Introduction

More than 40% of compounds identified through combinatorial screening programs are poorly soluble in water. These molecules are difficult to formulate using conventional approaches such as solutions, suspensions, and amorphous dispersions and are associated with innumerable formulation-related performance issues. Drug nanoparticles have been shown to improve bioavailability and enhance drug exposure for oral and parenteral dosage forms. This technology provides the discovery scientist with an alternate avenue for screening and identifying superior analogs. For the toxicologists, the approach provides a means for dose escalation using a formulation that is commercially viable.

Due to the increased surface energy of finely milled particles, excipients must be empirically screened to determine if they provide enough stability to the system. Physical/chemical stability, zeta potential, particle size, and PDI must all be quantified to understand the nanosuspension’s properties and predict its stability.

In this study, a design of experiment (DOE) approach is used for modeling Adaptive Focused Acoustic® (AFA®) technology as a method for producing nanosuspensions in preclinical amounts. A series of common excipients are screened and tested for stability and particle size reduction. The most important factors in milling are identified and tested in the DOE.

Experiments and Results

AFA Particle Reduction Factors

- To model the amount of variables listed in a 2-level full factorial DOE experiment would be take 256 runs, which would require significant bandwidth and material.
- For simplification, factors that were predicted to have no or little effect on output were tested one variable at a time (OVAT) in an effort to exclude them from the factorial model.
- Based on our preliminary experimental data: API concentration, polymer concentration, surfactant concentration, power and milling time are major contributing factors for the final API particle size.
- The DOE was performed to quantitate which factors contributed the most towards particle reduction, as well as understand any interactions between factors.

Vehicle Selection

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Excipient Components</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HPMC/SDS</td>
<td>Has a high success rate in nanosizing APIs under 500 nm.</td>
</tr>
<tr>
<td>2</td>
<td>PVP/Pluronic F 68</td>
<td>A combination that has been effective in nanosizing from experimentation.</td>
</tr>
<tr>
<td>3</td>
<td>HPMC/Pluronic F 68</td>
<td>Varied nonionic and ionic surfactants and polymers for versatility</td>
</tr>
<tr>
<td>4</td>
<td>PVP/SDS</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>HPMC/Sodium Cholate</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Parameters selected in the DOE experiment are highlighted blue. Parameters which were either controlled or showed little effect on output are in gray.

Vehicle Selection

- The runs were performed in random sequence and the particle size and PDI are entered into Design Expert 10 as responses.
- Particle Size Range: 73.94 – 561.7nm PDI Range: 0.221 - 0.428
- Center points Runs: 249.4 nm, 0.267 PDI. Model curvature is insignificant by ANOVA.

ANOVA Results

- R Squared: 0.9646
- Model Significance: <0.0001
- Curvature: Insignificant
- Lack of Fit: Insignificant

- R Squared: 0.780
- Model Significance: 0.0019
- Curvature: Insignificant
- Lack of Fit: Insignificant

- Confirmation runs were performed using a DOE solution: 25mg/mL API, 1.70% PVP, 0.50% F68, 330 PIP, 5.25 Hours.

Conclusions

- Identified at what levels parameters contributed and impeded particle size reduction and PDI output.
- Using a DOE solution, can predict particle size output of compound A nanosuspensions within ~35 nm. With a PDI < 0.225
- Parameters can be adjusted based on specific formulation needs.
- (Concentration requirement, excipient balance, chemical stability)
- Established a starting point for vehicle selection for new compounds that can be altered to better provide stability for various physical differences between compounds.

References