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# High-Loaded Dosage Forms: Novel Platform Expands Dispersion Utility

Spray-dried amorphous solid dispersions (ASDs) show enormous promise in the delivery of drug compounds with low solubility. A novel platform expands the utility of this approach, enabling creation of ASD solid dosage forms with high drug loadings to meet patient needs.

# High-Loaded Dosage Forms

The prevalence of active compounds with low aqueous solubility exceeds 70% in drug pipelines, preventing development of many compounds as effective medicines. Spray-dried amorphous solid dispersions (ASDs) are effective in increasing drug solubility and enhancing the bioavailability of such compounds, but the amount of excipients in ASDs may be too large to attain the high drug loadings needed for some therapies. Lonza has developed a novel platform that addresses this challenge, reducing tablet mass by nearly half and maintaining high drug loading, physical stability, and supersaturation. A case study is presented.

## The Need for Enabling Technology

An estimated 70% to 80% of active compounds in current pharmaceutical pipelines require bioavailability-enhancing technologies to render them viable drug candidates. Amorphous solid dispersions (ASDs) have demonstrated effectiveness in enhancing the bioavailability of drugs with low solubility and/or slow dissolution in gastrointestinal (GI) fluids.

In ASDs, drug is dispersed within a matrix (typically, a polymer) to stabilize the drug in the amorphous state, enhancing physical stability and providing much better solubility than can be attained with crystalline drug. Spray-drying is a particularly effective method used to form ASDs, creating homogeneous dispersions with polymers and other excipients that

- improve physical stability during use and storage by increasing the glass-transition temperature ($T_g$) of the ASD;
- increase solubility, often 2- to 100-fold; and
- improve the dissolution rate and/or sustainment of supersaturation in GI fluids.

For most spray-dried ASDs, a single polymer is used to perform all of these functions, but the resulting mass of the ASD tablet can make patient compliance difficult to achieve—either in terms of tablet size or the number of tablets required—for applications that require high drug loadings.

## A Novel Formulation Platform

Lonza has developed a novel formulation platform that makes it possible to meet the requirements for a successful high-loading spray-dried ASD dosage form. In this approach, the "work" of the single dispersion polymer is divided: (1) a high-$T_g$ polymer (such as Eudragit L100, $T_g$= 190°C) is used in ASD to ensure physical stability at a high drug loading, and (2) a the spray-dried lower-$T_g$ concentration-sustaining polymer [such as hydroxypropyl methylcellulose acetate succinate (HPMCAS)] is used external to the ASD (i.e., in the tablet) to ensure supersaturation is maintained. This approach, illustrated in Figure 1, allows the size of the finished dosage form to be decreased by 40% while maintaining all of the desired product performance attributes, as illustrated in the case study presented here.

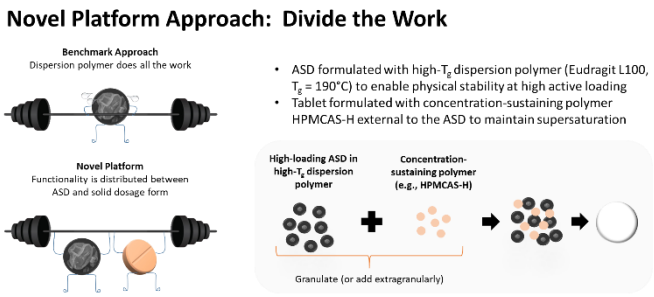


**Figure 1**
Illustration of novel formulation platform for high-loading dosage forms

## Case Study: High-Loading Erlotinib Tablets

For this case study, the weakly basic, low-$T_g$ drug erlotinib ($T_g$ = 41°C) was used as a model low-solubility compound due to its poor physical stability and propensity to crystallize during *in vitro* dissolution testing.

The new formulation platform was used to prepare high-loading ASD tablets. To significantly increase the active loading of the tablet, Eudragit L100 [poly(methyl methacrylate-co-methacrylic acid, 50/50 ratio, (PMMAMA)] was used as the dispersion polymer. The $T_g$ of Eudragit is 70°C higher than that of HPMCAS-H (190°C vs 120°C). A 65% erlotinib and 35% Eudragit L100 ASD was spray-dried from a methanol spray solution. When tablets were prepared using this high-loading

ASD, HPMCAS-H was used as the concentration-sustaining polymer "exterior" to the ASD intermediate. As a control, a benchmark formulation was prepared by spray-drying a 35% erlotinib and 65% HPMCAS-H ASD from a methanol solution. The 35% active loading was selected since it was the maximum drug loading used in formulations that passed a 4-week accelerated stability challenge. Tablets were then prepared from the spray-dried benchmark ASD. A negative control formulation was also prepared: an ASD containing 65% erlotinib and 35% Eudragit L100, with no HPMCAS-H added to the tablet formulation. The tablet formulations were tested for physical characteristics, dissolution performance, physical stability, and manufacturability.

### Physical Characteristics

When the ASD tablets were prepared, the high-loading tablets, prepared with HPMCAS-H as the concentration-sustaining polymer, had a tablet drug loading of 25%, and a total mass of 350 mg. In contrast, the benchmark tablets had a drug loading of 17% and a total mass of 575 mg. This equates to a 50% increase of active loading per tablet and a 40% reduction in tablet mass.

### Dissolution Performance

Dissolution test results, shown in Figure 2, showed equivalent *in vitro* dissolution performance between the high-loading and benchmark formulations and better performance than that of the negative control. Tests showed rapid dissolution in the simulated GI fluids and sustained supersaturation for the benchmark and high-loading tablet formulations.

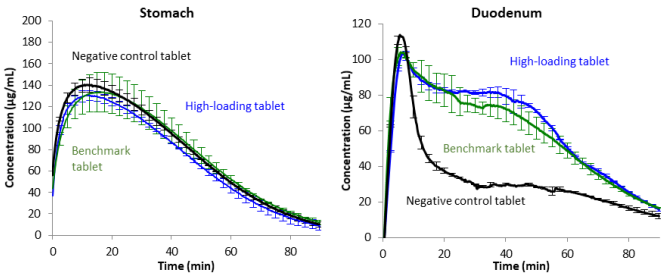


Figure 2
Dissolution Results for High-Loading, Benchmark, and Negative Control Tablets

Experimental Details: Concentration time profiles in the stomach (left) and duodenum (right) in a controlled-transfer dissolution test. Gastric medium: 50 mL pH 2 HCl + 240 mL water [combined volume contained 34 mM NaCl and 0.02 wt% simulated intestinal fluid (SIF) powder]. Intestinal medium: 50 mL pH 6.5 67 mM phosphate buffer solution (PBS) and 0.5 wt% SIF powder. Gastric emptying $t_{1/2}$ = 15 min. Gastric secretion = 2 mL/min $10^{-2}$ N HCl with 34 mM NaCl. Duodenal secretion = 2 mL/min pH 6.5 67 mM PBS + 0.5 wt% SIF powder. Concentrations determined via Pion ultraviolet (UV) detection.

### Physical Stability

Accelerated physical stability tests were conducted at elevated temperatures and humidities with high-loading and benchmark ASD intermediates. Both sets of ASDs were physically stable for 4 weeks at 40°C/75% RH. Benchmark formulations containing higher drug loadings—50% and 60%—were not stable after storage for even 1 week.

### Manufacturability

A 5-kg blend of the high-loading ASD formulation was spray-dried, granulated on a Gerteis Mini-Pactor® roller compactor, and tableted on a Korsch XL 100 rotary tablet press. The high-loading ASD tablet formulation was tested for tensile strength, solid fraction, content uniformity, disintegration, and friability. Tabletability profiles were generated on the final blend at 100 msec (clinical scale) and 10 msec (commercial scale). The quality attributes of the high-loading ASD tablets were excellent and the tabletability of the formulation was excellent, based on typical dwell times for clinical- and commercial-scale equipment.

## Conclusions

The successful use of the novel formulation platform is demonstrated by the case study for erlotinib, a rapidly crystallizing, low-$T_g$ drug. We have demonstrating that by using two polymers—one "inside" the ASD and one "outside" the ASD in the tableting formulation—excellent *in vitro* performance, stability and manufacturability can be achieved, while reducing tablet mass by 40% relative to the benchmark formulation. Eudragit L100 polymer has a high $T_g$, enabling a higher active loading in the spray-dried ASD and producing excellent physical stability. HPMCAS-H sustains drug supersaturation upon dissolution and maintains good performance. This case study demonstrates that this platform can be used to prepare tablet formulations with high drug loadings, decreasing the size of tablets or the number of tablets that must be consumed by the patient for efficacy.