Rheological study of copovidone and solid dispersion blend used for hot melt extrusion

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ABSTRACT: The focus of this work is to generate rheological parameters using AR 2000EX rheometer for PVP VA64 and Compound A – PVP VA64 blend at different temperatures, which can then be subsequently used to identify hot melt extrusion process conditions. Addition of Compound A to the neat PVP VA64 shows a drop in storage modulus and loss modulus as compared to the neat PVP VA64. It appears that Compound A is acting as a plasticizer by increasing the separation of the polymer chains and thus results in reduction of viscosity of Compound A blends compared to polymer only samples. For both systems, based on low standard error of fit, Cross model was chosen as the best fit for the rheological data and temperature dependency of viscosity was assessed by Williams–Landel–Ferry (WLF) model. This approach can be applied to screen formulations with new chemical entities (NCEs) and generate rheological information with various extruding polymers at fixed/variable drug loading in polymer matrix to determine suitability for hot melt extrusion process and appropriate temperature for conducting hot melt extrusion. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43278.

INTRODUCTION

Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 6:4 by mass and this pharmaceutical grade compendial excipient is available under the trade name Kollidon® VA64 from BASF. Traditionally, this excipient has been employed in pharmaceutical product development as binder in dry granulation and wet granulation processes and is soluble in water and alcohols. Lately, it has been also employed for preparation of amorphous solid dispersions by spray drying and hot melt extrusion process. Copovidone acts as a crystallization inhibitor and prevents crystallization of the amorphous drug.[1–5]

During early stages of drug product development, the availability of active pharmaceutical ingredient (API) is often limited and hence at times limits the number of hot melt extrusion runs. In such a case, employing an extrusion simulator can assist in gaining vital knowledge about the extrusion process. In this study, Copovidone (obtained from BASF, Ludwigshafen, Germany) and proprietary Compound A (obtained from Chemical Development department of Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) was employed for generating rheological parameters which can then be subsequently inputted into the simulator for selection of optimum process conditions for the extrusion process at different scales and evaluate the

impact of screw configuration on the extrusion process. For the in-house hot melt extrusion technology development, Compound A was used as the model drug at 33% loading with PVP VA 64 (Compound A:PVP VA64/1:2). The compound A has poor aqueous solubility (intrinsic solubility estimated 18 $\mu g\ mL^{-1}$), moderate hydrophobicity (log P) of 2.6 and pK_a of 2.5 (shows pH dependent solubility). The Compound A has melting point of 207.6°C and decomposes above 275°C. Compound A was selected as model compound because it is difficult to convert to amorphous form and has high inherent tendency to crystallize. Polyvinylpyrrolidone-*co*-vinyl acetate 64 (Copovidone) was selected as a suitable polymeric crystallization inhibitor to prepare solid dispersion based on preliminary screening studies, during which various extrusion polymers at different ratios were evaluated by hot stage microscopy, DSC analysis, and accelerated physical stability studies. Based on initial screening, a 1:2 Compound A and PVP VA64 formulation was selected to prepare solid dispersions.[4] Selection was based on polymer's ability to provide supersaturation to varying extent, solubilization of drug, thermal stability, and extrudability.[4]

Amorphous polyvinyl-based polymers used in hot melt extrusion have been studied where viscoelasticity was used in predicting HME conditions were discussed. For PVP VA64, temperature sweep studies up to 165°C have been conducted

where the loss modulus and storage modulus was studied with oscillation temperature sweep.[6] BASF has studied melt viscosity of PVP VA64 as a function of temperature in range of 150–200°C and has shown optimal melt viscosity range for the HME for PVP VA64. In addition, BASF, also investigated plasticizers at 1 radian/second such as Kolliphors®, polyethylene glycol at 20% level which were effective in reducing viscosity. However, these are permanent plasticizers trapped along with the extruding polymers which will lower the glass transition (T_g) permanently and has the potential to induce crystallized amorphous drug. Transient solubilizer/plasticizer such as water has been employed in the hot melt extrusion process where it is quickly evaporated out after the extrusion process and is not permanently trapped inside the dispersion matrix.[7,8] Viscosity at zero shear rate from Cross model at a given temperature is often employed to estimate initial viscosity of the material inside the extruder for various drug polymer combinations.[9,10] For hydroxypropyl methyl cellulose acetate succinate (HPMCAS) temperature dependence of zero rate viscosity was assessed by Arrhenius model.[10]

Methodology for rheological measurements of commonly used polymers for hot melt extrusion (HME) need to be developed to understand the effect of shear force and high temperatures on polymer viscosity. Once developed, the viscosity parameters can then be generated for various drug loading in polymers for extrusion and subsequently be applied in simulation of HME process by using one-dimensional computational software, to understand the extruder and identify suitable extrusion process conditions for successful scale up from lab scale to commercial scale. Development of mathematical models and assumptions used in models for single screw plasticating extruders has been extensively covered in literature. At large, they have focused on the melt conveying section of the extrusion process. Information presented by Tadmor and Klein (1970) is for three functional zones—solids conveying, melting, and melt conveying. This is also the foundation for early work and valuable for design and macroscopic modeling of extruder systems.[11]

Input parameters and material properties including rheology parameters are required to be entered into the simulator software so that simulations can be performed to assess the impact of varying extrusion process conditions on output parameters. This will allow for selection of optimum process conditions for the extrusion process and help with streamlining of experiments at different scales including the ability to assess the impact of changes in screw configuration on HME process. This approach would result in significant API and time saving due to reduced experimentations and better process understanding.

Rheology of polymers employed for HME process is very much dependent on its chemical and morphological structure.[12] In addition, the viscosity of the extruding polymer is also impacted by factors such as pressure, molecular weight, filler, lubricant, temperature, and plasticizers.[12] Factors like pressure, branching, side groups, and molecular weight can contribute to the increase of entanglements between polymer chains and will increase the overall viscosity of the system as these factors affect the ability of chains to slide past each other. In contrast, the
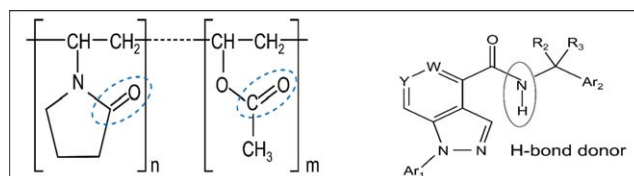

Figure 1. Kollidon® VA64 polymer structure (left: —-H-bond acceptor) and generic structure of compound A (right: — H-bond donor). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

plasticizers perform by spacing out the molecules and effectively reducing the viscosity. Low molecular weight polymer and API that exhibit miscibility with molten polymer are frequently effective as plasticizers.

The chemical structure of Kollidon® VA64 chemical and proprietary compound A is illustrated in Figure 1. The compound A has hydrogen bond donor group as shown in Figure 1. Hence, compound A is estimated to form hydrogen bonding with polymers containing hydrogen bond acceptor groups such as PVP VA64, which could result in formation of stable amorphous dispersion. Kollidon® VA64, a vinyl pyrrolidone-vinyl acetate copolymer is an amorphous white or slightly yellowish free flowing powder which is soluble in water and alcohol. The weight average molecular weight reported by the manufacturer, BASF, for Kollidon® VA64, ranges from 45,000 to 70,000. The bulk density of Kollidon® VA64 powder is in the range of 0.2–0.3 g mL^{-1} and the typical particle size is in the range of 50–250 μm. In comparison, the compound A is a proprietary drug molecule which is a white to off white crystalline powder and has poor aqueous solubility. The molecular weight is ~300–400 and the bulk density is in the range of 0.2–0.3 g mL^{-1}.

Rheology of HME polymers can be studied at various high temperatures and shear rate using capillary or parallel plate rheometer. In the current study parallel plate rheometer was used to generate rheological parameters for PVP VA64 and Compound A – PVP VA64 blend.

In the present study a systematic rheological study was conducted with PVP VA64 alone and Compound A that has propensity to hydrogen bond with PVP VA64. In the present work, frequency sweep test results for polymer PVP VA64 and Compound A – PVP VA64 blend at different temperatures using AR2000 EX rheometer are summarized and the temperature dependency of viscosity across both the systems was assessed by Williams-Landel-Ferry (WLF) model. Approach presented in this study can be applied to formulations comprising of new chemical entities (NCEs) and for generating rheological information for the simulation of HME process.

EXPERIMENTAL

Standard Calibration Check

Polydimethyl siloxane (PDMS) putty, a viscoelastic rheological reference standard with known relaxation time was used for the calibration of the AR 2000EX rheometer (TA Instruments, New Castle, DE). This standard was obtained from TA Instruments where phase angle at 30°C and specific frequency was specified.

Table I. Working Parameters for the Hot Melt Extruder

Process conditions	Leistritz micro—18 mm
Batch size (g)	>500
Screw speed (RPM)	125-400
Length/diameter	35/1
Feed rate	0.6-2.1 kg h^{-1}
Extrusion temperature (°C)	180
Melt temperature (°C)	~180
Melt pressure (PSI)	125-194
Actual torque (%)	29-57
Specific energy (kw hr^{-1} kg^{-1})	0.223-0.721

The PDMS standard was run at 30°C with angular frequency range of 0.100 to 100 rad s^{-1} with 10 points per decade and strain of 5%.

In this calibration test, the cross point for PDMS was determined. The cross point is the intersection of the G' (storage moduli) and G'' (loss moduli) lines as a function of angular frequency.

Preparation of Compacts and Frequency Sweep at Various Temperatures
The AR 2000EX rheometer from TA Instruments equipped with 25-mm parallel plate geometry, which has adjustable gap height and allows usage of sample of variable thickness was employed for rheological measurements. For rheological profiling of extrusion blends (Compound A:PVP VA64 blend/1:2 ratio and PVP VA64 alone), compaction of around 700–800 mg of neat polymer or physical mixture was done using Carver-Press (Wabash, IN) that was equipped with a 16-mm round die at a constant platen travel speed. Prior to measuring rheological parameters, these compacts were vacuum treated at 54°C using vacuum oven (National Appliance Company, Model 5851, Portland, OR) at 25–30″ mm of Hg for removal of free water present in polymer and entrapped air. Vacuum-treated compacts of blends were employed to minimize presence of air and moisture and provide consistency in viscosity measurements.

Parallel plate geometry enclosed inside the ETC (environmental test chamber) on the AR 2000EX rheometer was heated to the desired test temperature and the gap between the parallel plate was zeroed. A vacuum-treated compact was placed on the center of lower plate and upper plate was brought in contact with specimen gradually. The initial gap was set at 0.05-mm above the target to facilitate excess sample trimming and ensuring that it is flushed with the plate edges. The upper plate was lowered to the final gap setting (1000 μm) prior to start of oscillatory frequency sweep, which measures the frequency dependency of viscoelastic properties of material. Frequency-dependent response was measured at various temperatures over range of 0.01 to 100 rad s^{-1} at 5% constant strain. A fresh specimen was used for sweep at each temperature.

Hot Melt Twin Screw Extrusion Working Parameters
As previously stated in this manuscript, input parameters and material properties including rheology parameters and process data are required to be entered into the simulator software so that simulations can be performed to assess the impact of varying extrusion process conditions on output parameters and which will allow for selection of optimum process conditions.

For the Compound A – PVP VA64 physical blend, Leistritz's (American Leistritz Extruder Corporation, Somerville, NJ) 18-mm extruder was employed. The 18-mm extruder consisted of seven heating zones, corotating twin screws, and a die plate with 3-mm round die opening. All heating zones were maintained at 180°C during the extrusion run. The screw profile consisted of various types of conveying elements and a set of kneading elements of 30°, 60°, and 90°angle to provide adequate mechanical shear energy for formation of amorphous solid dispersion. The 18-mm extruder was equipped with a twin-screw gravimetric dosing feeder (K-Tron, Pitman, NJ). The extrusion process was monitored by recording melt temperature, melt pressure, and torque values throughout the extrusion run. For information, the various extrusion process conditions and additional system details for the Leistritz's 18-mm extruder are shown in Table I.

RESULTS AND DISCUSSION

Rheometer Standard Calibration Check
Polydimethyl siloxane (PDMS) putty, a viscoelastic rheological reference standard with known relaxation time from TA Instruments was used for the calibration of the AR 2000EX rheometer. The computed crossover frequency (W_c) was 5.05 rad sec^{-1} and crossover value (G_c) was 240,200 dynes cm^{-2} (24020 Pa) for PDMS standard. These generated values were within the error limits specified by TA Instruments (Figure 2). As per manufacturer, periodic check may be done to ensure optimum operation of the equipment; however, it is not required to be run every single day prior to running test articles.
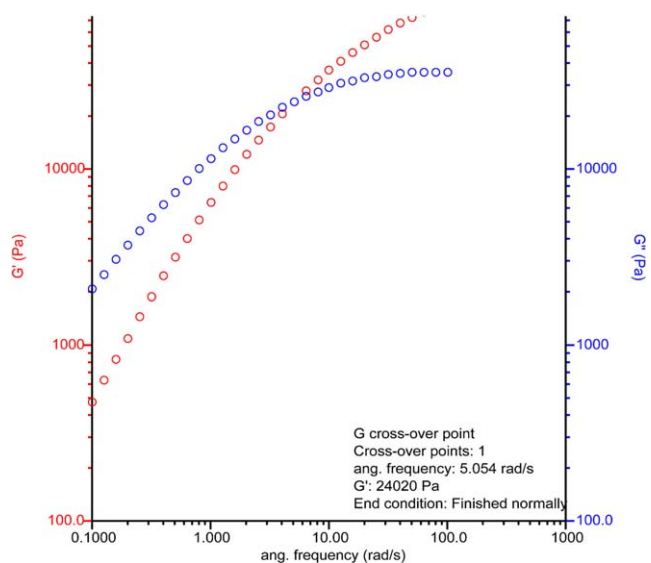

G cross-over point
Cross-over points: 1
ang. frequency: 5.054 rad/s
G': 24020 Pa
End condition: Finished normally

Figure 2. Oscillatory rheological data for PDMS at 30°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
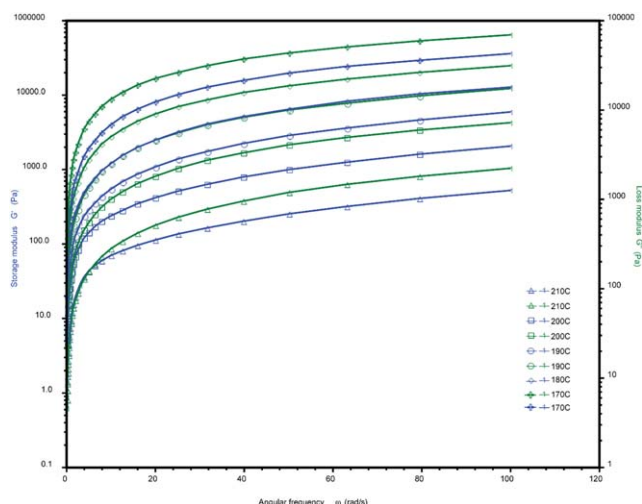
Figure 3. Storage and loss modulus of neat PVP VA64 at various temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Rheological Measurement Using Parallel Plate Geometry

During the frequency sweep test, frequency is varied and dynamic moduli, G' (storage modulus) and G'' (loss modulus) are determined from the sinusoidal stress response. For testing purposes, frequency sweep was conducted in the linear region of 5% constant strain where results are independent of the applied strain. Figures 3 and 4, show frequency-dependent response for neat PVP VA64 and Compound A-PVP VA64 blend (1:2 ratio) at various temperatures over range of 0.01 to 100 rad s^{-1}. The extent of viscoelastic properties storage modulus (G') and loss modulus (G'') for the PVP VA64 for individual sweeps decreases with increase in temperature for the frequency range studied.

Similar to neat PVP VA64, the extent of viscoelastic properties storage modulus (G') and loss modulus (G'') for the blend
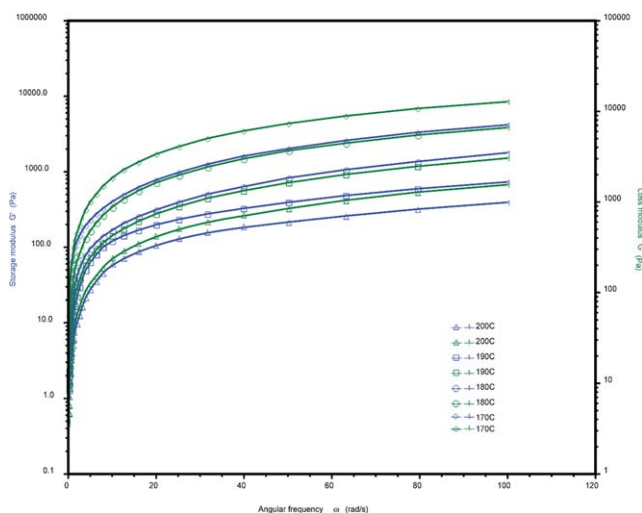

Figure 4. Storage and loss modulus of Compound A - PVP VA64 (1/2) at various temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
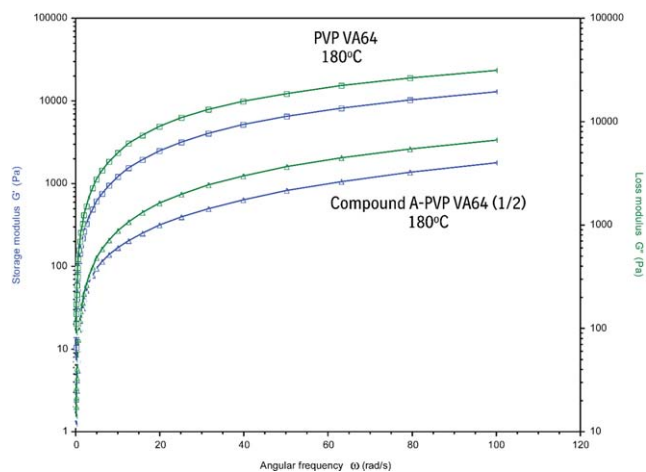

Figure 5. Storage and loss modulus of PVP VA 64 and Compound A-PVP VA64 (1/2) at 180°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Compound A/PVP VA64 (1/2) for individual sweeps decreases with an increase in temperature for the frequency range studied. The magnitude and profile of storage modulus (G') and loss modulus (G'') is also dependent on the molecular structure. Upon addition of Compound A to the neat PVP VA64, drop in storage modulus and loss modulus is noted as compared to the neat PVP VA64 which is indicative of drop in elasticity. Drop in melt viscous modulus (G'') aka "loss modulus" represents drop in melt viscosity. It appears that Compound A is acting as a plasticizer by increasing the separation of the polymer chains and thus results in reduction of viscosity of Compound A/PVP VA64 blends compared to polymer only samples. This is also evident by the reduction of the glass transition temperature (T_g) of neat PVP VA64 ($T_g = 110°C$) as compared to the Compound A – PVP VA64 blend ($T_g = 96°C$) where hydrogen bonding between the two components was observed.[4] Hydrogen bonding between PVP VA64 and compound A can prevent the interaction between polymer chains, hence the structured arrangement between polymer chains will be disrupted, which can result in lower viscosity of the blend due to plasticization effect of compound A.

To show the difference more explicitly, Figure 5 shows the storage and loss modulus profile at fixed temperature of 180°C for the neat polymer PVP VA64 and blend of Compound A – PVP VA64.

van Gurp-Palmen Plot (vGP)—for Polymer Melt

Generally, time temperature superposition (TTS) treatment of data is done where the material property at specific end-use temperature can be predicted over a longer time scale.[13] For TTS, the assumptions are that processes involved in terms of relaxation or rearrangements at molecular level are occurring at higher rates at higher temperatures and there is a direct equivalency between frequency of measurement (i.e., time) and temperature. Therefore, the time through which these processes occur can be reduced by conducting experiments at elevated temperatures and transposing the resulting data to temperature
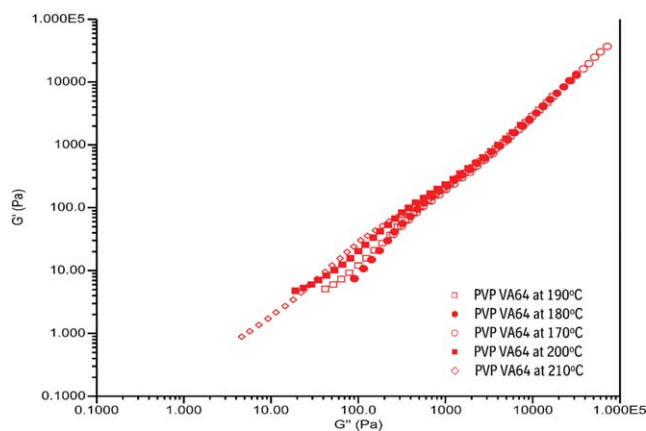
Figure 6. Plot of log G' versus log G'' for PVP VA64 at various temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of interest. The result of this is a "master curve" where the material property at specific end-use temperature can be predicted over a longer time scale.[13] Furthermore, it should also be noted that there are cases where this relationship does not apply such as dilute solutions, cross-linked gelled systems, particulate dispersions, elastic liquids with constant viscosity (a.k.a. Boger fluids).[14]

Before attempting to apply the time temperature superposition (TTS) treatment, rheological data was plotted as log G' versus log G'' to assess whether the systems are independent of temperature. It has been demonstrated that such plots are sensitive to variations in the morphological state of the systems.[15]

In 1998, Van Gurp and Palmen (vGP) presented an approach for verification of time temperature superposition (TTS) principle where they plotted the phase angle (δ) of rheological data versus the corresponding absolute value of the complex shear modulus $|G^*|$ which is sensitive to changes in relaxation processes. Complex shear modulus as shown below is the overall resistance to deformation of a material, regardless of whether
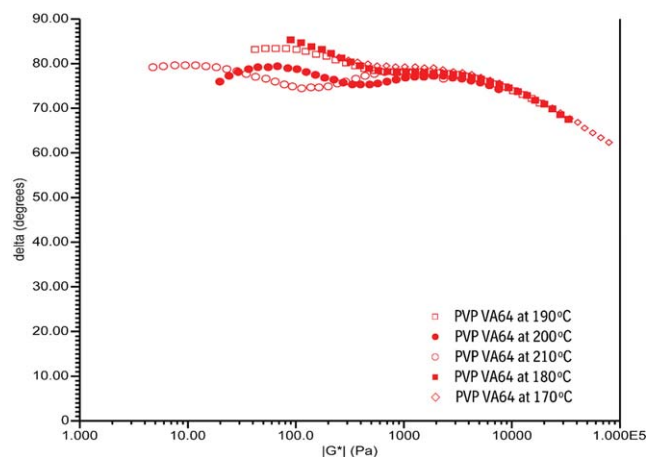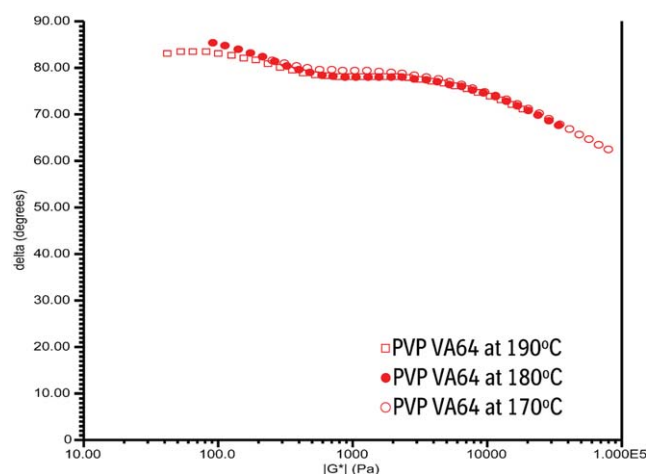

Figure 8. vGP plot of PVP VA64 for 170, 180, 190°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that deformation is recoverable (elastic) or nonrecoverable (viscous).

$$|G^*| = G' + G'' \qquad (1)$$

If plot of phase angle (δ) versus complex shear modulus $|G^*|$ shows that isothermal frequency curves merge into a common line for systems then the TTS principle holds.[15] In this article this plot will be referred to as the vGP-plot.

$$\delta = tan^{-1}\left[\frac{G''(\omega)}{G'(\omega)}\right] \qquad (2)$$

Likewise, there are instances where TTS does not hold and reasons associated with this have been discussed by vGP.[15]

A plot of log G' versus log G'' for PVP VA64 at various temperatures as shown in Figure 6, does appear to show temperature dependency for $\geq$200°C and temperature independence below 200°C. Visual inspection of the experimental results for 200 and 210°C, appear to exhibit temperature dependency. Hence, in

Figure 7. vGP plot of PVP VA64 at various temperatures. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
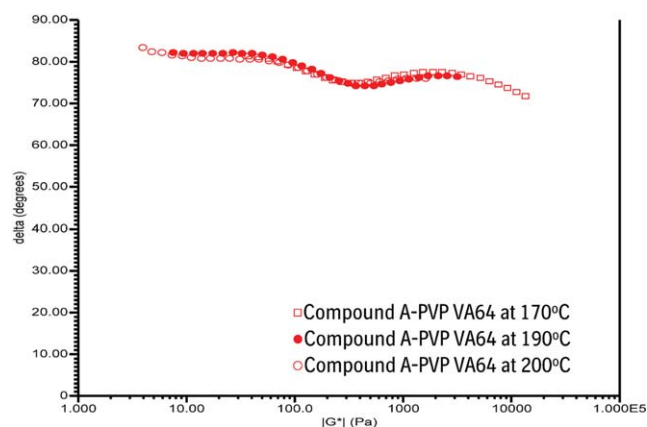

Figure 9. vGP plot of compound A-PVP VA64 for 170, 190, 200°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
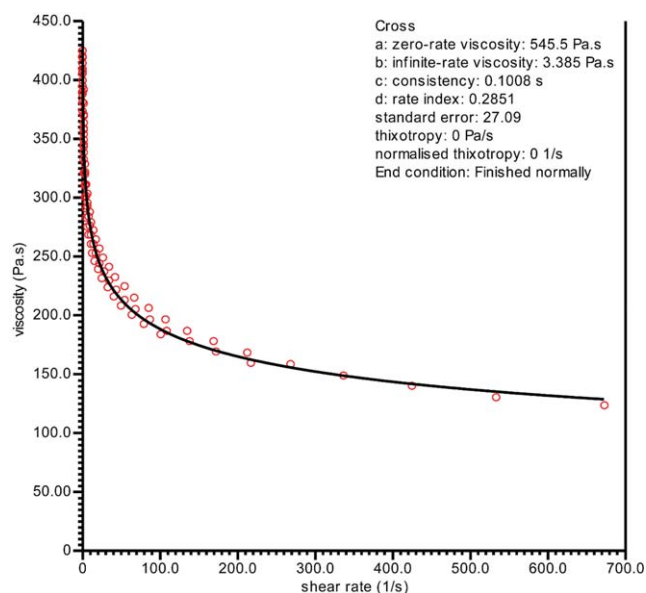
Figure 10. Master curve for PVP VA64 at 190°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

this case the TTS is applicable below 200°C. Physical changes of the microstructure at higher temperatures (≥200°C) appear to be one of the likely contributors to this behavior.

Figure 7 shows the vGP for PVP VA64 across temperature range of 170–210°C. Based on phase angle (δ) versus complex shear modulus $|G^*|$ plot (Figure 8), isothermal frequency curves merge into a common line for temperatures below 200°C indicating that the TTS principle holds for the temperature range of 170–200°C.

vGP plots for PVP VA64 alone and blend of Compound A and PVP VA 64 (1/2) are shown in Figures 8 and 9, respectively. The observed 90° plateau in the vGP plot for both the systems is equivalent to the terminal flow range in the master curve plot and indicates viscous behavior for the systems. Largely, the curve is characterized by a single minimum/one point of inflection.

The "master curves" for PVP VA64 and Compound A-PVP VA64 are shown in Figures 10 and 11 where the material property at specific end-use temperature was predicted over a longer time scale. In essence, this master curve is a single curve that covers the PVP VA64 polymer and Compound A-PVP VA64 polymer blend behavior over a broader range of shear rates at a given temperature.

The origins of Cox-Merz "rule" has been extensively discussed in literature.[16] Cox–Merz "rule" is an empirical relationship, which states the dependence of the steady state shear viscosity on the shear rate, and can be estimated from the dynamic viscosity.

The complex viscosity $|\eta^*|$ is expressed as follows: where $|G^*|$ is the complex modulus and ω is the angular frequency.

$$|\eta^*| = |G^*|/\omega \qquad (3)$$

This can be applied to predict viscosity at varying shear rates from oscillatory measurements.[17] TA Instrument software is equipped with various models that can be applied for fitting the rheological data. It should be noted that for the studied two systems, it is possible that they can have more than one model fit to the data. In such a case, a simple model is generally chosen.

After the Cox–Merz transformation, model fit to the data was examined in terms of the standard error of the fit. For the PVP VA64 system and Compound A - PVP VA64 system, Cross model was chosen as the best fit (see Tables II and III for summary of Cross model parameters).

Flow equation relating viscosity to shear rate was proposed by Cross. According to the Cross model, viscosity (η) versus shear rate profile can be separated into three regions. In the first lower Newtonian region, viscosity essentially remains constant at lower shear rate which is expressed as zero rate viscosity (η_0). The second region is the power law region where decrease in viscosity is observed with increasing shear rates in the system. The third region is the second Newtonian region, where viscosity essentially remains constant with increasing shear rates and is designated as infinite rate viscosity (η_∞) and indicates how the material going to behave under high shear conditions. In the Cross model, k is the consistency factor, γ is the shear rate and m is the rate index.

$$\eta = \eta_\infty + \frac{\eta_0 - \eta_\infty}{(1 + (k\gamma)^m)} \qquad (4)$$

For the PVP VA64 alone system, the standard error was 2.7–2.8% (Table II) while that for Compound A – PVP VA64 system the error was 1.5–2.4% (Table III). Generally, a low standard error term is indicative of a good model fit. Also, visually the model appears to be fitting both the data sets satisfactorily. As expected, the zero rate viscosity and consistency factor
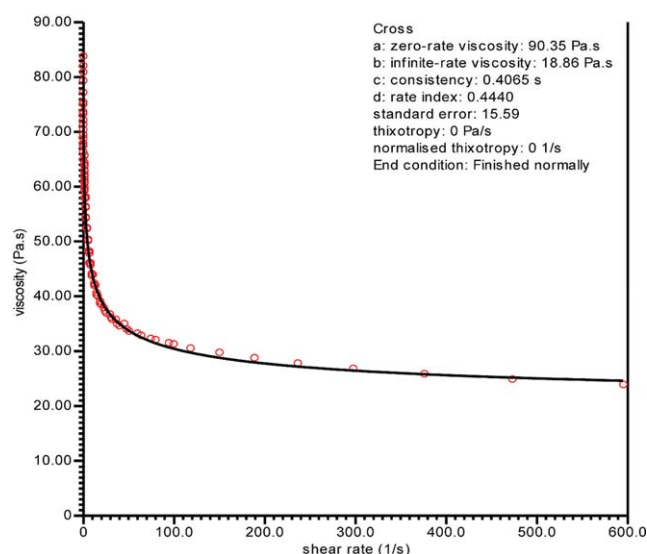

Figure 11. Master curve for compound A-PVP VA64 at 190°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table II. Summary of Cross Parameters: For PVP VA64 at Various Temperatures

Reference temperature (°C)	Zero rate viscosity (Pa s)	Infinite rate viscosity (Pa s)	Consistency (s)	Rate index	Standard error (%)
170	3555	1.835E-3	0.7664	0.2754	2.8
180	1199	3.480E-4	0.2524	0.2756	2.8
190	546	3.385	0.1008	0.2851	2.7

Table III. Summary of Cross Parameters: For Compound A—PVP VA64 at Various Temperatures

Reference temperature (°C)	Zero rate viscosity (Pa s)	Infinite rate viscosity (Pa s)	Consistency (s)	Rate index	Standard error (%)
170	469	118	1.877	0.5006	2.4
180	208	43	0.9577	0.4437	1.5
190	90	18	0.4065	0.4440	1.5

of Cross model decreases with increase in temperature. This initial viscosity (i.e., viscosity at zero shear rate) of PVP VA64 ranges from 3555 to 546 Pa s for temperature ranging from 170 to 190°C. Likewise, the viscosity at zero shear rate for the blend comprising of Compound A – PVP VA64 varies from 469 to 90 Pa s for the same temperature range. This drop in viscosity is attributed to the presence of low molecular weight Compound A at 33% level, which is solubilized in the molten polymer and acting as plasticizer in the system. Furthermore, the hydrogen bonding between PVP VA64 and compound A can prevent the interaction between the polymer chains hence the structured arrangements between the polymer chains will be disrupted, which can result in lower viscosity of blend due to plasticization effect of compound A.[18,19]

This data also suggests that Compound A-PVP VA64 blend should offer less resistance during the extrusion process and readily extrudable in the hot melt extruder. When HME of this blend was conducted, it required lower motor load/torque/power during extrusion compared to PVP VA64 alone at the same extrusion temperature which confirms the predictions from rheological measurements.
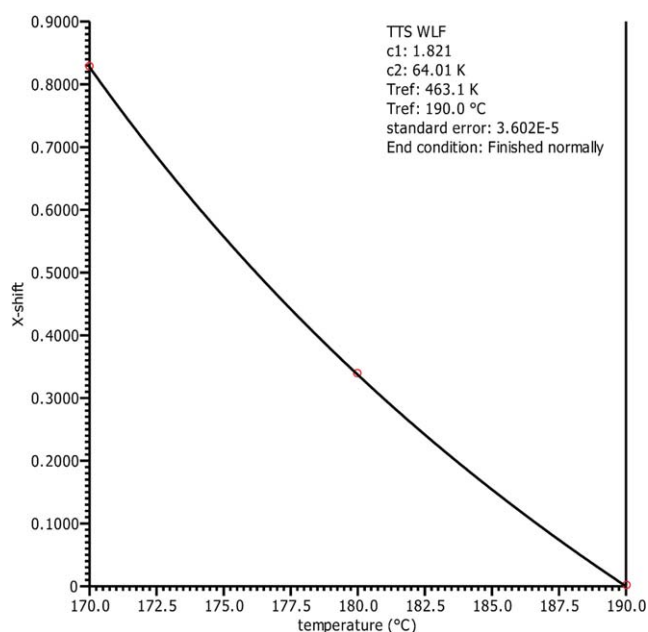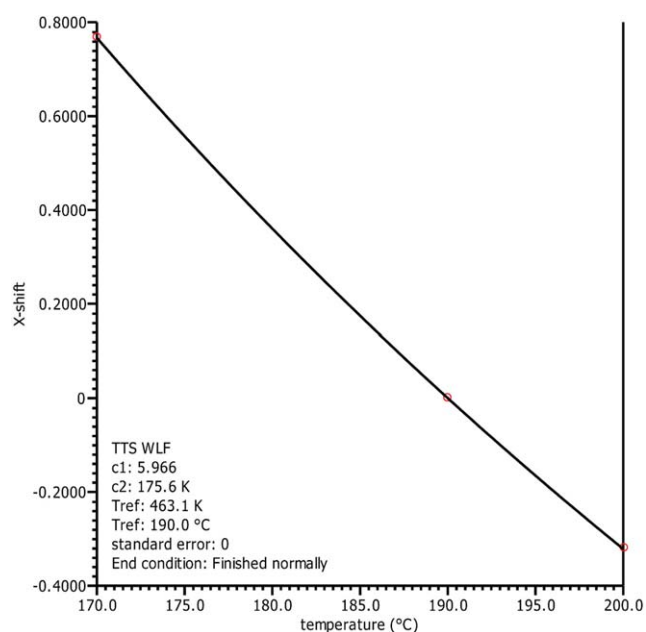

Figure 12. PVP VA64 WLF curve at 190°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 13. Compound A – PVP VA64 WLF curve at 190°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table IV. Summary of WLF Parameters: For PVP VA64 at Various Temperatures

Reference temperature (°C)	C1	C2	Standard error	Apparent activation energy at various test temperatures (kcal mol^{-1})		
				170°C	180°C	190°C
170	2.868	49.59K	3.6E-5	51.9	37.6	28.8
190	1.821	64.01K	3.6E-5	54.0	37.5	27.9

Temperature Dependence Evaluation

The temperature dependency of viscosity was assessed by the extent of shifting along the horizontal (x axis) in a TTS plot required to align the individual experimental data points into the master curve and can be described by two commonly used theoretical models: Williams–Landel–Ferry (WLF) and Arrhenius equation. The selection of these equations depends on the system/operating temperature range in relation to the glass transition temperature. Arrhenius is generally applied for regions above glass transition (T_g) + 100°C.

$$a_t = \exp\left[\frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_o}\right)\right] \quad (5)$$

where a_t is the shift factor, E is the activation energy associated with relaxation, R is the gas constant (kcal K^{-1} mol^{-1}), T is the test temperature (K), T_o is the reference temperature (K).

WLF is generally applicable for regions between T_g and T_g+ 100°C. In addition to the earlier discussion in this article, the principle of time temperature superposition has been extensively discussed for investigation of viscoelastic properties for amorphous polymers.[20]

For the PVP VA64 alone system the glass transition temperature (T_g) was 110°C and T_g for Compound A – PVP VA64 system was 90°C.[4] Hence, due to our interest in HME, for both systems, the WLF model was chosen and following is the expression for the WLF shift factor.[20]

$$\log a_t = \frac{-C_1\left(T - T_{ref}\right)}{C_2 + T - T_{ref}} \quad (6)$$

where a_t is the shift factor, C_1 and C_2 are WLF constant, T is the test temperature (K), and T_{ref} is the reference temperature (K). The WLF constants for both the systems generated at various temperatures are summarized in Tables IV and V. Figures 12 and 13, show typical WLF curves that were generated

at a reference temperature of 190°C for both PVP VA64 and Compound A – PVP VA64.

Apparent temperature-dependent activation energy in terms of WLF constants (C_1 and C_2) can be expressed as[20]

$$Apparent\ Activation\ Energy = \frac{2.303 R C_1 C_2 T^2}{(C_2 + T - T_0)^2} \quad (7)$$

where R is the gas constant (0.001985 kcal K^{-1} mol^{-1}), C_1 and C_2 are WLF constants, T is the test temperature, T_o is the reference temperature. WLF constants that were generated at various temperatures were then subsequently applied to calculate apparent energy of activation.

Apparent energy of activation values at various test temperatures for PVP VA64 and Compound A – PVP VA64 are summarized in Tables IV and V, respectively. Examination of the apparent energy of activation values at 170 and 180°C show that for the PVP VA64 alone system these values are greater than that for the Compound A-PVP VA64 system at the corresponding temperatures. This appears to suggest that for PVP VA64 alone, the flow behavior is more sensitive to temperatures (170 and 180°C) as compared to presence of 33%DL of Compound A at same temperatures.

In comparison, for 190°C, the apparent activation energy for PVP VA64 with 33% Compound A appears to be relatively greater as compared to PVP VA64 alone at the same temperature. At this temperature the blend (with 33% Compound A) flow behavior appears to be more sensitive to temperatures. This may be attributed to the fact that at this temperature, Compound A is completely dissolved into the molten polymer matrix and influencing the PVP VA64. As previously reported, Compound A once completely dissolved in molten PVP VA64, does exhibit hydrogen bonding interactions.[4] At temperature of 190°C ($\geq$190°C), there appears to be stronger interactions between the Compound A and PVP VA64. Stronger interactions at high temperature do appear to result in higher resistance to flow and higher activation energy for flow.

Table V. Summary of WLF Parameters: For Compound A—PVP VA64 at Various Temperatures

Reference temperature (°C)	C1	C2	Standard error	Apparent activation energy at various test temperatures (kcal mol^{-1})		
				170°C	180°C	190°C
170	6.536	149.8	5.466E-5	39.2	36.0	33.3
190	5.966	175.6	0	38.8	35.9	33.3

Cross parameters and energy of activation for the PVP VA64 and Compound A – PVP VA64 blend were generated using the plate–plate rheometer. These parameters can be subsequently in-putted into a hot melt extrusion process simulator to evaluate the success of HME process under different conditions.

CONCLUSIONS

The present work summarizes the frequency sweep test results for polymer PVP VA64 and Compound A – PVP VA64 at different temperatures using AR 2000EX rheometer. For both systems, based on low standard error of fit, Cross model was chosen as the best fit for the rheological data. Temperature dependency of viscosity across both the systems was assessed by Williams–Landel–Ferry (WLF) model. Cross model parameters and energy of activation values generated for the PVP VA64 polymer, and PVP VA64 with 33% drug loading can be applied to process simulator for virtual compounding of HME process. This rheology method can be applied to screen formulations with active pharmaceutical ingredients and generate rheological information with various extruding polymers at variable drug loading in polymer matrix in order to assess the success of HME process and identify HME process conditions. The present work demonstrates that rheological parameters (viscosity at zero shear rate) can be used to understand the influence of addition of active pharmaceutical ingredient on rheology blend and to determine suitable extrusion process conditions.

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