



Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - I: Polyvinylpyrrolidone and related polymers.

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Original Article

ABSTRACT

Polymers are essential components of melt extruded products. The objective of the present study was to generate physicochemical data of polyvinylpyrrolidone-based polymers and copolymers that are used in hot melt extrusion (HME). This study focused on investigating the importance of viscoelasticity for predicting HME processing conditions. Powder X-ray diffraction (XRD) patterns of polymers were recorded to determine the physical nature of the polymers. Differential scanning calorimetry (DSC) and thermogravimetric analyses (TGA) were carried out to determine their glass transition temperature (T_g) and weight loss due to degradation (T_d), respectively. Rheological studies were conducted to quantitate storage modulus (G'), loss modulus (G''), $\tan \delta$ and complex viscosity (η) of the polymers at various temperatures. Powder XRD analyses showed that all polymers were amorphous in nature, with distinct single or dual halos. DSC showed that the amorphous polymers had single T_g values. The conversion of the polymers, from solid to liquid forms, with increasing temperature was established by the $\tan \delta = 1$ values. The overall complex viscosity for all polymers decreased with increasing temperature. The complex viscosity of one of the polymers, Soluplus[®], was correlated using torque analysis through HME to establish an extrudable temperature range. The results are expected to assist in the selection of polyvinylpyrrolidone-based polymers for HME. Once the appropriate polymers are selected, further studies may be carried out using drugs, plasticizers and, so on, to optimize processing conditions.

KEY WORDS: Polyvinylpyrrolidone, PVP, vinyl pyrrolidone, vinyl acetate, Soluplus[®], Kollidon[®] VA 64, DSC, TGA, T_g , viscosity, hot melt extrusion

INTRODUCTION

The formulation of poorly water-soluble drugs into bioavailable dosage forms is one of the most challenging aspects of current drug development (1). In recent years, solid dispersion has emerged as one of the most promising approaches to

formulating poorly water-soluble drugs. In such formulations, the drug is usually dispersed in a water-soluble carrier either in a molecular or an amorphous state (2, 3). After oral administration, the water-soluble matrix of the solid dispersion dissolves in the gastrointestinal (GI) fluids, releasing the drug either in solution or as a finely divided precipitate that re-dissolves rapidly. Despite great promise, only a small number of products based on principles of solid dispersion have been commercialized. This has been attributed to manufacturing difficulties and

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stability issues associated with such products (2). Often the drug and the carrier were dissolved in a common organic solvent which was then evaporated using various evaporation techniques, including spray drying. It is, however, difficult to find a solvent that can dissolve a water-insoluble drug and a water-soluble carrier at the same time in a reasonably acceptable volume. Handling and the evaporation of large volumes of organic solvents are also problematic. The situation is now changing because hot melt extrusion (HME) allows for the production of solid dispersions, where the mixtures of the drug substance, amorphous polymer, and optionally, plasticizer and surfactant are passed through twin-screw extruders at elevated temperatures thereby eliminating the need for an organic solvent.

The application of the HME technology to prepare solid dispersions has been reviewed previously (4, 5, 6). A typical melt extruder consists of a feeding port, co-rotating or counter-rotating screws, with conveying and mixing zones, heated barrel and an output die. The drug-polymer mixture is fed onto the rotating twin screws that are confined in a heated barrel. The solids are conveyed and mixed along the length of the screws where the material melts and homogenizes. Theoretically, in the case of drug and polymer mixtures, the polymer melts and the drug particles are solubilized in the molten matrix. Hence, a typical processing temperature lies between the glass transition temperature (T_g) of the polymer and the melting point of the drug. Processing aids such as plasticizers can be added to reduce the temperature. Once the mixture is homogenous, the molten product is expelled out of the die, cooled and further processed into the final dosage form.

The selection of polymeric carriers for HME is critical for the successful development of drug products (6). A polymer's molecular weight, viscosity, T_g , etc., can influence processing conditions and the performance of the drug products produced by HME. However, no studies comparing systematically the chemical and physical properties of different polymers for their

suitability in drug formulations have been reported in the literature. In many reports, the T_g values of different polymers were compared (4, 5, 6), and it has been usually assumed that the processing temperature of the polymers during melt extrusion should be approximately 20-30°C greater than T_g (7). However, this 'plus 20 to 30°C rule' may not be valid for a number of polymers. It has been reported that a commonly used polymer, Soluplus[®], was processed by HME at 150°C, which was more than two times greater than its T_g of about 70°C (8). Kolter *et al.* reported that, it is the melt viscosity, rather than T_g , that determines the processing temperature of a polymer since it is the torque produced within the extruder, which depends on the viscosity of the polymers or its mixtures with drugs, that determines whether the extrusion is possible or not (9). In addition to extrudability, an optimal processing temperature is also required to prevent any degradation of the drug during manufacturing. The processing temperature also influences the miscibility of the drug-polymer mixtures and thereby the dissolution rate, bioavailability, and so on.

There are many polymeric excipients available for use as carriers in solid dispersions (10). Recently there has been a systematic attempt to characterize polymers that may have potential for the use in HME products (11, 12). This, as well as, two other reports (11, 12) describe the thermal and viscoelastic properties of polymers belonging to three classes i.e., polyvinyl-based polymers, cellulosic polymers, and methacrylic acid/methacrylate copolymers, respectively. The powder X-ray diffraction (XRD) patterns of the polymers are also provided to show the physical forms of the polymers.

The specific objective of this study was to generate a database of the physical, thermal and rheological properties of polyvinyl-based polymers that can be used in future product development by providing an understanding of how these properties affect the melt extrusion process. For example, the behavior of polyvinylpyrrolidones (PVP) is affected greatly by

their molecular weight (13). PVP and its copolymers are commonly used in solid dispersions. For example, PVP K30 was used to prepare solid dispersions by melt extrusion to increase dissolution rate (14, 15). They are also known to stabilize drugs in their amorphous state in the solid dispersion through forming hydrogen bonds with the drug.

In another example, the nimodipine solid dispersion with PEG 2000 was stabilized using PVP K17 (16). Poly(vinylpyrrolidone-co-vinyl acetate), a block copolymer consisting of water-soluble and water-insoluble blocks is another polymer that can be used in the HME process. Finally, poly(vinyl caprolactam-co-vinyl acetate-co-ethylene glycol) graft copolymer (Soluplus[®], BASF), which was specifically developed for its drug-polymer interaction and usability in hot melt extrusion, has in recent years generated much interest in the pharmaceutical industry (17). Once the basic physicochemical properties of PVPs and their copolymers relevant to HME are known, the information can then be used for product development. How these properties are influenced by the presence of drug, plasticizer, etc., can also be studied.

Background

The thermal and viscoelastic properties of polymers play critical roles in their performance as carriers for drugs during melt extrusion and therefore the relevant terms used are detailed briefly here.

Glass transition temperature (T_g)

The T_g of an amorphous polymeric system is a temperature below which the writhing thermal motions cease. Long-range convolutional readjustments of polymer chains are restricted below T_g , thus making the material stiff (18). Thermal motions that take place above the glass transition temperature result in a leathery state (Figure 1) (19). Thus, at T_g , the material softens but still maintains a leather-like consistency. As the temperature increases, a rubbery mass with plastic properties is formed. Even though the

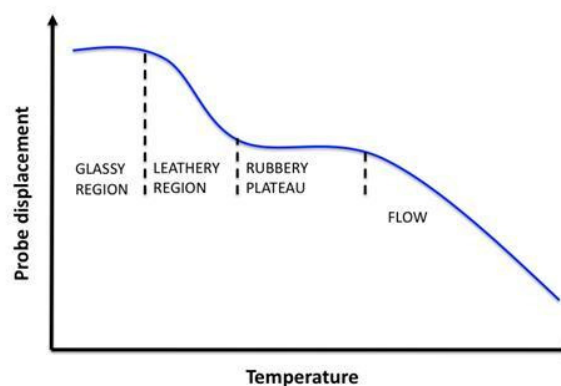


Figure 1 Schematic representation of the viscoelastic properties of a polymer at different temperatures (reproduced from reference 19).

rubbery material may have a high viscosity, it can be molded and processed. At higher temperatures, the polymer chains disentangle and relax completely and the material flows well. When using such polymers in melt extrusion they have to be in the rubbery to flow regions of the diagram shown in Figure 1. This will ensure proper melting, flow and solubilization of the drug in the polymer. Glass transition temperature by itself cannot suggest a processing condition for the polymeric system. Additional thermo-mechanical analysis is necessary to predict the extrusion conditions of the polymeric material.

Viscoelastic properties

Viscoelastic properties of materials are related to rheology, which is defined as the science of deformation and flow (20). It involves measurements of equivalent shear rate during controlled polymeric flow by applying a fixed force. Therefore the viscosity of the system can be determined by applying shear stress (σ) and measuring shear rate ($\dot{\gamma}$) or, *vice versa*. Thermoplastic polymers exhibit two different types of behaviors, viscous and elastic, during their transition from the glassy state to the rubbery state and then to the viscous state, where one type of behavior is predominant during the different transition states. The viscous response, i.e., the loss of a rigid structure, the result of applied stress over strain is termed loss modulus (G''). Polymers also exhibit an ability to recover

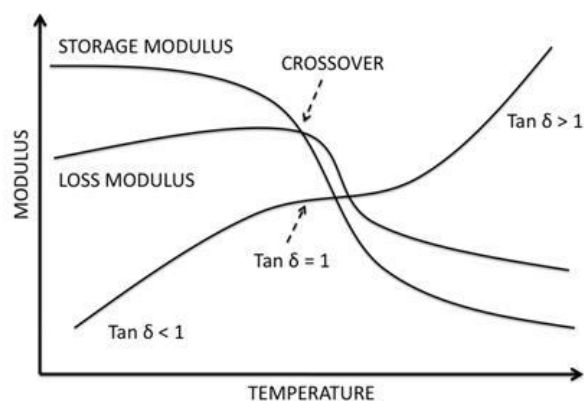


Figure 2: Schematic representation of the storage modulus, loss modulus and their $\tan \delta$ values below crossover ($\tan \delta < 1$), at crossover ($\tan \delta = 1$) and above crossover ($\tan \delta > 1$) as a function of temperature

after an applied stress over strain, and this behavior is known as the elastic (G') or storage

modulus. During viscoelastic measurements, if the plots of G' and G'' , as a function of temperature are overlaid, then initially, at lower temperature, the material is glassy and G' has a higher value than G'' . As the temperature increases above a certain point, G' decreases while G'' decreases at a slower rate. This is shown schematically in Figure 2. The ratio of G'' to G' is called the loss tangent or $\tan \delta$. When both curves intersect ($\tan \delta = 1$) or reaches closest to each other ($\tan \delta \approx 1$), the polymer undergoes a transition from a glassy state to a rubbery state. Thus, the $\tan \delta = 1$ temperature value and the T_g may represent the same phenomenon, although the corresponding temperatures could be different. These terms are further described below.

Storage modulus (G')

The storage modulus is a measure of the energy stored and recovered per cycle, when different systems are compared at the same strain amplitude (21). The storage modulus is a measure of the stored elastic energy, which shows how solid the material is. With an increase in temperature, the G' value gradually decreases. This shows that the material becomes less solid

and more liquid-like.

Loss modulus (G'')

The loss modulus is a measure of the energy dissipated or lost as heat per cycle of sinusoidal deformation, when different systems are compared at the same strain amplitude (21). In other words, the loss modulus describes the viscous properties of the polymer, or how liquid the sample is at a particular temperature and frequency.

The loss tangent ($\tan \delta$)

$\tan \delta$ is the ratio of the viscous property of the polymer (energy lost) to the elastic property (energy stored) of the polymer (21) (shown in Equation 1). Thus, a $\tan \delta$ value is obtained when G'' is divided by G' .

$$\tan \delta = G''/G' \quad \text{Eq. 1}$$

Where, $\tan \delta = 1$ point in the schematic graph (Figure 2) signifies the conversion of the solid-like form of a polymer into the liquid-like form. Above the temperature corresponding to $\tan \delta = 1$ (Figure 2), the polymer transforms to the rubbery state and then to a molten state as the temperature increases. Below the crossover point, storage modulus dominates over loss modulus, thus giving a value of $\tan \delta < 1$. Above the crossover point, the material acts more like a liquid, giving a value of $\tan \delta > 1$. Thus, $\tan \delta$ is a better representation of the extrudability of the polymer than T_g because it represents not only the thermodynamic aspect of the material, but also its kinetic attributes. The changes in the $\tan \delta$ value and viscosity can be determined in the presence of plasticizers and drugs.

Complex modulus (G^*)

This is the overall resistance to deformation of a material, regardless of whether the deformation is recoverable (elastic) or nonreversible (viscous). Thus Equation 2 shows

$$G^* = G' + G'' \quad \text{Eq. 2}$$

Complex viscosity (η)

Complex viscosity (η) is a frequency dependent viscosity function, which is also referred to as dynamic viscosity (21). Complex viscosity is typical for most non-ideal polymer systems, which includes most viscoelastic pharmaceutical polymers. The complex viscosity and steady flow viscosity are nearly identical at low frequencies, and a distinct decrease in complex viscosity is observed at higher angular frequencies. With an increase in temperature, the complex viscosity of a polymer decreases due to the conversion from a stiff mass to a flowing material.

Complex viscosity is denoted by Pascal-seconds (Pa.s), which is equal to N.s/m². Two parallel plates are considered with a fluid in between them, and a pressure of 1 pascal is applied to push the top plate parallel to the other. If the top plate moves at a distance equal to the distance between the two plates in one second, then the fluid has a complex viscosity of one Pa.s.

Materials

The different polymers used in this study are listed in Table 1. PVPs of varying molecular weight (Kollidon[®] 12PF, Kollidon[®] 17PF, Kollidon[®] 25, Kollidon[®] 30, Kollidon[®] 90F), vinyl pyrrolidone-vinyl acetate (6:4) copolymer (Kollidon[®] VA 64) and poly(vinyl caprolactam-covinyl acetate-ethylene glycol) graft polymer (Soluplus[®]) were donated by BASF[®] Corporation (Tarrytown, NJ), and poly(vinylpyrrolidone-covinyl acetate 1.3:1) was purchased from Sigma-Aldrich (St. Louis, MO). All the materials were used as received.

Methods

Powder X-ray diffraction (XRD)

The powder X-ray diffraction patterns of the polymers were measured using Shimadzu XRD-6000 (Shimadzu, Kyoto, Japan), equipped with Ni filtered Cu-K α as the X-ray source. The samples were prepared into thin films by the 'side-ways filling method' on a glass micro sample holder.

Continuous scans were recorded at a voltage of 60 kV and 55 mA at a scan rate of 2° per minute across the scan range of 10-60° 2 θ .

Thermogravimetric analysis (TGA)

Approximately 4-6 mg of polymer samples were analyzed using a thermogravimetric analyzer, TGA Q50 (TA instruments, DE, USA). The samples were heated from 25°C to 300°C at a heating rate of 5°C/minute in a nitrogen environment. The TGA measures the weight change as a function of temperature. The first stage of weight loss at <100°C was assumed to be due to moisture loss. The second weight loss mid-point on the thermogram was taken as the degradation temperature.

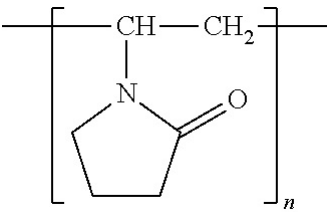
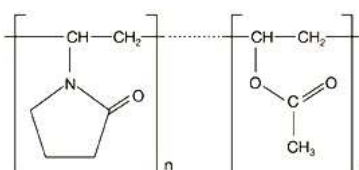
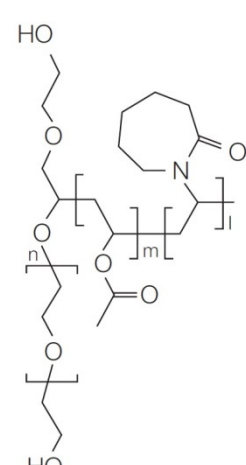
Differential scanning calorimetry (DSC)

The DSC scans were recorded using a Q200 modulated DSC analyzer equipped with a refrigerated cooling accessory (TA instruments, DE, USA). Samples weighing 3 to 6 mg were sealed in a Tzero[®] aluminum pan and equilibrated at 35°C for 3 minutes. The pans were then heated from 35°C to 200°C at a ramp rate of 3°C per minute and modulation of 1°C per minute. The results were analyzed by separating reversible phenomenon, such as T_g, from nonreversible phenomena. A step change in the reversing heat flow signal was considered to be T_g.

Rheology

The samples were analyzed for their viscoelastic properties using Discovery Hybrid Rheometer (DHR-2) with an oven heating assembly (TA instruments, DE, USA). A diagram detailing how the samples were analyzed is shown in Figure 3. Briefly, different polymers, 1 gram each, were compressed into slugs of 25 mm in diameter and approximately 2 mm in thickness using a Carver press at 5000 pounds of pressure for 5 seconds. Parallel plate geometry with a diameter of 25 mm was employed (Figure 3A). The disc was placed between the parallel plates (Figure 3B and 3C) after zero gap calibration and the sample was equilibrated at a velocity of 0.5 rad/sec at 5 to

Table 1 Physicochemical, thermal and rheological properties and extrudable temperature ranges of different polymers

CHEMICAL NAME	TRADE NAME	T_g (°C)	Tan $\delta = 1$ (°C)	EXTRUDABLE TEMPERATURE RANGE (°C)	STRUCTURE
POLY-VINYLPYRROLIDONES (PVP)					
Polyvinylpyrrolidone (MW 2000 – 3000)	Kollidon® 12 PF	72	117	152 – 167	
Polyvinylpyrrolidone (MW 7000 – 11000)	Kollidon® 17 PF	140	142	*	
Polyvinylpyrrolidone (MW 28000 – 34000)	Kollidon® 25	153	156	*	
Polyvinylpyrrolidone (MW 44000 – 54000)	Kollidon® 30	160	161	*	
Polyvinylpyrrolidone (MW 1000000 – 1500000)	Kollidon® 90F	177	193	*	
POLY(VINYL PYRROLIDONE-CO-VINYL ACETATE) BLOCK COPOLYMER (PVPcoPVA)					
Vinyl pyrrolidone : vinyl acetate 1.3:1		115	-	173-190	
Vinyl pyrrolidone : vinyl acetate 6:4 (MW 45000 – 70000)	Kollidon® VA64	105	115	157-177	
GRAFT COPOLYMER					
Poly(vinyl caprolactam-co- vinylacetate-ethylene glycol) graft polymer (MW 90000 – 140000)	Soluplus®	72	85	142-166	

* Within the experimental temperature range, the viscosity values for the polymers were more than 10000 Pa.s, which were higher than the extrudable viscosity range.

10°C below the degradation temperatures (T_d). An oscillation temperature sweep (ramp down) was then performed at a cooling rate of 5°C/min and at the angular frequency of 0.1 rad/sec. The applied strain was 0.5%, within the linear viscoelastic region, determined by a dynamic strain sweep. Storage modulus, loss modulus, tan $\delta = 1$ and complex viscosity were obtained using TRIOS software of TA Instruments.

Torque analysis by HME

Torque analysis by HME was carried out to study the effect of change of viscosity on the extrudability of the polymers. Soluplus® was chosen as a model candidate for such a correlation. Thermo Scientific Process 11 melt extruder (Bridgewater, NJ, USA) was used for the study. The neat polymer was added to the extruder with medium-shear twin screws co-rotating at 100 RPM. The polymer was conveyed through the melt extruder at various temperatures

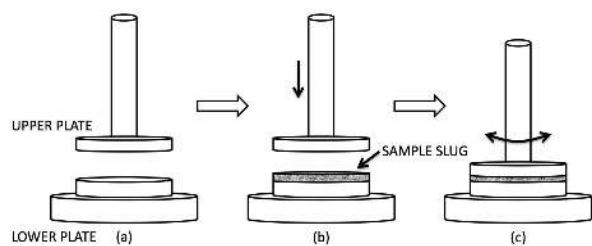


Figure 3: Schematic representation of thermomechanical analysis by rheometer. (a) 25 mm parallel plate geometry; (b) placement of 25 mm polymer disc prepared using carver press; (c) oscillation temperature sweep analysis.

starting at 200°C and then decreasing the barrel temperature at steps of 5°C until the maximum torque capacity of the equipment was reached. The value of the equilibrium torque attained by the equipment at each temperature was recorded.

RESULTS AND DISCUSSION

Traditional parallel plate rheological analysis is carried out by first heating the plate assembly and the polymer sample is then added into a circular ring temporarily attached to the lower plate. The sample is homogenized to ensure a flat surface of a specified geometry and absence of air bubbles. The traditional method is time consuming and the samples are not uniform in terms of binary and ternary mixtures. The rheology method developed here (see Methods and Figure 3) addresses the above issues. The advantages of a slug was that there was no trapped air, the mixture was uniform and the slug diameter matched the parallel plate geometry. There were few sample-to-sample variations, less time consumed preparing the samples, and the extent of a viscosity drop in the binary mixtures could be quantified resulting in highly reproducible samples.

Polyvinylpyrrolidones, or povidones, belong to a water-soluble class of polymers obtained by radical polymerization of N-vinylpyrrolidone (13). They are largely used as binders in the pharmaceutical industry. The PVPs include Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 25, Kollidon® 30 and Kollidon® 90 F (Table 1),

which are structurally similar but have different molecular weights. Copolymers of polyvinylpyrrolidones with polyvinylacetate, or copovidones, are also water-soluble (22). The copovidones include Kollidon® VA 64 (PVPcoPVA 1.3:1) copolymers, which are usually used as binders, granulating agents, retardants and film formers. Another polyvinyl based polymer Soluplus® is a graft copolymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (23). It has an amphiphilic chemical structure and is primarily used as a solubilizer in solid dispersions. According to its manufacturer, Soluplus® was specifically designed to be used in hot melt extrusion (9).

Powder XRD

All polymers were characterized for their physical, thermal, and viscoelastic properties. The powder XRD was used to determine whether the polymers were crystalline, semi-crystalline or amorphous solid powders. Figure 4 shows the powder XRD patterns between 10° and 30° 2θ. The analysis showed that all polymers were amorphous because there were no distinct characteristic peaks observed for any of the polymers. All PVP polymers (Figure 4-I to 4-V) had a similar pattern with characteristic halos at 2θ = 12° and 20.5°. The copovidone copolymers (Figure 4-VI and 4-VII) had halos at 2θ = 12.5° and 22°. Soluplus® also had an amorphous XRD pattern with a single halo at 2θ = 19.5°.

DSC

The differential scanning calorimetric (DSC) analysis was carried out on all polymers to obtain their T_g values (Figure 5A and 5B). Since all polymers used in the present investigation are solid at room temperature, the polymer chains appeared to be frozen below the T_g with low molecular mobility. The material could be placed in the glassy region as shown in Figure 1. As the temperature increased, a thermodynamic change occurred above a certain temperature due to the increased thermal motion of the polymer chains. This temperature was denoted as T_g or glass transition temperature. Beyond this temperature,

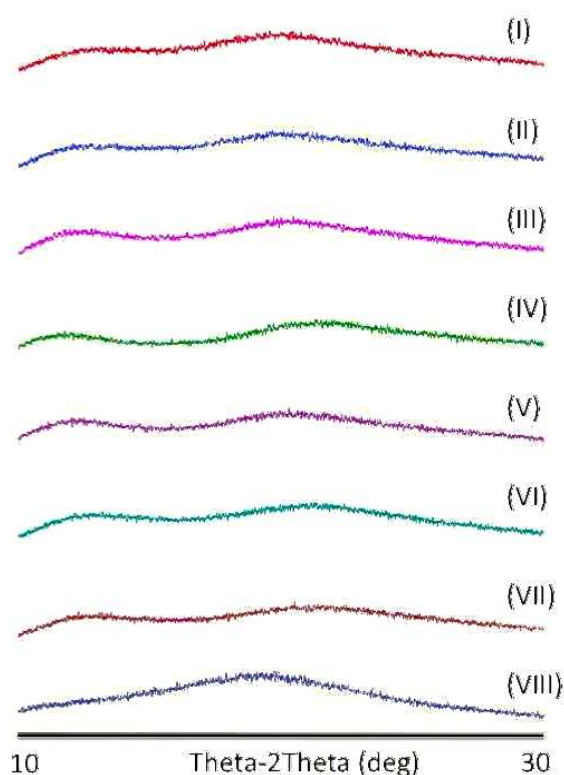


Figure 4 Powder XRD patterns of the polymers (I) Kollidon® 12 PF (PVP, MW 2000 – 3000), (II) Kollidon® 17 PF (PVP, MW 7000 – 11000), (III) Kollidon® 25 (PVP, MW 28000 – 34000), (IV) Kollidon 30® (PVP, MW 44000 – 54000), (V) Kollidon® 90 F (PVP, MW 1000000 – 1500000), (VI) PVPcoPVA [Poly(vinyl pyrrolidone-co-vinyl acetate) block copolymer 1.3:1], (VII) Kollidon® VA 64 [Poly(vinyl pyrrolidone-co-vinyl acetate) block copolymer 6:4], (VIII) Soluplus® [Poly(vinyl caprolatam-co-vinylacetate-ethylene glycol) graft polymer]

the polymer chains moved freely and the material behaved like rubber. It has been reported that factors such as molecular weight (MW) and cross-linking can influence the T_g of polymers (24). The longer the chain length, the greater the molecular weight, resulting in more stiffness in the polymer structure. If the polymer chains are cross-linked with other plastic materials, such as low molecular weight polyethylene glycol (PEG), the glass transition of the resultant copolymer decreases.

For PVPs, the T_g values are denoted by endothermic change in baseline thermal profiles of reversible heat flow. The values were recorded

by thermal scans (Figure 5A), as well as, shown in Table 1. The lowest T_g value was observed for Kollidon® 12 PF which has a molecular weight of about 2000 to 3000 Da. As the length of the polymer chain increased, T_g increased as well. Thus, for Kollidon® 17 PF (MW 7000 to 11000 Da.), the T_g value increased to 140°C. The T_g increased further with the increase in molecular weight for Kollidon® 25, Kollidon® 30 and Kollidon® 90 F (Figure 5A and Table 1). For copovidones, the T_g for PVPcoPVA 1.3:1 was 115°C and for Kollidon® VA 64 was 105°C (Figure 5B-VI and 5B-VII). The molecular weights of both copolymers were in the range of 45000 to 70000 Da. However, their T_g values were much lower than that of straight chain polymers of comparable molecular weight

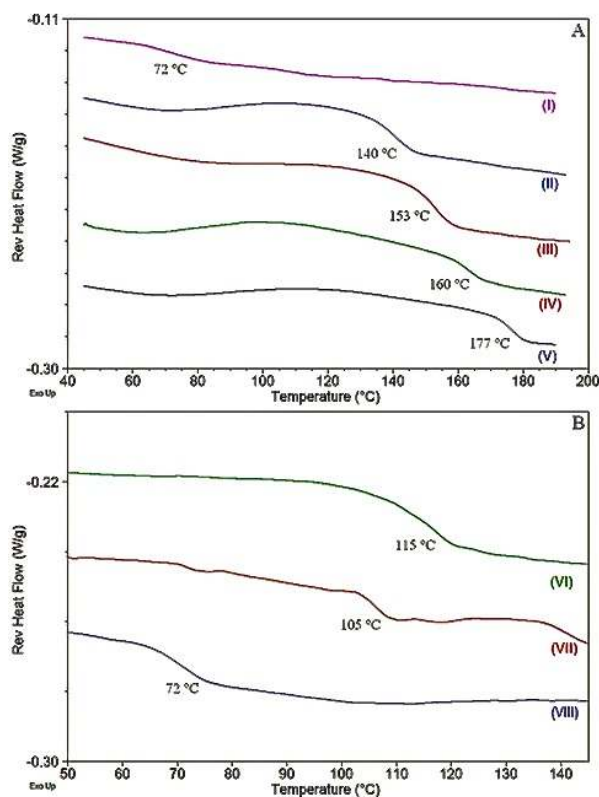


Figure 5 DSC thermograms of the polymers. (I) Kollidon® 12 PF (PVP, MW 2000 – 3000), (II) Kollidon® 17 PF (PVP, MW 7000 – 11000), (III) Kollidon® 25 (PVP, MW 28000 – 34000), (IV) Kollidon 30® (PVP, MW 44000 – 54000), (V) Kollidon® 90 F (PVP, MW 1000000 – 1500000). (VI) PVPcoPVA [Poly(vinyl pyrrolidone-co-vinyl acetate) block copolymer 1.3:1], (VII) Kollidon® VA 64 [Poly(vinyl pyrrolidone-co-vinyl acetate) block copolymer 6:4], (VIII) Soluplus® [Poly(vinyl caprolatam-co-vinylacetate-ethylene glycol) graft polymer].

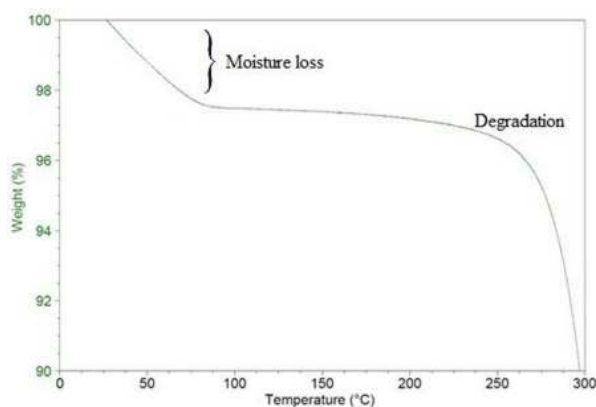


Figure 6 Thermogravimetric analysis (TGA) of Soluplus® [Poly(vinyl caprolactam-co-vinylacetate-ethylene glycol) graft polymer] as a function of temperature.

(Kollidon® 30, $T_g = 160^\circ\text{C}$). The reason for the decrease in glass transition temperature may be attributed to copolymerization with PVA which has a low T_g of 38°C (25). For Soluplus®, there is graft polymerization between the polyvinyl caprolactam, the polyvinyl acetate and the ethylene glycol, which further reduced the T_g to 72°C . A low T_g value for Soluplus® was expected allowing melt extrusion at a relatively lower, processing temperature.

TGA

Table 2 shows the thermal properties of polymers determined by thermogravimetric analysis (TGA). The polymers used in this study were hydrophilic with hygroscopic properties with some moisture content at room temperature. It is essential to quantitate the amount of moisture since it could lower the glass transition temperature due to plasticization. Figure 6 shows the TGA scan of Soluplus®, which is representative of the different polymers used. As the temperature was increased, the moisture evaporated and the sample experienced an initial weight loss, which could be correlated with the moisture content. As the temperature, increased there was a point above which additional decrease in the sample weight was observed, which was taken as the thermal degradation temperature (T_d).

The moisture content and the thermal degradation temperatures of the different polymers used are provided in Table 2. In all the cases, the moisture loss occurred below the glass transition temperatures shown in Table 1, indicating that the T_g values were not influenced by adsorbed moisture.

Table 2 TGA analysis of polymers

POLYMER	MOISTURE CONTENT (% w/w) ^a	DEGRADATION TEMPERATURE ($^\circ\text{C}$)
Kollidon® 12PF	2	196
Kollidon® 17PF	4.5	217
Kollidon® 25	6	166
Kollidon® 30	6	171
Kollidon® 90F	3.5	194
Kollidon® VA 64	2.5	270
Soluplus®	3	278

^aRepresents weight loss due to dehydration at $<100^\circ\text{C}$

The thermal degradation temperatures of Kollidon® 25, Kollidon® 30 and Kollidon® 90 F as determined by TGA are, 166, 171 and 194°C , respectively, while their T_g values are 153, 160 and 177°C , respectively. Since polymers must be heated to temperatures considerably higher than their T_g values, these results show that some polymers may degrade during HME and cannot be used unless their T_g values can be decreased substantially by using plasticizers or drugs that may act as plasticizers. In contrast, a comparison between Table 1 and Table 2 shows that the differences between the T_g and T_d were much greater for Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® VA 64 and Soluplus®, and therefore, it was possible to heat the polymers beyond their T_g values. It should, however, be pointed out that the T_d values recorded in Table 2 were due to gross degradation of the polymers together with weight loss. It is possible that the chemical degradation was initiated before the weight loss. Nonetheless, the T_d values in Table 2 provide a guideline for temperatures that should be avoided during HME.

Viscoelastic properties

As mentioned previously, upon heating polymers change from rigid glassy solids below T_g to viscous rubber above T_g and then to free flowing liquids (Figure 1). The viscoelastic properties of polymers during these transitions should be carefully examined to assess their behavior during the melt extrusion process. Figure 7 illustrates the change from a 'solid-like' property of a polymer, Soluplus[®], to a 'liquid-like' property as the temperature increased. Here, the transition can be explained through the following terms, that is storage modulus (G'), loss modulus (G''), complex viscosity (η^*) and loss tangent ($\tan \delta$). As stated previously, storage modulus indicates elastic behavior and loss modulus represents the viscous trait of a polymer. At temperatures below 85°C, the solid-like behavior was predominant in the polymer and thus the values of storage modulus were higher than the loss modulus. $\tan \delta$ is the ratio of loss modulus to storage modulus. Thus, at $< 85^\circ\text{C}$, the $\tan \delta$ value was < 1 . The overall complex viscosity of the polymer at such a temperature was also high, indicating that the material was very stiff. Figure 5 shows that the T_g of Soluplus[®] is 72°C . As the temperature increased to its T_g , a thermodynamic change took place and the polymer chains relaxed. Although thermodynamic changes occurred, kinetic change was still minimal. At such a temperature, the

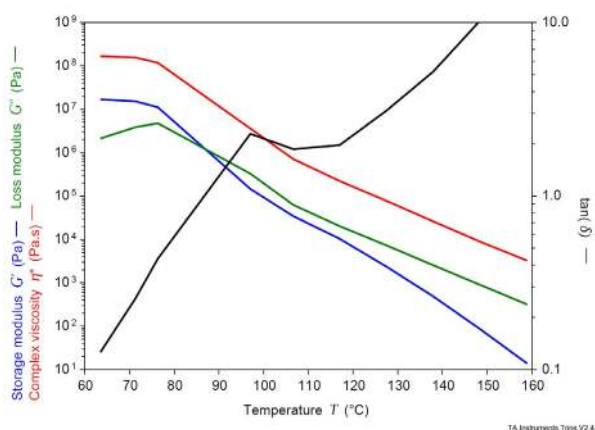


Figure 7 Loss modulus, storage modulus, complex viscosity and $\tan \delta$ of Soluplus[®] [Poly(vinyl caprolatam-co-vinylacetate-ethylene glycol) graft polymer] as a function of temperature.

material was still in the leathery region of Figure 1. As the temperature was further increased, both storage modulus and loss modulus gradually decreased, and at a certain temperature, the two moduli intersected. Most pharmaceutical polymers are viscoelastic, which means that the polymers have both solid-like and liquid-like traits at different temperatures. At the point of intersection of the two moduli, the elastic characteristic of the polymer was equal to its viscous property, and the value of $\tan \delta$ was equal to 1 (since $\tan \delta = G''/G'$). In simple words, beyond this point the polymer behaved more like a liquid than a solid. Therefore, the $\tan \delta = 1$ point is of significance for melt extrusion because the viscous component determines the extrudability and flow of the polymer in the melt extruder. For Soluplus[®], $\tan \delta = 1$ was at 85°C , which was about 13°C higher than the T_g of the polymer. On further heating beyond the $\tan \delta = 1$ temperature, the viscous component of the polymer became predominant. The material behaved increasingly like a liquid as the $\tan \delta$ value increased above 1. Both the storage and the loss moduli decreased gradually with temperature, and, as a consequence, there was an overall drop in complex viscosity of the material.

Similar viscoelastic analyses were made for all polymers, and the results for Kollidon[®] VA 64, Kollidon[®] 12 PF and Kollidon[®] 30 are shown in Figures 8, 9 and 10, respectively. The $\tan \delta = 1$ temperatures of the polymers are shown in Table 1. All the data indicated that the extrusion conditions of a polymer when using an HME process should be based on its $\tan \delta$ value, and not its T_g . Thermomechanical analysis of a polymer not only considers the disentanglement and kinetic movement of the polymeric chains, but also mass effect. While the DSC analysis uses a 3 to 6 mg sample to determine its T_g , rheological testing uses about 500 mg to 1 g per sample. The polymeric materials have a range of temperatures where the softening takes place, unlike crystalline materials that have characteristic melting temperatures above which they are liquid. This broad range of softening temperature of a polymeric material can also be influenced by the amount of material. Thus, rheological analysis

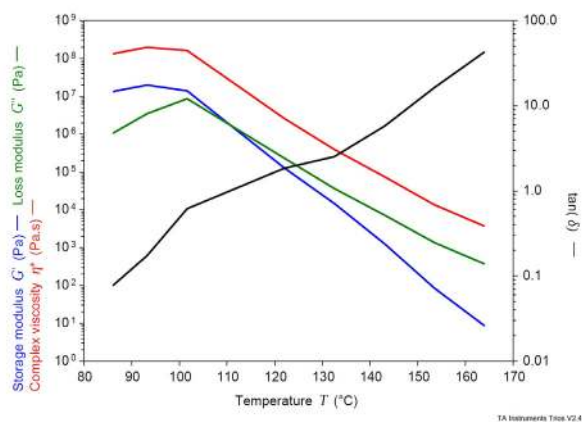


Figure 8 Loss modulus, storage modulus, complex viscosity and $\tan \delta$ of Kollidon® VA 64 [Poly(vinyl pyrrolidone-co-vinyl acetate) block copolymer 6:4].

provides a better prediction for melt extrusion processing, which uses material in the weight range above a few grams per minute.

The difference between T_g and the temperature equivalent to $\tan \delta = 1$ for Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30 was short (1-3°C) (Table 1). At these temperatures, the complex viscosities of the samples were about 1×10^7 Pa.s. The materials are very stiff at such a high viscosity. Figures 8, 9 and 10 show that even though the loss and storage moduli crossed over close to T_g , the materials were still too stiff to be considered a liquid.

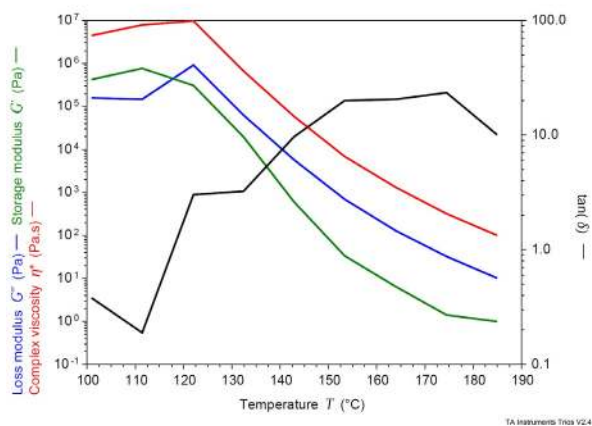


Figure 9 Loss modulus, storage modulus, complex viscosity and $\tan \delta$ of Kollidon® 12 PF (PVP, MW 2000 – 3000).

The complex viscosities of all polymers as a function of temperature are summarized in Figure 11, where increasing temperature showed a drop in viscosity. For the PVP based polymers, the viscosities were as follows, Kollidon® 90 F > Kollidon® 30 > Kollidon® 25 > Kollidon® 17 PF > Kollidon® 12 PF, indicating that the complex viscosity increased with an increase in molecular weight. The pattern of increase in viscosity with the increase in molecular weight was the same as for the sequence of increase in T_g . The slopes of povidones with higher molecular weight were steeper than that of the lower molecular weight polymers. Figure 11 also shows that the processing windows of higher molecular weight polymers were short due to narrow temperature ranges from $\tan \delta = 1$ temperature to thermal degradation temperature (T_d) (Tables 1 and 2). The copolymers (PVPcoPVA 1.3:1 and Kollidon® VA 64) and graft copolymer (Soluplus®) plots showed gradually declining slopes whereas the decrease in viscosity with an increase in temperature was less profound. This gave such polymers larger extrusion windows of over 20°C at the viscosity range from 1000 to 10000 Pa.s (Table 1). The explanation of rational for choosing the above viscosity range is explained further below.

Torque analysis

The result of the HME torque analysis of

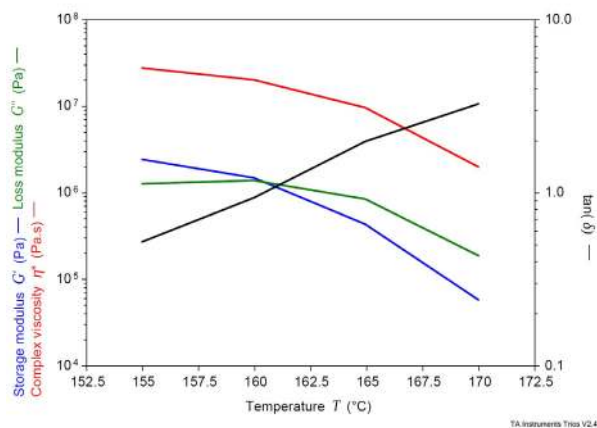


Figure 10 Loss modulus, storage modulus, complex viscosity and $\tan \delta$ of Kollidon® 30 (PVP, MW 44000 – 54000).

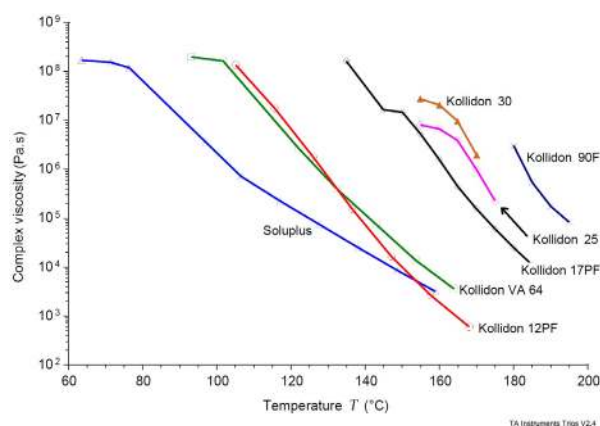


Figure 11 Thermomechanical analysis of neat polymers.

Soluplus[®] as a function of temperature is shown in Figure 12. The moment of force exerted on the twin screws is referred to as torque. In the Process 11 melt extruder, a torque value of 12 Nm is equivalent to 100%, which was the maximum torque the extruder could withstand before stopping. At 200°C, the torque exerted on the screws was about 10%, which gradually increased with decreasing temperature. The torque was 50% at about 155°C and exceeded 100% at about 120°C, below which the equipment stopped working due to the high viscosity of the polymer. The conventional 'plus 20 to 30°C' rule for the extrudability of polymer does not follow in this case since almost 100% of the equipment torque was reached at approximately 120°C, which was about 50°C above the T_g of the polymer (72°C). The torque dropped below 80% above 140°C and further decreased to 30% at about 170°C.

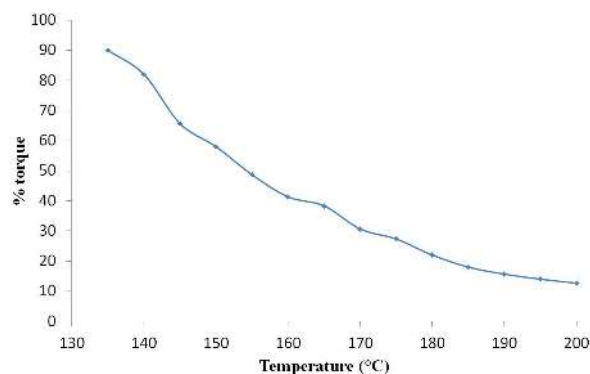


Figure 12 Extrusion-torque profile for Soluplus[®] at various temperatures.

The percentage torque obtained from the melt extruder was correlated with the complex viscosity of Soluplus[®] recorded in Figure 7 and is shown in Table 3.

Table 3 Temperature and melt viscosity of Soluplus[®]

TEMPERATURE (°C)	COMPLEX VISCOSITY (Pa.s)	% TORQUE
120	> 60000	> 100
140	10000	80
170	1000	30

The complex viscosity at 120°C was over 60000 Pa.s, suggesting that the material was very stiff and could not be extruded using the present equipment. The viscosity dropped to a range of 10000 to 1000 Pa.s between 140°C and 170°C, which could be considered an extrusion range since the torque exerted on the screws in this temperature range was 80 to 30%. Above 170°C, the material had a viscosity less than 1000 Pa.s and a torque value below 30%. This indicates that the material was free flowing and the matrix did not have a structure for successful extrusion into definite shapes.

It should be recognized that the 'plus 20 to 30°C' rule for the melt extrusion of polymers has been mentioned in the literature only as a general guide. The processing temperature of neat polymers, as seen here, could be much higher than their respective T_g values, therefore indicating that the 'plus 20 to 30°C' rule failed. The actual processing temperatures of formulations could be somewhat lower due to the presence of plasticizers, if any, and/or drugs that may act as plasticizers. In such cases the processing temperatures could well be within the 20 to 30°C of the T_g values of the polymers.

The extrudable temperature range shown in Table 1 was determined using the Process 11 melt extruder where a 100% torque was reached at 12 Nm using moderate shear screw design. It is possible that higher torque may be reached by using larger melt extruders and thus allowing for more rigid materials to be extruded. However, as

shown in Figure 11, the slopes of the complex viscosity graphs in the exponential scale as a function of temperature are very steep indicating that there would not be much of an advantage to lower the melt extrusion temperature by using larger equipment. Moreover, if the materials are stiff and rubbery and do not flow well, the drugs may not mix or dissolve adequately in the polymer during the melt extrusion. The extrudable viscosity of 10000 Pa.s and lower was first reported by Kolter *et al.* (9), and the results of the present investigation validate these findings. If 10000 to 1000 Pa.s is selected as the extrudable viscosity for a polymer or a formulation and the processing temperature is identified accordingly, it will be easier to scale up the process from a smaller extruder to manufacturing scale where a larger extruder would be used.

CONCLUSION

Physical, thermal and viscoelastic analyses of polyvinyl based polymers were conducted to support their application in hot melt extrusion. All polymers were amorphous with distinct single or dual halos in their powder XRD patterns. The structural differences in PVPs and the related polymers influenced their thermal and viscoelastic properties. For straight chain PVPs, the glass transition temperatures (T_g) increased with an increase in molecular weight. All polymers had about 2-6% moisture ascertained by TGA. The conversion of solid polymers to liquid form with increasing temperature was determined using thermomechanical analysis where G'' , G' , $\tan \delta$ and η were highlighted. The complex viscosity of a graft copolymer, Soluplus[®], was successfully correlated with the amount of torque exerted on the co-rotating twin screws of a melt extruder. Based on the viscoelastic analysis, the processing temperature ranges of different polymers for melt extrusion could be determined.

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