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FORMULATION INNOVATION: PARTNERSHIPS USHER IN NEXT WAVE OF SOLID DOSAGE FORMS

When we talk about medication, we often name a treatment by its form—taking a tablet, using an inhaler, swallowing some cough syrup—rather than its active pharmaceutical ingredient, or API.

"APIs are the part of the drug that produces the desired pharmacological effect," says Stephen Hoag, director of the applied pharmaceuticals lab at the University of Maryland, Baltimore. "Yet APIs aren't something a patient can use. Formulation turns them into a usable drug product."

Choosing an appropriate solid dosage form for an API supports the ingredient's effectiveness and can make a treatment accessible to patients.

Credit: Aenova

Therefore, developing the right formulation and manufacturing technology is of central importance in a drug's life cycle, according to Klaus Pollinger, head of manufacturing science and technology, business unit solids at Aenova, a leading contract development and manufacturing organization (CDMO) for the global pharmaceutical industry.

Over 80% of marketed pharmaceutical drugs are manufactured in solid forms such as tablets, capsules, or powders.[1] These solid dosage forms improve adherence to a treatment regime because patients can typically take tablets and capsules without assistance from medical providers.[2] Solid dosage form drug products can also be effectively distributed across the globe, making them affordable and widely accessible to different patient populations.

The long-standing, well-standardized practice of formulation now faces new challenges. Some advanced APIs are not compatible with established approaches to formulation because of issues with stability, solubility, or other physicochemical characteristics. Innovative delivery approaches, such as soft gels, amorphous solid dispersions, and timed release formulations can improve patient access to solid dosage form drugs and treatments.

For some pharmaceutical companies, finding the right partner with access to formulation expertise can be critical to breaking into the solid dosage form space or to improve current formulation and development pipelines, Pollinger says.

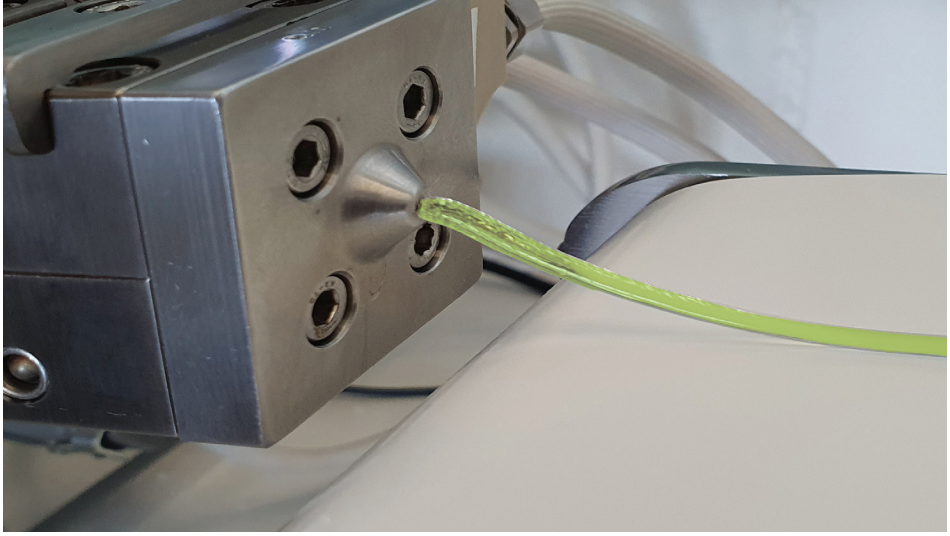
ENHANCING API BIOAVAILABILITY

Since most of the human body is a water-based environment, solubility is an important characteristic that can impact bioavailability. More than 70% of new pharmaceutical drugs being developed have low bioavailability.[1] "You need some sort of strategy to improve this solubility, or at least tune it to your favor," says Dolores Serrano, associate professor in the school of pharmacy at Complutense University of Madrid.

In addition to the constant challenge of solubility, Pollinger says, permeability is a concern with many APIs. An API may dissolve within the digestive system, for example, but may not be able to cross through the various cellular barriers needed to reach its target. Any orally administered API needs to permeate the walls of the gastrointestinal tract to be absorbed into the bloodstream.

Well-established formulation strategies overcome the bioavailability and solubility obstacles for traditional drugs. The formulation process is a crucial part of any drug development pipeline. It involves adding ingredients, known as excipients, to the API. Fillers, a fundamental excipient, add bulk to a small amount of active ingredient. Coatings can mask taste, as well as slow release in the digestive tract. Solid APIs may also be physically compressed into tablets or suspended in a gel, which can then be taken orally.

For many innovative APIs, however, traditional approaches to solid dosage



For APIs with low bioavailability, hot-melt extrusion is a technique for creating solid dosage formulations with improved solubility.

Credit: Aenova

formulation to solve challenges of bioavailability and solubility don't work, Pollinger says. By partnering with experienced CDMOs, companies can gain access to new formulation methods that improve the bioavailability of difficult-to-formulate APIs.

One promising technique to improve API formulation is amorphous solid dispersion. APIs are mixed with a carrier substance that is a noncrystalline solid. This amorphous state puts the API mixture in a higher energy state that makes the mixture more soluble than if it was completely in a crystalline state.

Hoag says amorphous dispersion is advantageous because a drug in an amorphous form requires less energy to go into a liquid, dissolved state. As a result, drugs formulated this way tend to dissolve more quickly and have better solubility, making them more available in the body. This improved solubility also improves bioavailability for some drugs.[3]

CDMOs such as Aenova offer amorphous solid dispersion and associated technologies including hot-melt extrusion, spray drying, and coprecipitation as ways to improve formulation of specific APIs (see sidebar on page 4: Modern approaches to solid dosage formulation).

Other approaches are available if amorphous solid dispersion does not provide a suitable solution. "Solid dosage forms do not necessarily always need to be completely solid," Pollinger says. APIs can be engineered into nanoscale particles—the design of which is his expertise. "Incorporating APIs in lipid solutions or using a soft gelatin capsule often provide a promising formulation approach," Pollinger adds.

Investing in advanced formulation is more than keeping up with the times: it's big business. The global API market generated an estimated $185 billion in revenue in 2020 and is expected to reach $331 billion in revenue by the end of 2030.[4]

MODERN APPROACHES TO SOLID DOSAGE FORMULATION

The following processes can help improve the bioavailability of APIs by overcoming some challenges associated with drug formulation:

- *Amorphous solid dispersion*, which involves mixing and distributing an API with a carrier molecule that keeps the mixture in a semisolid amorphous state
- *Hot-melt extrusion*, which involves melting polymeric materials in a machine called a screw extruder along with an API and carrier molecules to achieve molecular-level mixing of the material
- *Spray drying*, which is involves converting a liquid solution into a dry power
- *Coprecipitation* which involves an API being co-crystallized with an additive

INNOVATIVE DELIVERY SYSTEMS

Beyond improving bioavailability, modern approaches to formulation can enhance targeted drug delivery. As researchers continue to better pinpoint the causes of disease, drugs can be designed to reach specific biomolecule, cell, or tissue targets.

Pollinger says targeted drugs often require more sophisticated delivery systems to ensure they reach their site of action. In this context, a delivery system refers to how a dosage form, or physical form of a drug, releases an API and delivers it to a target tissue. Formulation, combined with choice of dosage form, can create a delivery system that improves drug efficacy and reduces systemic side effects. For example, dry powder inhalers have emerged as promising delivery systems for drugs that cannot survive the digestive system and for drugs to treat pulmonary diseases.

"You can design a powder and formulation together with a device that allows you to bring the API directly to the site of action, in this case the lungs," Pollinger says. "This approach can improve the efficacy of the drug and also make it more convenient for patients to take their medicine."

In addition, Pollinger says, better understanding of disease and treatment management has opened the door to more nuanced formulation approaches as manufacturers attempt to develop drug delivery systems to release APIs at specific times.

Microdosed capsule fillings (left) can be used in dry powder inhalers (right), which can help deliver active pharmaceutical ingredients directly to the target tissue, in this case the lungs

Credit: Aenova

Coating small spheres of an API (left) with polymers (right) creates pellet formulations for sustained release or targeted delivery.

Credit: Aenova

Serrano gives sustained release formulations as an example. “With formulation, you can manipulate or tune the release of an API,” she says. “Sometimes you want to have an immediate release because you want the APIs to be delivered fast, such as for a painkiller. In other cases, like drugs to treat hypertension, you really want to have a sustained-release profile instead.”

Sustained-release formulation and delivery can also help patient compliance: instead of taking multiple drugs a day for an all-day effect, patients need to take only one.

Particulate delivery systems have emerged as promising for many drugs. In these systems, API-containing particulates are packed into pellets, multilayer pellets, or mini tablets that are designed for the targeted release of one or more APIs. Updated delivery systems can even be useful to boost therapeutic efficacy and reduce side effects for established drugs, Serrano says. “Just because a conventional formulation is good and is always going to be there, we can still improve the formulation with innovative approaches that are coming up.”

PICKING A CDMO PARTNER

The challenges that arise in formulating drug dosages, designing delivery systems, and manufacturing can be complicated and varied. For instance, Hoag cites issues with stability, release, patient acceptance, product performance, and safety.

Choosing a CDMO partner with specific experience in solid dose formulation can offer immediate access to broad technologies and skilled, well-coordinated teams—and that can translate to savings. “Partnering with a CDMO during development, and also across the full product life cycle, can improve timelines, reduce resource needs, and significantly mitigate project risk,” Pollinger says.

For example, Serrano says, scaling up production of a drug or using a new formulation technique can be less than straightforward. A CDMO offering services from development to large-scale manufacturing and packaging can be beneficial to clearing related hurdles.

Whether an API is an existing drug or a novel therapeutic, patients can benefit

from a fresh approach to formulation. With the aid of an experienced partner, modern approaches to solid dosage formulation are more accessible, making it easier to develop better drugs for the clinic.

EXPANDING OPPORTUNITIES WITH CDMO PARTNERSHIPS

CDMOs can provide benefits beyond their scientific abilities. Many have partnerships with academic institutions and with biotechnology and pharmaceutical companies of various sizes, which gives partners access to an extended network of potential collaborators. When looking to partner with a CDMO, consider its past and present partnerships. For example, Aenova has partnered with many pharmaceutical firms, from start-ups to large companies, to aid in the development and commercial supply of life-saving medicines.

Specifically, Aenova has contributed to projects related to

- enhancing the oral bioavailability of an oncology product to improve treatment access to a broader patient population;
- improving the formulation of a drug product using a dry-powder inhaler platform coupled with a capsule microdosing approach to boost targeted delivery
- and developing systems designed to release APIs in a specific manner by using particulate delivery systems such as encapsulated solid dosage forms and tableted pellet systems.

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The Aenova Group is a leading global contract manufacturer and development service provider for the pharmaceutical and healthcare industry. As a one-stop store, Aenova develops, produces and packages all common dosage forms, product groups and active ingredient classes from pharmaceuticals to dietary supplements for human and animal health: solid, semi-solid and liquid, sterile and non-sterile, high and low dose, OEB 1 to 5 (Occupational Exposure Band). Around 4,200 employees at 16 sites in Europe and the USA contribute to the success of the Aenova Group. **www.aenova-group.com**.

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