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Comparison of Amorphous Dispersions of Piroxicam in Plasdone™ S-630 copovidone Prepared by Spray Drying and Hot-melt Extrusion

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Introduction

Amorphous solid dispersion technology is a proven technology that can create amorphous APIs with increased solubility, leading to enhanced bioavailability. Research has established that stable solid dispersions can be prepared through both spray drying and hot-melt extrusion (HME). The purpose of this study was to compare the stability, quality and performance of amorphous solid dispersions prepared by hot-melt extrusion and spray drying. The study also evaluated the effectiveness of Plasdone S-630 copovidone as a polymeric carrier in both processes.

Methods

Materials. Piroxicam USP was supplied by RIA International, LLC, East Hanover, NJ. Melting point = 198–200°C. Plasdone S-630 copovidone was supplied by Ashland Specialty Ingredients, Wilmington, DE. T_g = 106°C

Spray-drying solutions were prepared by dissolving 5% total solids into 2:1 (w/w) mixture of dichloromethane and methanol. All solvents conform to USP, NF, and/or FCC specifications. Solid dispersions made by both spray drying and hot-melt extrusion were evaluated at 30% and 40% drug load.

Melt Extrusion. Hot-melt extrusion was performed on a Coperion ZSK-18 extruder with the following specifications:
Screw diameter [mm] = 18
Maximal spec. torque Md/a^3 [Nm/cm^3] = 11.3
Rotation speed range [min^{-1}] = 120-1200
Motor (max.) power consumption [kW] = 11.7
Da/Di = 1.55
Slit extrusion die [mm] height x width x length = 2 x 20 x 20
Gravimetric powder feeders (1 for polymer + 1 for API)
Screw configurations are depicted in Figure 1.

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 14–18, 2012, Chicago, Illinois.

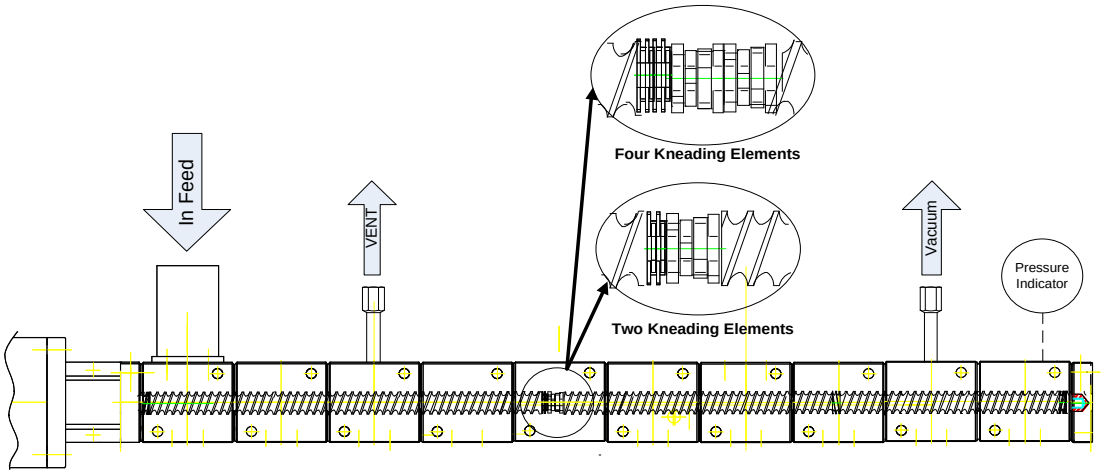

Figure 1. Hot-melt extrusion setup

Polarized Light Microscopy (PLM). Microscopy work was performed using an Olympus BX51 microscope equipped with a variable polarizer.

Spray-drying. Spray-drying was performed on a GEA SD Micro* Spray-Dryer using a 0.5 mm two-fluid Schlick nozzle. Formulations were spray dried targeting an inlet temperature of 85°C, a process gas flow rate of 25 kg/hr, an atomizing gas pressure of 0.5 bar, and an atomizing gas flow rate of 1.5 kg/hr. The liquid feed rate was adjusted to achieve an outlet gas temperature of 55°C. Spray-dried dispersions were vacuum dried for 65 hours at 40°C under -25 in. Hg reduced pressure.

X-ray Powder Diffraction (XRPD). X-ray diffraction was performed on a Bruker D8 Focus, using a copper tube element and a PSD: LynxEye detector. The following data acquisition parameters were used: volts: 40 kV, power: 40 mA, scan range: 4.0000–39.9960° 2θ, number of steps: 1685, time/step: 0.3 s, collection time: 549 s, rotation speed: 15 rpm, mode: continuous.

Kinetic Solubility. Dissolution was performed using a Pion µDISS Profiler. Piroxicam samples were added to 20 ml of FeSSIF heated to 37°C and the vials were maintained at a constant stirring speed of 300 rpm. Each spray-dried powder was weighed so that 2.0 mg of drug was added to each vial; compensation was made for the drug load of the samples. Dissolution measurements were taken by *in situ* fiber optic probes at various time points and these measurements were analyzed at a wavelength of 350 nm for the amount of piroxicam API dissolved.

Design of Experiments

Using a 2^3-factorial design of experiments, as detailed in Table 1, eight experiments were conducted to evaluate the effect of drug load, screw configuration and screw speed on the amorphous content, physical stability and solubility enhancement of the extrudate. Samples were extruded at a constant 2 kg/hr feed rate at barrel temperatures, as described in Table 2.

Table 1. Design of experiments

Factor	Level -1	Level +1
Screw design	2	4
Rotation speed	500	700
API:polymer ratio	30:70	40:60

Table 2. Barrel temperature profile

Polymer	T_1 [°C]	T_2 [°C]	T_3 [°C]	T_4 [°C]	T_5 [°C]	T_6 [°C]	T_7 [°C]
PVP/VA	40	85	100	110	125	130	140

Results and Discussion

The melt extrudates and spray-dried powders were characterized by polarized light microscopy (PLM), x-ray powder diffraction (XRPD), and kinetic solubility in order to evaluate the amorphous characteristics of the samples and the expected solubility enhancement of the API. The physical stability of the extrudates was also investigated at 25°C/60% relative humidity (RH) for one year and 40°C/75% RH for six months.

Physical Characteristics. As seen in Table 3, the 30% drug load extrudates were transparent whereas the extrudates produced using 40% drug load were opaque, suggesting that the 30% extrudates may be amorphous and the 40% extrudates were probably crystalline. Table 3 also summarizes the resulting motor load (M) and melt temperature (T_m) and specific energy input (SEI) of the extrusion process.

Table 3. Extruded samples

Kneading elements	Drug loading	N [rpm]	M [%]	T_m [°C]	SEI	Visual
2	30	500	53	171	1.049	Transparent
2	30	700	33	172	0.9144	Transparent
4	30	500	47	157	0.9302	Transparent
4	30	700	30	161	0.8313	Transparent
2	40	500	54	166	1.0688	Opaque
2	40	700	33	169	0.9144	Opaque
4	40	500	48	155	0.95	Opaque
4	40	700	30	157	0.8313	Opaque

Initial Physical State and Stability. Counter to the physical appearance of the extrudate, the XRPD data show that the 30% drug load extrudate produced at 500 rpm with two kneading blocks is partially crystalline (see Figure 2) and the other 30% extrudates and spray dried dispersion are amorphous. After one year at room temperature or six months at 40°C and 75% RH, the extrudates produced at 500 rpm with two or four kneading blocks re-crystallized (see Figures 3 and 4). The spray-dried dispersion and extrudates produced at 700 rpm remain amorphous under both stability conditions. At the 40% drug load, the spray dried dispersion was initially amorphous but all extrudates were partially crystalline (see Figure 5). The XRPD results were confirmed by polarized light microscopy (images not shown).

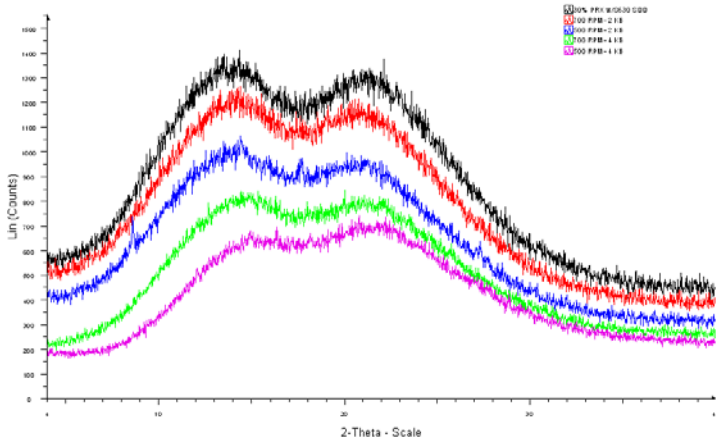

Figure 2. XRPD results for 30% drug load samples after production

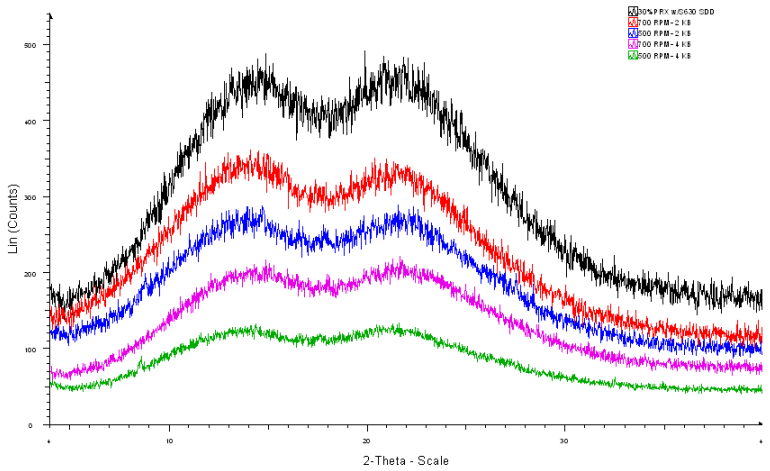

Figure 3. XRPD results for 30% drug load samples after one year at 25°C and 60% RH

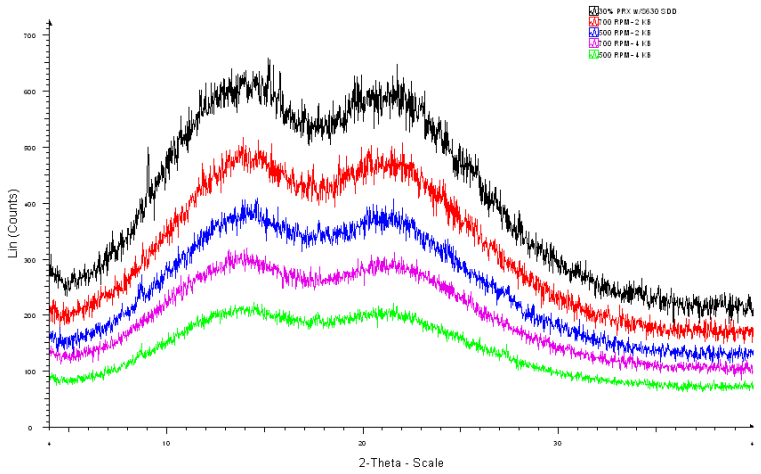

Figure 4. XRPD results for 30% drug load samples after six months at 40°C and 75% RH

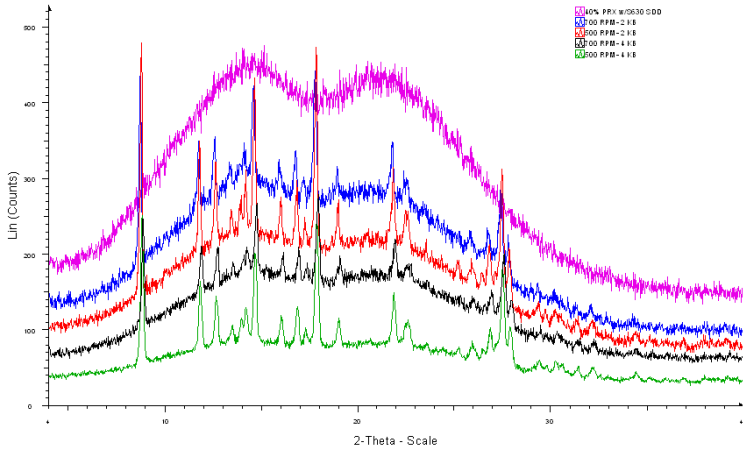

Figure 5. XRPD results for 40% drug load samples after production

Kinetic Solubility Results. Kinetic solubility results showed that extruded and spray-dried samples produced at both 30% and 40% API load showed significant solubility enhancement over the crystalline API. The spray-dried dispersions always showed higher C_{max} solubility followed by faster rate of recrystallization than the

comparable extrudates, suggesting that particle size and wettability may play a key role in solid dispersion recrystallization. For the melt-extruded samples, increasing the screw speed increases the C_{max} and area under the curve (AUC) solubility, increasing the drug loading reduces the C_{max} but increases the AUC solubility, and increasing the kneading blocks only slightly increases the C_{max} and AUC solubility. See Figures 6 through 9.

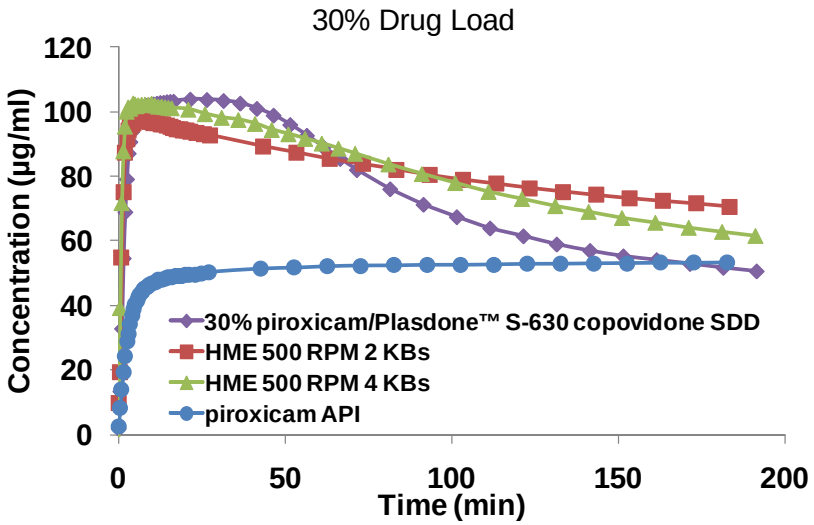

Figure 6. Kinetic solubility of spray-dried and 500 rpm extruded samples

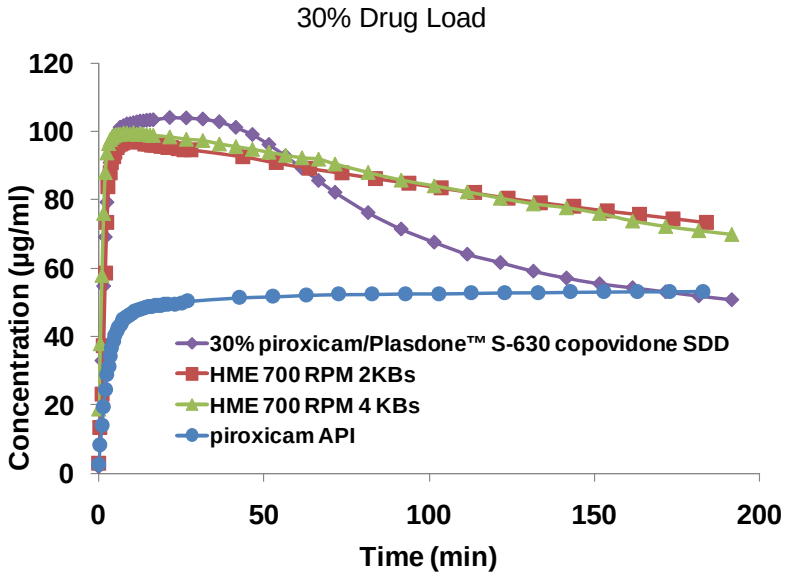

Figure 7. Kinetic solubility of spray-dried and 700 rpm extruded samples

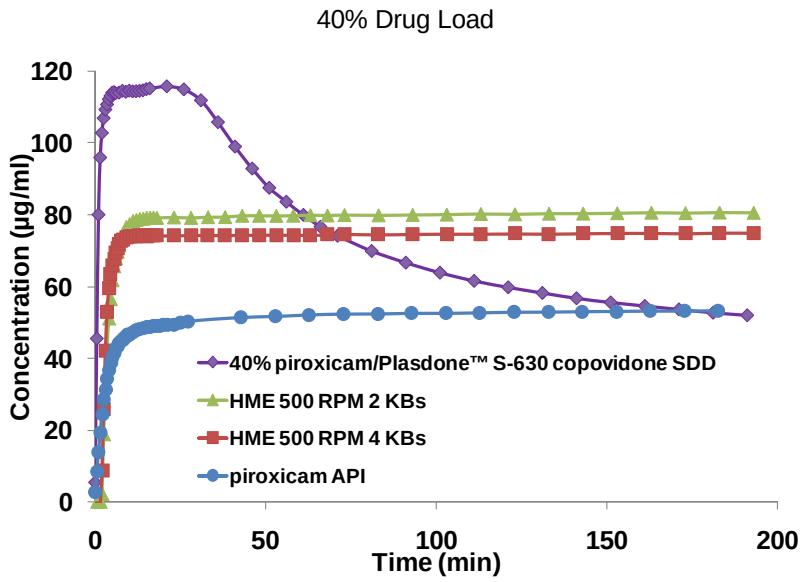

Figure 8. Kinetic solubility of spray-dried and 500 rpm extruded samples

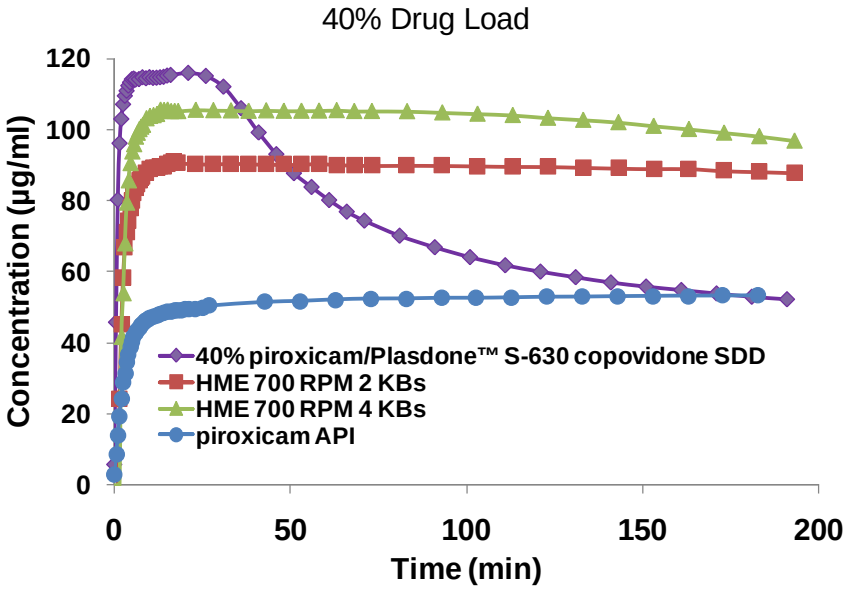

Figure 9. Kinetic solubility of spray-dried and 700 rpm extruded samples

Factor Impact on Motor Load, Melt Temperature and SEI. From the design of experiments, the impacts of screw design, rotation speed and API:polymer ratio were studied on the motor load, melt temperature and SEI.

Figure 10 illustrates that increasing the screw speed reduces the motor load, drug loading has no impact on motor load, and at low screw speeds, more kneading blocks reduce the motor load. Figure 11 illustrates that more kneading blocks reduce the melt temperature; drug loading and screw speed have very little impact on the melt temperature. Figure 12 illustrates that drug loading has no effect on the SEI but increasing screw speed and adding more kneading blocks reduces the SEI. Increasing the screw speed and adding additional kneading blocks increases the shear and reduces the melt viscosity of the solid dispersion, thereby reducing the SEI.

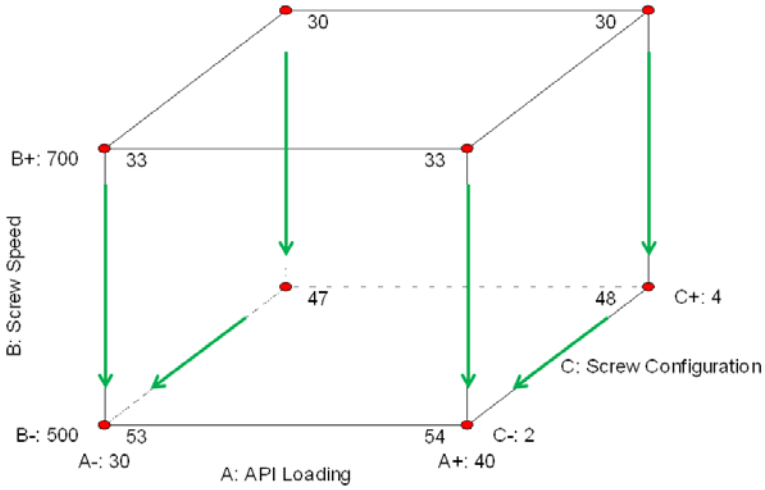

Figure 10. Motor load response cube

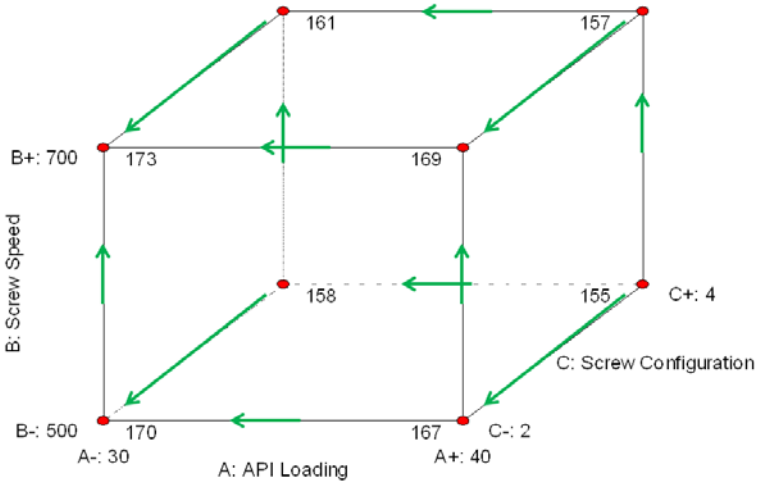

Figure 11. Melt temperature response cube

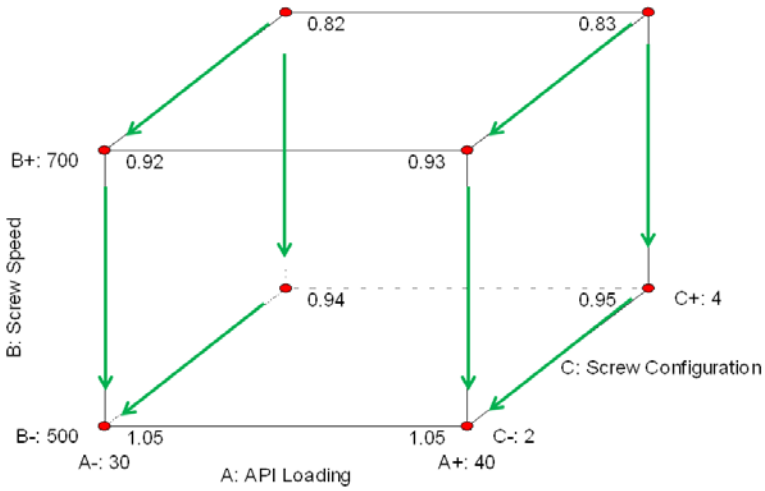

Figure 12. SEI response cube

Factor Impact on Critical Quality Attributes. From the design of experiments, the impacts of the three factors, screw design, rotation speed and API:polymer ratio, were studied on four critical quality attributes: initial physical state, accelerated stability physical state, C_{max} solubility and AUC solubility, as depicted in the cube-based response plots in Figures 13–16.

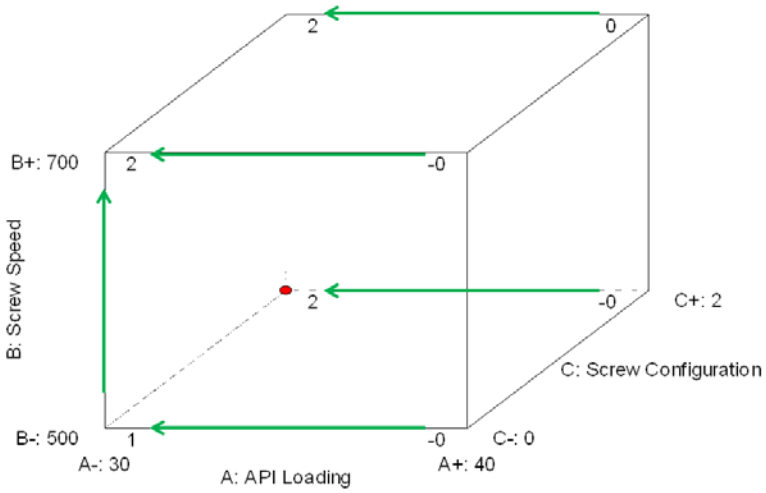

Figure 13. Initial physical state response cube

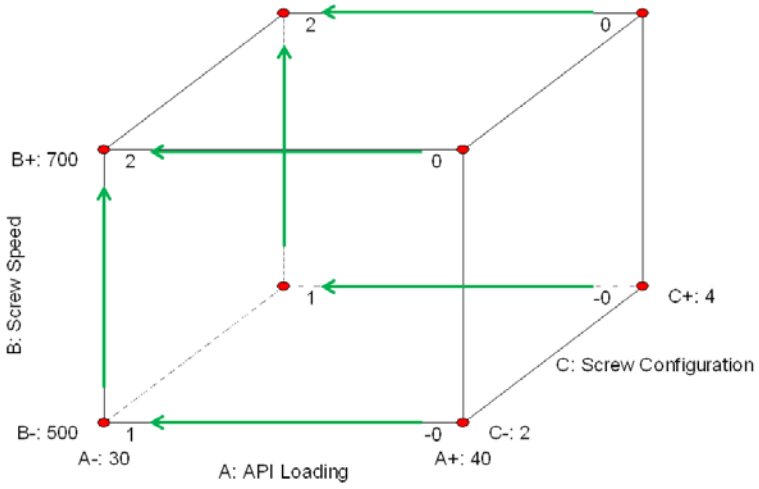

Figure 14. Accelerated stability physical state response cube

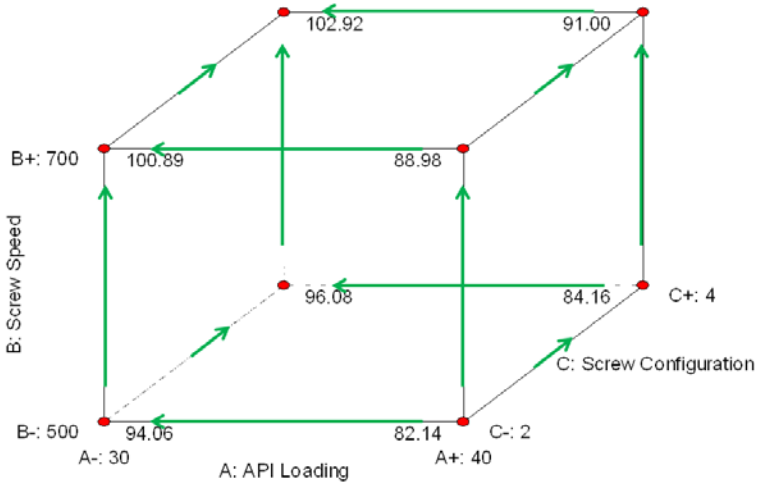

Figure 15. C_{max} solubility response cube

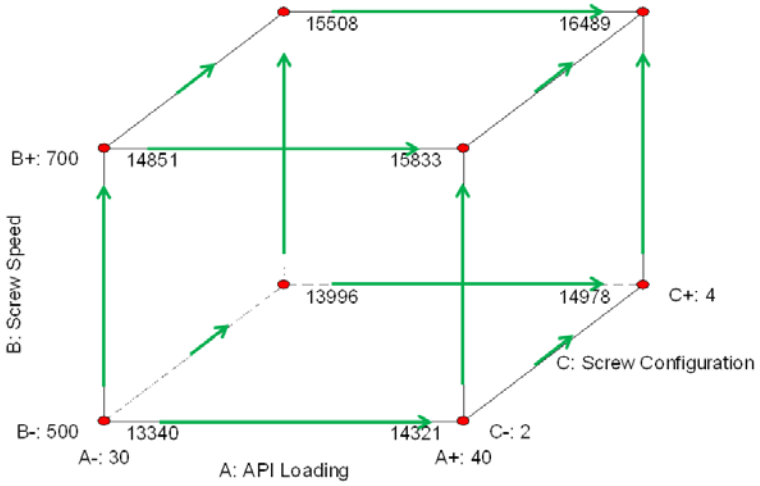

Figure 16. AUC solubility response cube

Figure 13 illustrates that increasing the drug loading increases initial crystallinity and at the 30% API loading, the higher screw speed produces initially amorphous material. Figure 14 illustrates that lower API load samples are more stable under accelerated stability conditions and at the 30% API loading; the higher screw speed produces a more stable product. Figure 15 illustrates that increasing the screw speed increases the C_{max}, increasing the drug loading reduces the C_{max}, and more kneading blocks only slightly increase the C_{max}. Figure 16 illustrates that increasing the screw speed increases the AUC solubility, increasing the drug loading increases the AUC solubility, and more kneading blocks only slightly increase the AUC solubility.

Conclusions

Plasdone™ S-630 copovidone was found to be an excellent polymeric carrier in preparing piroxicam solid dispersions. At the experimental conditions tested, spray drying is better suited for preparing amorphous solid dispersions with higher drug loading. Screw configuration and melt temperatures have very little impact on the critical quality attributes of the product. Increasing the screw speed leads to an emptier machine, which reduces torque and increases shear. The increased shear decreases the melt viscosity, requiring less specific energy input, which leads to a solid dispersion with higher C_{max} and higher AUC during dissolution, better initial amorphous content, and better long-term stability.