PTR-092

Plasticizer Compatibility and Thermal and Rheological Properties of Plasdone™ povidone And copovidone polymers for Hot-melt Extrusion Applications

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Introduction

Solid dispersion technology is a key enabling technology for bioavailability enhancement of poorly soluble compounds. Research in the past decade in solid dispersions and process technology has established that stable solid dispersions can be prepared at commercial scale through hot-melt extrusion. Polymer selection is critical in producing a successful amorphous solid dispersion that enhances dissolution and prevents the active pharmaceutical ingredient (API) recrystallization. The preferred polymer must also be amenable to the process technology. In hot-melt extrusion, thermal properties and melt rheology must be considered when selecting a formula. The glass transition temperature, T_g, of the polymers defines the lower end of the processing temperature window; typically extrusion is performed at temperatures between 20–40°C above the T_g of the polymer. High T_g polymers are preferred for physical stability, but are more difficult to process by melt extrusion without plasticization by adjuvants and/or the API. Often, plasticizers are required to successfully melt extrude the solid dispersions below API and polymer degradation temperatures. In this study, plasticizer compatibility of Plasdone povidone and copovidone polymers is assessed by melt rheology and differential scanning calorimetry. Additionally, the thermal and rheological properties of Plasdone povidone and copovidone polymers are assessed.

Methods

Thermal Gravimetric Analysis (TGA)

TGA experiments were performed using TA Instruments Q500. Thermal decomposition of Plasdone povidone and copovidone polymers was characterized by TGA using two methods; first, the sample was heated from ambient to 600°C at different heating rates under air and nitrogen purges. Second, different samples were held at fixed temperatures from 140–230°C for 30 minutes.

Differential Scanning Calorimetry (DSC)

DSC experiments were performed using a TA Instruments DSC Q2000. Glass transition temperatures of the polymers and plasticized polymers were measured using a heat cool heat method where the samples were heated at 20°C/min to 100°C and held there for 5 minutes to remove residual moisture. Next, the samples were cooled at 50°C/min to 0°C before performing a modulated heating cycle ramping at 2°C/min through the glass transition temperature of the polymer.

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

Compendial Testing

Plasdone™ povidone and copovidone polymers were processed on a Dynisco Laboratory Mixing Extruder at 180°C and tested to ensure that the polymers still met all USP requirements after being extruded.

Viscosity

Dynamic oscillatory flow tests were carried out in the linear viscoelastic region using a strain-controlled ARES-G2 rheometer equipped with a temperature control chamber (TA Instruments). Granular samples were loaded on the 25 mm stainless steel parallel plate setup with the help of a melt ring. Samples were not dried before testing. Dynamic strain sweep, frequency sweep, temperature sweep and time sweep tests were conducted for each sample under nitrogen and air purge.

Results and Discussion

Thermal Properties

Table 1 shows the glass transition temperature, K-value and molecular weight of various grades of Plasdone povidone and copovidone polymers.

Table 1. Physical properties of Plasdone povidone and copovidone polymers

Plasdone™ Povidone or Copovidone Grade	Weight Average Molecular Weight	K-Value Viscosity	Glass Transition Temperature (°C)
K-12	4,000	10.2–13.8	120
K-17	10,000	16.0–17.5	140
K-25	34,000	24–26	160
K-29/32	58,000	29–32	164
K-90	1,300,000	85–90	174
S-630	24,000–30,000	25.0–31.0	109

Figures 1 and 2 illustrate TGA thermograms for Plasdone S-630 copovidone that was isothermally heated to 170°C and 230°C for 30 minutes to measure initial moisture loss and potential degradation from prolonged exposure to elevated temperatures. The same experiment was performed at all the temperatures shown in Figure 3 (TGA results not shown). After heating, the sample exposed to 170°C was colorless but the sample that was exposed to 230°C was a dark yellow color, which is indicative of degradation.

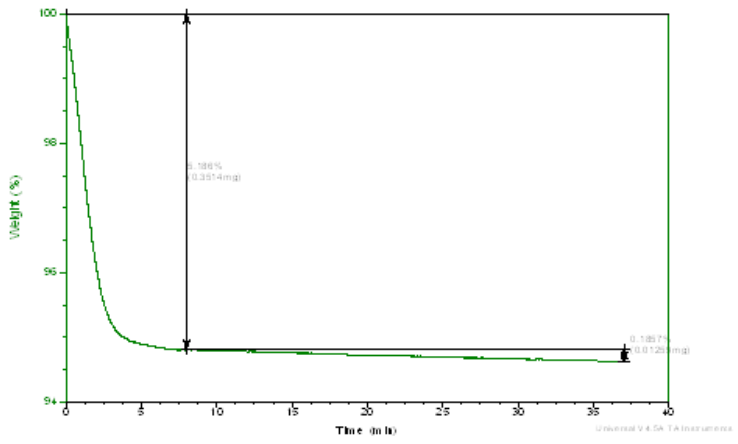

Figure 1. Plasdone S-630 copovidone, isothermal @ 170 °C for 30 minutes

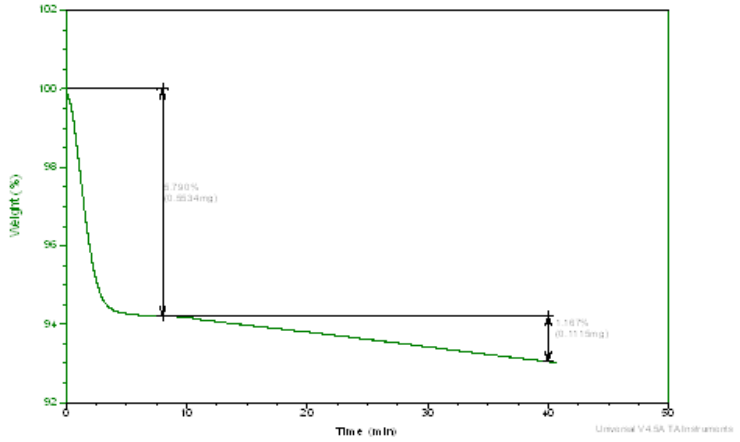

Figure 2. Plasdone™ S-630 copovidone, isothermal @ 230 °C for 30 minutes

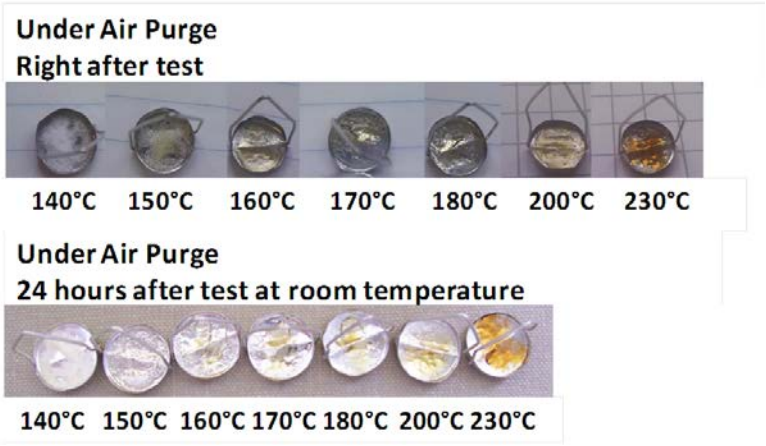

Figure 3. Plasdone S-630 copovidone, after exposure to various temperatures for 30 minutes

All Plasdone povidone and copovidone polymers exhibit similar degradation behavior; temperature ramps from ambient to 600°C show short-exposure degradation from 270–300 °C and 30-minute isothermally heated samples show weight and color changes appearing at 190–200 °C. Figure 4 illustrates the recommended melt extrusion processing window for neat Plasdone povidone and copovidone polymers; the polymer processing window is restricted between the T_g of the material and the onset of degradation. However, the T_g of the polymers can be reduced with the addition of API and/or plasticizers.

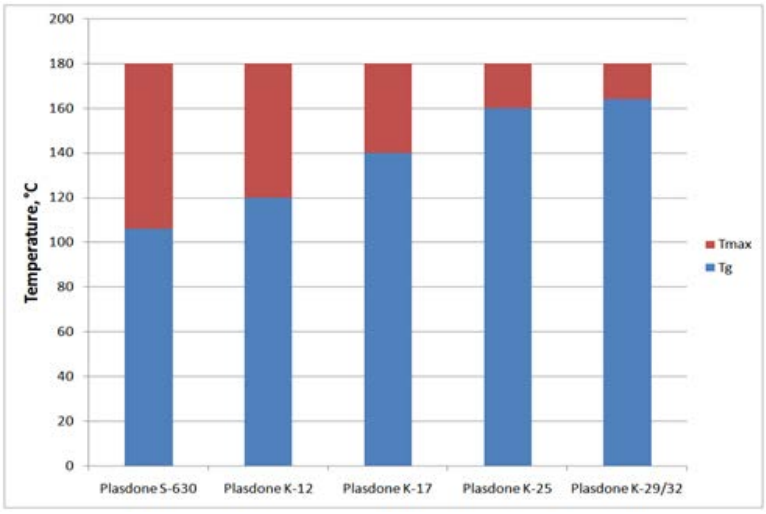

Figure 4. XRPD results for 40% drug load samples after production

Several plasticizers, as seen in Tables 2 and 3, were spray dried at 10% level with Plasdone™ povidone and copovidone polymers from ethanol or 2:1 (w/w) dichloromethane:methanol solutions under standard spray drying conditions to produce homogenously mixed plasticized polymers. Polymers were vacuum oven dried and tested for T_g. Results are available in Tables 2 and 3. All plasticizers reduced the T_g of Plasdone K-29/32 povidone, suggesting that all plasticizers tested are compatible with Plasdone povidone polymers. All plasticizers reduced the T_g of Plasdone S-630 copovidone except Pluronic based plasticizers. Certain plasticizers more markedly reduce the T_g of Plasdone povidone and copovidone polymers and may therefore be used at lower amounts to more significantly reduce the T_g of Plasdone povidone and copovidone polymers.

Table 2. T_g of Plasdone K-29/32 povidone with plasticizers

Plasticizer compatibility at 10% (w/w) level with Plasdone™ K-29/32 povidone		
Plasticizer	T_g (°C)	Enthalpy (J/g°C)
None	163.67	0.1603
Dibutyl sebacate	120.62	0.1325
Diethyl phthalate	117.58	0.0983
Pluronic F-68	99.8	0.0601
Pluronic F-127	112.7	0.1054
Glycerol monostearate	124.36	0.1385
Polyethylene glycol	140.18	0.1378
Sodium lauryl sulfate	131.24	0.1211
Sodium docusate	110.67	0.0263
Triethyl citrate	109.99	0.0394
Triacetin	112.17	0.0528
Tween 80	142.96	0.0735
Vitamin E-tocopheryl polyethylene glycol	117	0.094

Table 3 T_g of Plasdone™ S-630 copovidone with plasticizers

Plasticizer compatibility at 10% (w/w) level with Plasdone™ S-630 copovidone

Plasticizer	T_g (°C)	Enthalpy (J/g°C)
None	107.77	0.1839
Dibutyl sebacate	89.51	0.0641
Diethyl phthalate	99.53	0.1511
Pluronic F-68	110.34	0.2218
Pluronic F-127	117.51	0.5494
Glycerol monostearate	94.34	0.1204
Polyethylene glycol 3350	95.54	0.1248
Sodium lauryl sulfate	82.65	0.122
Sodium docusate	91.99	0.0607
Triethyl citrate	95.54	0.1034
Triacetin	94,29	0.1145
Tween 80	87.09	0.1066
Vitamin E-tocopheryl polyethylene glycol	95.53	0.1493

Rheology

The melt rheology of neat Plasdone povidone and copovidone polymers was characterized by measuring melt viscosity at different temperatures (Figure 5), measuring viscosity as a function of shear rate at constant temperature (Figure 6), and measuring viscosity as a function of time at constant temperature to generate additional thermal stability and plasticizer permanence data (Figure 7). The time sweep experiment shown in Figure 9 is effective in predicting the permanence of a plasticizer in a formulation or potential polymer cross-linking during extrusion. An increase in the viscosity of a polymer with a volatile plasticizer is indicative of plasticizer volatilization; in the example shown, this effect is apparent in the sample containing 10% TEC where the slope of the line is greater than that of the neat polymer. If the slope of the viscosity as a function of time does not increase after addition of plasticizers then the plasticizer is likely to be permanent through the extrusion process.

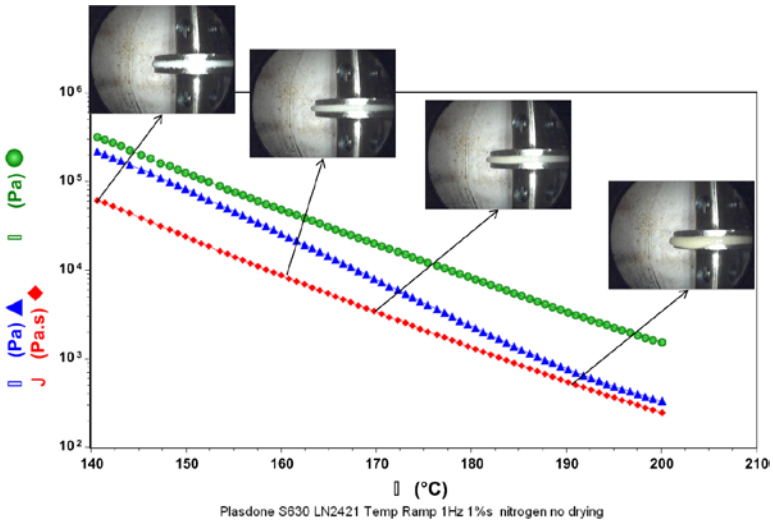

Figure 5. Strain sweep experiment of Plasdone S-630 copovidone with increasing temperature

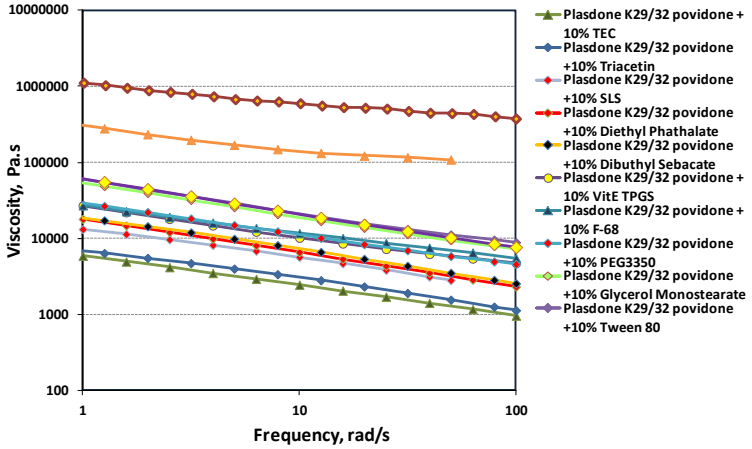

Figure 6. Frequency sweep experiment of plasticized and neat Plasdone™ K-29/32 povidone samples

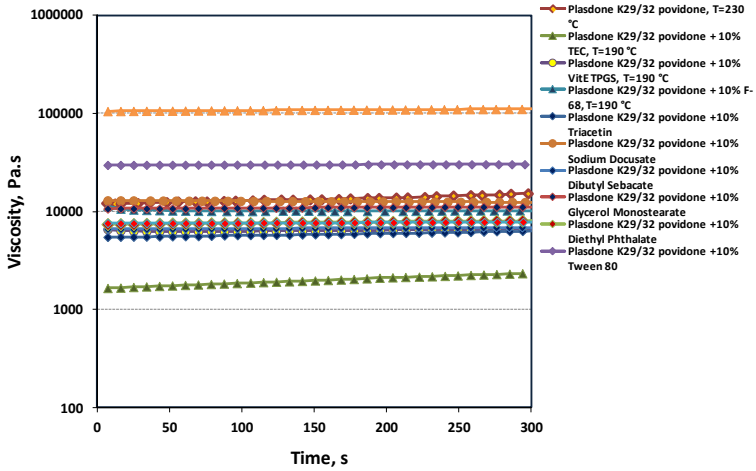

Figure 7. Time sweep experiments of plasticized and neat Plasdone K-29/32 povidone samples

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The viscosity of Plasdone™ povidone and copovidone polymers at various temperatures is shown in Figure 8, the ideal hot-melt extrusion processing window for these polymers is between ~700 and 100,000 mPa•s, while maintaining temperatures below the degradation point of 180 °C. Figure 9 shows the effect that various plasticizers have on the processing window for Plasdone K-29/32 povidone.

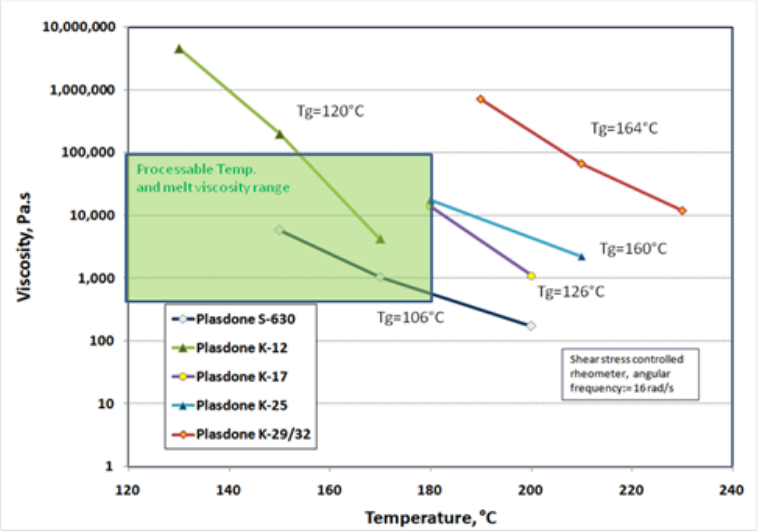

Figure 8. Plasdone™ povidone and copovidone polymer melt rheology

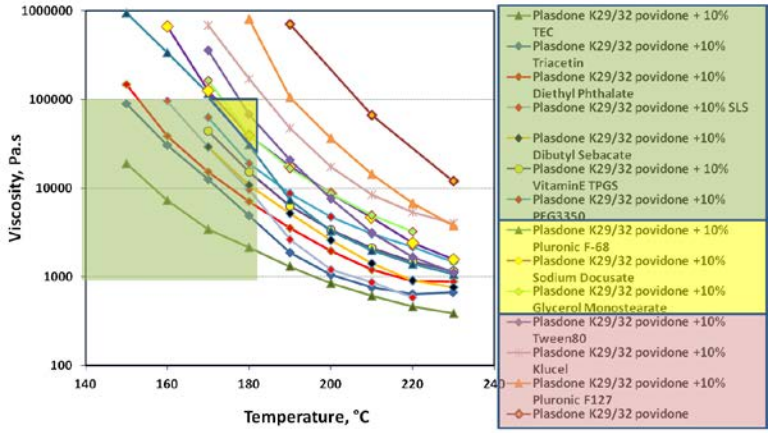

Figure 9. Processing window for Plasdone K-29/32 povidone

Conclusions

All Plasdone povidone and copovidone polymers demonstrate thermal stability at temperatures below 180 °C; consequently, an upper limit of 180 °C is recommended for melt extruding these polymers. Plasdone S-630 copovidone and Plasdone K-12 povidone have ideal rheological characteristics for melt extrusion. Plasdone K-29/32 povidone will either require plasticization by the API or by other adjuvants in order to successfully melt extrude solid dispersions below 180 °C. Although T_g is a good measure of plasticizer compatibility, melt rheology is better able to determine plasticizer efficiency.