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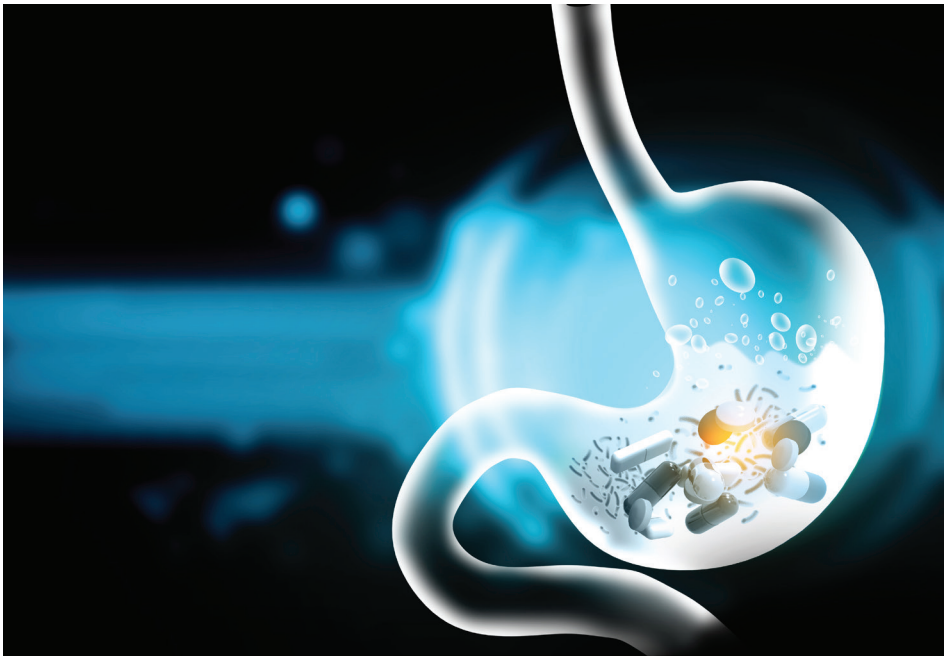
INCREASING THE BIOAVAILABILITY OF ONCOLOGY DRUGS WITH AMORPHOUS SOLID DOSAGE FORMULATIONS

Taking a pill is convenient for patients, but some drugs are challenging to formulate into oral dosage forms that provide reliable bioavailability of the active pharmaceutical ingredient (API).

One factor that affects bioavailability is pH-dependent solubility of a drug in the gastrointestinal tract. Poor solubility under the pH conditions of the stomach or small intestine means a compound is less available to reach the bloodstream and exert its intended effect. Formulations other than crystalline solids can reduce a drug's sensitivity to physiologic variation and ensure more consistent bioavailability.



Most oral tyrosine kinase inhibitor forms are poorly soluble in the gut and can interact significantly with acid-reducing agents like proton pump inhibitors.

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Oral tyrosine kinase inhibitors (TKIs) are one class of drugs that can be highly susceptible to solubility issues in the gastrointestinal tract. These drugs slow tumor formation and cancer progression by inhibiting enzymes called kinases, which are involved with cell-signaling processes. Since the US Food and Drug Administration approved imatinib (Gleevec) in 2001, more than 40 TKIs are now available for the treatment of various solid and blood cancers.[1] TKIs tailored to specific kinase variations have marked an important milestone in delivering precision cancer therapeutics based on patients' unique genetics and resulting proteins.

Most crystalline TKI drugs have pH-dependent solubility that affects their bioavailability in an oral dosage form. TKIs are ionized at the low average pH of an empty stomach. Ionized TKIs are more soluble than nonionized compounds present at moderate pH in the stomach after patients eat or take antacids, as well as in the small intestines. Consequently, natural variations in gastric pH or variations due to eating or taking antacids can significantly impact drug absorption and, in turn, therapeutic efficacy.

"For these weakly basic kinase inhibitor drugs, solubility is highest at a low pH but significantly decreases at a pH of 5 or 6, for example. Having a dramatic difference in solubility and drug absorption between this low and high pH can drive a big difference in bioavailability," explains Deanna Mudie, senior principal engineer in Lonza's small-molecule division.

Alternative formulation techniques can still deliver the convenience of a pill while reducing TKIs' sensitivity to physiological variation, ensuring more consistent and higher bioavailability. "If you can reformulate so that 80–90% of the drug is absorbed at that higher pH, even if the drug is still more soluble at the lower pH, there's a ceiling to that change in bioavailability across pH," Mudie says.

VARIABILITY IN ORAL TKI BIOAVAILABILITY

The limited solubility of orally administered TKIs translates to significant challenges in effective dosing. "Because a large proportion of these drugs have poor intrinsic solubility, not very much of a given dose actually makes it to the bloodstream," Mudie says. "When that happens, much of that dose is essentially a waste."

Another issue that impacts TKI solubility is food and drug interactions that affect gastric pH. After a person eats, gastric pH rises and then returns to baseline, meaning that the timing between taking a pill and having a meal introduces variability that affects TKI solubility.

About 33% of cancer patients are prescribed acid-reducing agents (ARAs) to combat acid reflux, a common side effect of many oncology treatments.[2] ARAs, which include over-the-counter antacids as well as prescription proton pump inhibitors (PPIs) and histamine H2 receptor antagonists, also increase gastric pH, presenting another source of variability. In the case of PPIs, a single oral dose can raise gastric pH from 2.0 to over 6.0 within 3–4 h.[3] This elevation in pH significantly decreases the solubility of orally administered TKIs.

Because tyrosine kinase inhibitor solubility is highly dependent on gastric pH, patients often take them between meals and other drugs that reduce their solubility.
Credit: Pixel-Shot/Shutterstock

For patients taking TKIs, especially alongside ARAs, confidently achieving consistent bioavailability for a consistent therapeutic effect is a challenge. Daily oral administration of the TKI pazopanib alongside a common PPI, esomeprazole, decreased patients' maximum serum concentration of the TKI by 40%.[4]

To overcome this variability, patients are often advised to stagger TKI dosing between meals and acid-reducing medicines. This scheduling can present a new obstacle, however: maintaining patient compliance. As dosing regimens increase in frequency and complexity, many patients struggle to maintain compliance with their scheduled medications. Studies of patient compliance suggest that adherence is significantly higher among those taking once-daily medications than among those on a dosing schedule of three or more per day, as well as those with fewer food and concomitant drug restrictions.[5]

Even with excellent patient compliance, achieving consistent and predictable TKI absorption can remain difficult because of natural variation among individuals. "Even if you have decent bioavailability at normal gastric pH, [TKI solubility] is highly sensitive to physiological variables," Mudie says. "There can be a lot of variability between and among patients, especially in the presence of food and drugs like proton pump inhibitors."

Changing the formulation of a TKI from a crystalline solid to a salt, a cocrystal, an amorphous solid, or a lipid-based formulation can increase the drug's solubility and potentially overcome highly variable absorption across the spectrum of gastric pH.

Timing TKI administration around other medications and meals can result in complex dosing regimens, creating new inconveniences for patients and potentially reducing medication compliance.

Credit: Vladimir Vladimirov/Getty Images

LEVERAGING AMORPHOUS SOLID DISPERSION TO IMPROVE TKIS

Drug developers are now exploring alternative formulation methods to develop dosage forms with higher solubility across gastric pH conditions, mitigating issues with food-drug and drug-drug interactions.

One approach is using an amorphous rather than a crystalline drug form. While the crystalline form has a highly ordered and thermodynamically stable structure, the amorphous form is structurally irregular and thermodynamically unstable; this lack of order and higher level of activity makes it more soluble in gastrointestinal fluids than a crystalline form.[6]

Formulating with an amorphous drug form is less straightforward than with traditional approaches, however. The thermodynamic instability of the amorphous form means that it typically cannot be used on its own to produce an effective, shelf-stable drug product. To make a drug form that is both soluble in the gut and stable in its quality, manufacturers turn to alternative formulation methods. “We can stabilize that amorphous form with a polymer through an amorphous solid dispersion formulation,” Mudie says.

Amorphous solid dispersion (ASD) is a formulation method that stabilizes an amorphous drug form within a polymer matrix, typically a cellulose derivative, to yield a product that is both kinetically stable and soluble in gastrointestinal fluids. Studies of ASD formulations of APIs with pH-dependent solubility indicate that this method can produce drugs with higher, more consistent bioavailability across varying levels of gastric pH.[7]

For example, a 2021 study by Mudie and colleagues at Lonza compared the plasma exposure of standard crystalline and novel ASD formulations of acalabrutinib, a TKI used in the treatment of blood cancers, at both low and high gastric pH. While both forms produced comparable plasma drug concentration profiles at a gastric pH of 2, only the ASD form yielded an equally robust profile at a gastric pH of 6.[8] These findings suggest that ASD formulations of TKIs like acalabrutinib could be absorbed consistently even in the presence of food or antacids, potentially offering patients and clinicians more confidence in dosing with a single pill. AstraZeneca now has a tablet version of acalabrutinib as the maleate salt form, approved for use in the US, that can be taken with antacids following the same dosage strength and schedule as the capsule formulation.[9]

IMPLEMENTING ASD FORMULATION APPROACHES

Techniques for the production of ASDs generally fall into two broad categories: solvent-based methods, such as spray-drying, and melting-based methods, such as hot melt extrusion (HME). While each can be used to effectively manufacture ASDs, there are distinct differences that determine their suitability for a given application.

HME involves pumping an API and polymeric materials through a screw extruder at extremely high temperatures to achieve molecular-level mixing of the materials. HME is a common alternative to traditional methods for creating a variety of pharmaceutical dosage forms, including tablets, films, implants, and more. According to Mudie, HME offers several key advantages over spray-drying, including much higher throughput, lower cost of goods, and smaller manufacturing footprint.

In spray-drying, an organic solution of the API and polymer is forced through a nozzle or atomizer and rapidly dried with hot gas; the result is a fine powder of consistent particle size. Spray-drying can be more complex for manufacturers to scale up but offers a significant benefit: higher drug loading.

Spray-drying (left) and hot melt extrusion (right) are established technologies for producing amorphous solid dispersions.

Credit: Lonza

"With ASDs in general, combining an API with a stabilizing polymer essentially dilutes the drug, which results in either a physically larger dosage form or the need for more pills," Mudie says. "Once these forms surpass a certain size or a certain number of pills, it can have a detrimental impact on patient compliance." Producing ASDs with spray-drying typically results in higher drug loading than HME, mitigating these issues.[10] In Mudie's study, for example, ASD formulation using spray-drying resulted in a tablet 60% smaller than the traditional crystalline form.[8]

One limitation of spray-drying is its environmental impact—many spray-drying applications use organic solvents such as methanol or acetone to combine the API and polymer. Some compounds also have limited solubility in these organic solvents, necessitating updates to standard spray-drying approaches. According to Mudie, Lonza is focused on developing novel processes and processing aids to increase drug solubility in commonly used spray solvents. For example, by rapidly increasing temperature of the organic spray solvent above its boiling point in an approach called the temperature shift process, Mudie and her team can increase drug solubility to enable spray-drying. Adding processing aids, such as acetic acid, to the organic spray solvent can also improve the solubility of weakly basic drugs.[11]

As more novel anticancer drugs are developed and manufacturers seek to offer them in oral dosage forms, solubility issues associated with these drugs can create challenges in patient compliance and potentially limit their therapeutic efficacy. Contract drug and manufacturing organizations bring expertise in optimizing production of alternative formulations, enabling efficient manufacturing of high-quality, patient-friendly dosage forms. Continued advances in formulation methods can help create more consistently bioavailable oncology drugs, including oral TKIs, and overcome other persistent challenges in drug development and manufacturing.

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