higher energy levels than their crystalline counterparts, they naturally tend to recrystallize over time. Preventing this transformation requires careful control of both formulation composition and processing conditions.

Polymer selection is particularly critical. The polymer must stabilize the amorphous drug during storage while also preventing rapid crystallization during dissolution.

Key factors often considered during polymer screening include:

- drug-polymer miscibility
- hydrogen bonding interactions
- glass transition temperatures
- the ability to inhibit nucleation and crystal growth

Manufacturing adds another layer of complexity. Spray drying introduces variables related to solvent systems, drying kinetics, and particle engineering. Hot melt extrusion requires careful control of temperature and shear forces to avoid degradation or phase separation.

For many programs, the most significant challenges emerge during scale-up, when laboratory formulations must be translated into robust, reproducible commercial manufacturing processes.

How Forma Can Help

As medicinal chemistry continues to generate increasingly complex small molecules, the demand for solubility-enabling technologies will only grow.

For many development programs, the challenge is not simply demonstrating that an amorphous dispersion can improve solubility. The real challenge lies in translating that formulation into a scalable manufacturing process capable of supporting clinical development and commercial supply.

Successfully navigating that transition requires the integration of:

- formulation science
- analytical characterization
- process engineering
- commercial manufacturing expertise

Forma Life Sciences was built around this intersection.

Our teams focus on developing and manufacturing complex oral solid dosage forms designed to unlock poorly soluble molecules and translate promising drug candidates into viable medicines.

In today's drug development landscape, the question is no longer whether many molecules will require solubility-enabling technologies.

Increasingly, the question is who can successfully deliver those technologies at scale.

And for many modern small molecules, the answer begins with amorphous solid dispersions.

About Forma

Forma Life Sciences is a U.S. based contract development and manufacturing organization (CDMO) specializing in oral solid dosage formulation development, clinical manufacturing, and commercial drug product manufacturing. Headquartered in Irvine, California, Forma operates two cGMP facilities totaling more than 100,000 square feet and 27 GMP manufacturing suites, with capacity to produce over two billion tablet and capsule units annually. The company supports pharmaceutical and biotechnology partners from early clinical development through commercial scale production and offers expertise in spray-dried dispersion, amorphous solid dispersion systems, fluid bed granulation, and modified-release formulation technologies.