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CASE STUDY

Nanomilling from Screening to Scale-up

STUDY OVERVIEW

A client came to Altasciences' CDMO with a highly active compound which was headed towards clinical trials based on excellent *in vitro* activity and a good toxicity profile. However, due to very poor aqueous solubility and less than desirable bioavailability, improvements to the formulation were required to realize all the benefits of the drug's inherent activity. The solution suggested was a nanosuspension prepared by aqueous nanomilling so that when the particle size decreases from micrometer to nanometer range, the surface area to volume ratio increases dramatically, resulting in a significant increase in dissolution rate and an increase in bioavailability.

STUDY DETAILS

- Drug development phase: preclinical
- Class of drug: small molecule, BCS Class II/IV
- Routes of administration: oral and injectable

STUDY PURPOSE

The purpose of the investigation was to determine the suitability of nanomilling for a client's drug, and to develop a stable, nanoparticulate suspension formulation of the active pharmaceutical ingredient (API) that would improve bioavailability.

METHODS

- Standard nanomilling conditions for screening in a jar mill (roller milling)
- Drug concentration: 20-30%
- Milling media: ceramic yttria-stabilized zirconia beads (YTZ), 0.5-2mm, 50% v/v
- Aqueous phase: 6 aqueous phases each containing a different stabilizer
- Volume: 1-100 mL
- Drug requirement/jar: 0.02-2g
- Roller mill speed (RPM): 60-200 RPM
- Sampling timepoints: 1, 2, 4, 8, 24 hours
- Particle size distribution (PSD) method: D50 determined by laser diffraction (LD) on a Horiba LA-950

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METHODS AND RESULTS

Solid API was milled on a roller mill in a glass jar containing the drug (20% w/w), a series of pharmaceutically acceptable stabilizers, and YTZ ceramic milling media. The suspension was sampled at different timepoints for particle size measurements until the D50 plateaued. Each of the six stabilizers were found to be compatible with the process, which provided significant reduction in particle size from a D50 of ≈ 30um to < 300nm; three stabilizers promoted particle size reduction to < 200nm. These three also appeared to sufficiently stabilize the nanosuspension after milling, as determined by LD measurements following incubation at ambient conditions for 24 hours.

These three promising stabilizers were further investigated by repeating the milling at different drug loadings (10-40%), milling media sizes (0.5-2mm) and milling speeds (60-200 RPM) to determine the best conditions for scale-up for high-energy media milling. Each unique combination was monitored for particle size distribution by LD, with sampling times of 1, 2, 4, 8, and 24 hours.

Several of the conditions investigated were able to reach the minimum D50 of about 170nm. The suspensions were separated from the media and allowed to sit at ambient temperature for a week with daily sampling for evaluation of PSD stability. Two of these were shown to maintain the PSD over that time and one was selected for further scale-up.

Initial conditions for scale-up in a high energy media mill (NETZSCH DeltaVita) were as determined for the experiments above for milling media loading and size, stabilizer type and concentration, and drug loading. The only variables during initial scale-up and process development were milling speed and milling time.

The optimized conditions determined during roller milling translated smoothly to high-energy milling, and allowed for selection of optimized times and speeds to provide a stable nanosuspension for use in preclinical pharmacokinetic (PK) and toxicity studies.

CONCLUSION

It is possible to screen a panel of nanoparticle stabilizers at small scale in a simple and quick process, providing reliable data to determine the feasibility of nanomilling for the drug of interest. The protocol also identified suitable conditions for scale-up on a high-energy media mill for both preclinical and clinical batches. The combination of speed and affordability makes roller milling and nanosuspension formulation an excellent option for compounds with aqueous solubility issues.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.