A DOE Approach for Nanosuspension Preparation for Poor Solubility Pharmaceutical Compounds

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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

Covaris S220x (AFA)

Malvern Zetasizer Nano ZSP (DLS)

Figure 1: Instruments for particle milling and particle size measurement.

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 particle outcomes 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.

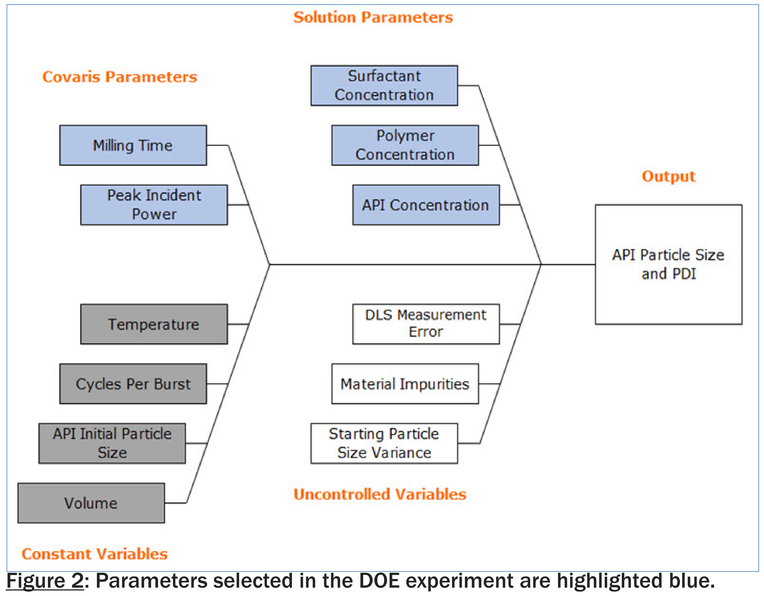

Figure 2: Parameters selected in the DOE experiment are highlighted blue. Parameters which were either controlled or showed little effect on output are in gray.

Vehicle Selection

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

- Compound A formed a stable nanosuspension that maintained its particle size for 1 Month using 2% PVP, 0.5% F68 as the vehicle.

Compound A DOE level

Factor	(-) Level	(+) Level
API Concentration (mg/mL)	5	25
PVP Concentration (%, w/v)	1	2
F68 Concentration (%, w/v)	0.5	1
Power (Watts)	200	350
Time (Hours)	3	6

References

1. Komasaka, Takao, et al. "Practical Method for Preparing Nanosuspension Formulations for Toxicology Studies in the Discovery Stage: Formulation Optimization and in Vitro/in Vivo Evaluation of Nanosized Poorly Water-Soluble Compounds." *Chemical and Pharmaceutical Bulletin*, vol. 62, no. 11, 2014, pp. 1073–1082., doi:10.1248/cpb.c14-00232.
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3. Liu, Tao, et al. "Production of Drug Nanosuspensions: Effect of Drug Physical Properties on Nanosizing Efficiency." *Drug Development and Industrial Pharmacy*, vol. 44, no. 2, 2017, pp. 233–242., doi:10.1080/03639045.2017.1386207.
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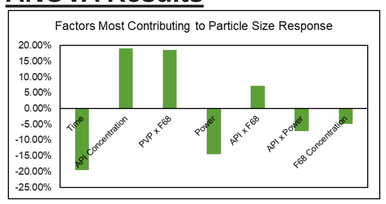
Fractional Factorial Design Layout and Output

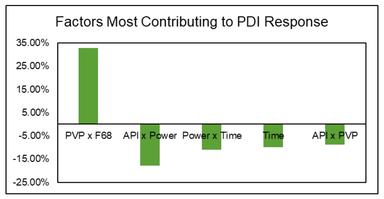
Run	Factor 1 A:API Conce... mg/mL	Factor 2 B:PVP Conc... %	Factor 3 C:F68 Conce... %	Factor 4 D:Power Watts	Factor 5 E:Time Hours	Response 1 Particle Size nm	Response 2 PDI
1	25	1	1	200	6	261.8	0.291
2	5	2	1	200	6	124.7	0.346
3	5	2	1	350	3	189.8	0.428
4	5	1	1	200	3	204.9	0.223
5	25	2	0.5	200	6	232.3	0.262
6	25	1	1	350	3	247.2	0.258
7	5	2	0.5	350	6	183.5	0.242
8	25	2	0.5	350	3	217.9	0.248
9	5	1	1	350	6	73.94	0.26
10	5	1	0.5	200	6	307.2	0.312
11	25	2	1	350	6	222.8	0.221
12	5	1	0.5	350	3	331.6	0.331
13	25	1	0.5	200	3	535.7	0.372
14	5	2	0.5	200	3	254.8	0.276
15	25	1	0.5	350	6	259.2	0.246
16	25	2	1	200	3	561.7	0.331
17	15	1.5	0.75	275	4.5	230.7	0.261
18	15	1.5	0.75	275	4.5	254.7	0.256
19	15	1.5	0.75	275	4.5	262.7	0.283

- 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.

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