



Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion - III: Polymethacrylates and polymethacrylic acid based polymers.

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Original Article

ABSTRACT

Polymers are a major part of final medicinal drug products prepared by hot melt extrusion (HME). Therefore it is necessary to understand their behavior when subjected to heat and mechanical stresses during the development of the HME processes. The aim of this work was to generate a database of the physicochemical properties for polymethacrylates and polymethacrylic acid based polymers relevant to HME. All six polymers tested were amorphous and had < 2% moisture. In differential scanning calorimetric (DSC) studies, the three homo block copolymers, Eudragit[®] E PO, Eudragit[®] RL PO and Eudragit[®] RS PO, had glass transition temperatures (T_g) of 57°C, 63°C and 64°C, respectively, and thermogravimetric analysis (TGA) showed weight loss due to thermal degradation at 250°C, 166°C and 170°C, respectively. Thermomechanical analysis was carried out to investigate the rheological properties of the polymers predicting that the melt extrusion ranges of Eudragit[®] E PO, Eudragit[®] RL PO and Eudragit[®] RS PO would be 127-150, 165-170 and 142-167°C, respectively. In contrast, the hetero block copolymers Eudragit[®] L 100, Eudragit[®] S 100 and Eudragit[®] L 100-55 had T_g values of 195, 173 and 111°C, respectively. Onsets of their degradation, as measured by TGA, were in the range of 173 to 176°C. The predicted HME processing temperatures of Eudragit[®] L 100, Eudragit[®] S 100 and Eudragit[®] L 100-55 were greater than 200°C and therefore these polymers cannot be processed by themselves without the addition of plasticizers.

KEY WORDS: Polymethacrylate, polymethacrylic acid, Eudragit[®], glass transition temperature, powder XRD, viscosity, $\tan \delta$, hot melt extrusion

INTRODUCTION

In recent years, solid dispersion has emerged as one of the most promising formulation strategies for developing poorly water-soluble drugs (1, 2). Among various methods of preparing solid dispersions, hot melt extrusion (HME) is receiving increasing attention due to several

potential advantages, such as material processing without solvents, mass densification of the processed material, ease of manufacturing and scale-up, and capability for continuous manufacturing (3,4). Despite the potential advantages, the technology is still in its nascent stage and there are only a few major melt-extruded products available in the market. This is because there is poor understanding of the variables that impact the HME processing conditions (4).

A typical setup of a melt extruder and various

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thermal and rheological properties of polyvinyl and cellulose based polymers have been presented previously (5, 6). It has been shown that the glass transition temperature (T_g), which is generally used as the guiding point for setting up the melt extrusion process, has very poor correlation with material flow within the extruder barrels. Rather, the viscosity of the polymers plays the most critical role in HME. It has been, for example, observed that the complex viscosity of a graft polyvinyl co-polymer, Soluplus[®], obtained using an oscillatory rheometer had a very good correlation with the torque profile generated during melt extrusion (5).

The objective of this study was to provide a systematic characterization of the viscoelastic and thermal properties of the methacrylate class of copolymers necessary for the successful development of melt extrusion processes. Only neat polymers were used based on the rationale that once the properties of the neat polymers are understood, they may be modulated by adding drugs, plasticizers, etc., if necessary. The relevant terms used throughout this article are T_g , degradation temperature (T_d), complex viscosity (η^*), the loss tangent ($\tan \delta$), storage modulus (G') and loss modulus (G''), which have been discussed previously (5).

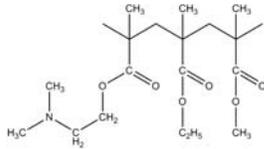
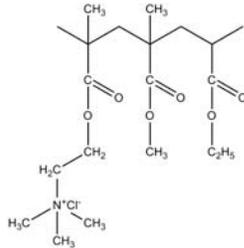
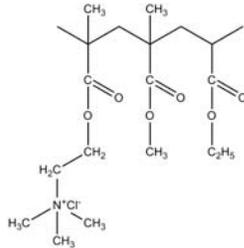
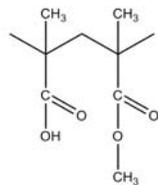
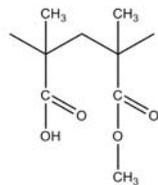
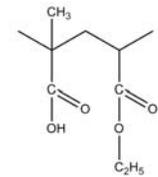
Polymers exhibit viscous and elastic responses when subjected to thermomechanical stress and strain. The summation of these two responses provides the complex modulus, from which the complex viscosity can be determined by employing a frequency factor. These responses can be plotted separately as a function of temperature as storage modulus (indicating the elastic nature of material) and loss modulus (indicating the viscous nature of material), and the ratios of these two responses provide $\tan \delta$. When $\tan \delta$ is plotted as a function of temperature, the temperature at which the y-axis corresponds to 1 is considered a “cross over temperature”, i.e., the temperature at which both loss modulus and storage modulus have equal y-axis values. Beyond this point, the pre-dominant

material property changes either from viscous to elastic or elastic to viscous (7). The material begins to flow above this temperature, and thus $\tan \delta = 1$ serves as an important guiding point for formulation scientists to develop a successful melt extrusion process. The present study also focused on any major weight loss at higher temperatures due to the potential degradation of materials. The onset of such a weight loss, as determined by TGA, was recorded as T_d . It should, however, be noted that a chemical degradation of a polymer could also occur before T_d . The results obtained here provides an indication of the effect of heating on the gross degradation of a material.

Methacrylates, which are commonly used as polymeric carriers in solid dispersions, may be classified according to their backbone chain as either homo block copolymers or hetero block copolymers. Some of the commercially available methacrylates used for solid dispersion are listed in Table 1 (8). Depending on the functional groups present in the side chains, these polymers differ in their pH-dependent solubility and therefore are used, with or without, other polymers, to target drug release in the desired parts of the gastrointestinal tract (GI). For example, Eudragit[®] L 100, Eudragit[®] L 100-55 and Eudragit[®] S 100 are anionic copolymers soluble above pH 5.5 and are generally used for enteric drug release. Eudragit[®] L 100 has been used as a polymer matrix to prepare a controlled release tablet of ketoprofen by the melt extrusion process (9). Eudragit[®] E PO consists of a dimethylaminoethyl group attached as a side chain which ionizes and makes the polymer dissolve in acidic pH. Therefore, Eudragit[®] E PO is generally used for immediate release formulations. For example, Chokshi *et al.* (10) formulated solid dispersions of indomethacin using Eudragit[®] E PO by HME.

The methacrylates can also form hydrogen bonds and are, therefore, used for the stabilization of solid dispersions. For example, it has been shown that nimodipine, a poorly water soluble drug, was

Table 1 General Description of Polyacrylates and Polyacrylic acids

CHEMICAL NAME	TRADE NAME	STRUCTURE
Homo block co-polymers of poly(methacrylates-co-acrylates)		
Butyl methacrylate: Dimethylamino ethyl methacrylate: Methyl methacrylate (1: 2: 1)(MW - 47000 Da)	Eudragit® E PO	
Ethyl acrylate: Methyl Methacrylate : Trimethylammonioethyl methacrylate chloride (1: 2: 0.2)(MW - 32000 Da)	Eudragit® RL PO	
Ethyl acrylate: Methyl methacrylate: Trimethylammonioethyl methacrylate chloride (1: 2: 0.1)(MW - 32000 Da)	Eudragit® RS PO	
Hetero block Co-polymers of poly(methacrylic acid- co-acrylates)		
Methacrylic acid: Methyl methacrylate (1: 1)(MW – 125000 Da)	Eudragit® L 100	
Methacrylic acid: Methyl methacrylate (1: 2)(MW – 125000 Da)	Eudragit® S 100	
Methacrylic acid: Ethyl acrylate (1: 1)(MW – 320000 Da)	Eudragit® L 100-55	

able to form hydrogen bonds with Eudragit® E PO through the interaction between the secondary amine group of nimodipine and the carboxylic group of Eudragit® E PO (11). Thus, due to their wide applicability for formulation design and capability of forming hydrogen bonds, methacrylates may be suitable for use in solid dispersions. The objective of the present study is to provide a detailed analysis of the thermal and viscoelastic properties of methacrylates to further improve their application in the pharmaceutical industry, especially as it relates to the HME process.

Materials

All polymers used are described in Table 1 together with their molecular weights (MW). They were donated by Evonik Corporation, Parsippany, NJ, USA, and were used as received.

Methods

Powder X-Ray Diffraction (XRD)

As described earlier (5), the powder XRD

patterns of polymers were measured using Shimadzu XRD-6000, equipped with Ni filtered Cu-K α as the X-ray source (Shimadzu, Kyoto, Japan). 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 and step size of 0.02°.

Thermogravimetric analysis (TGA)

Approximately 4-6 mg of polymer was analyzed using a thermogravimetric analyzer (Q50, TA instruments, DE, USA). A small weight loss between 25°C to 120°C was considered to be due to dehydration. The second and the major weight change in the TGA scan was considered as polymer degradation.

Differential scanning calorimetric (DSC) analysis

The DSC scans were recorded using a Q200 modulated DSC analyzer equipped with a cooling accessory (TA instruments, DE, USA) by using 3-6 mg of sample. The detailed method has been described previously (5).

Rheology

The samples were analyzed for their viscoelastic properties using Discovery Hybrid Rheometer (DHR-2) fitted with an oven heating assembly (TA instruments, DE, USA). As described previously (5), polymer samples weighing 1 gram each were compressed into 25 mm diameter and approximately 2 mm thick slugs using a Carver press at 5000 pounds of compression pressure for 5 seconds. The polymer disc was placed between parallel plates of rheometer, and a dynamic temperature oscillation sweep experiment was performed from high temperature to low temperature or from low temperature to high temperature at a rate of 5°C/min, angular frequency of 0.1 rad/sec and 0.5% strain. Various parameters such as $\tan \delta$, G'' , G' and η^* were determined and plotted as functions of temperature.

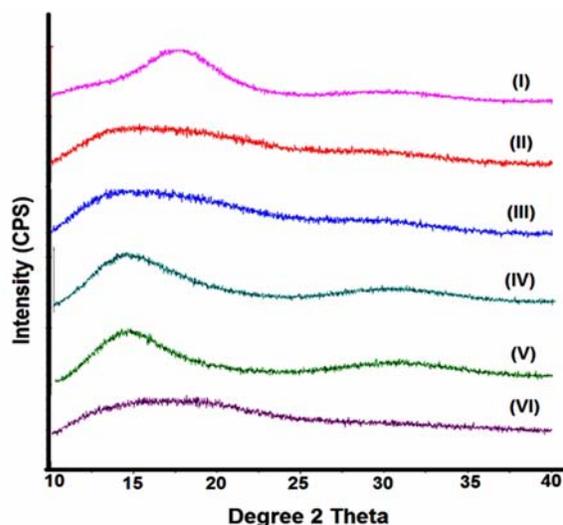


Figure 1 Powder X-ray diffraction analysis of methacrylate copolymers. Peak intensity (Y-axis) was plotted with Degree 2 theta angle (X-axis). Amorphous halos of various polymers obtained are as follows: (I) Eudragit® E PO, (II) Eudragit® RL PO, (III) Eudragit® RS PO, (IV) Eudragit® L 100, (V) Eudragit® S 100 (VI) Eudragit® L 100-55.

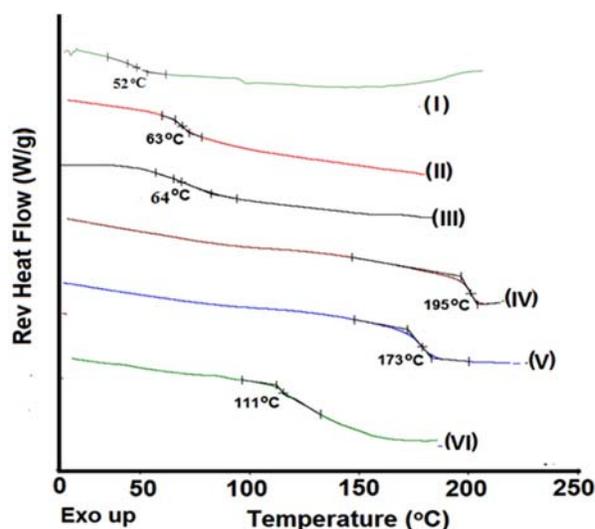


Figure 2 Differential scanning calorimetric analysis of methacrylate copolymers. Reverse heat flow obtained was plotted against change in temperature. Glass transition temperature for each polymers are shown on the graph and also as follows: (I) Eudragit® E PO, $T_g = 52^\circ\text{C}$, (II) Eudragit® RL PO, $T_g = 63^\circ\text{C}$, (III) Eudragit® RS PO, $T_g = 64^\circ\text{C}$, (IV) Eudragit® L 100, $T_g = 195^\circ\text{C}$, (V) Eudragit® S 100, $T_g = 173^\circ\text{C}$ and (VI) Eudragit® L 100-55, $T_g = 111^\circ\text{C}$.

Table 2 Thermal and Rheological Properties of Polyacrylates and Polyacrylic acid Relevant to HME with Predicted Extrusion Temperature Range

POLYMER	GLASS TRANSITION TEMPERATURE (T_g), (°C)	DEGRADATION TEMPERATURE (T_d) ^(a) (°C)	MOISTURE CONTENT (% w/w)	CROSS OVER TEMPERATURE ($\tan \delta \approx 1$), (°C)	PREDICTED EXTRUSION TEMPERATURE RANGE (°C)
Eudragit [®] E PO	52	250	0.2	49, 105 ^(b)	127- 150
Eudragit [®] RL PO	63	166	0.1	92, 133 ^(b)	165-170
Eudragit [®] RS PO	64	170	1	92, 118 ^(b)	142- 167
Eudragit [®] L 100	195	176	0.02	145, 215 ^(b)	> T_d
Eudragit [®] S 100	173	173	0.2	140, 215 ^(b)	> T_d
Eudragit [®] L 100-55	111	176	2	128	> T_d

a) Degradation temperature determined by second and higher weight loss in TGA Analysis.

b) On the $\tan \delta$ versus temperature plots, two temperature events were observed when $\tan \delta$ value was equal to or very close to 1. An example of $\tan \delta$ versus temperature plot is provided in Figure 4.

RESULTS AND DISCUSSION

The powder XRD patterns and DSC scans of different polymethacrylates are shown in Figures 1 and 2, respectively. The powder XRD patterns of all polymers were devoid of sharp peaks and displayed broad halos, which are characteristic features of amorphous substances. Depending upon the polymer backbone, slight differences were observed in powder XRD patterns of various polyacrylates with either a single or double halos in their pattern as shown in Figure 1.

Modulated DSC analysis was performed to separate non-reversible phenomenon, such as moisture release, from reversible phenomenon such as T_g . The results were plotted and shown in Figure 2 as reversible heat flow with a change in temperature. The amorphous nature of polymers was confirmed by the presence of a glass transition temperature and absence of a melting endotherm. Various factors such as molecular weight, chain length of polymer, chemical composition of the monomers, and structural arrangement of co-polymers are known to affect T_g (12).

For the methacrylates, it was observed that branched copolymers such as Eudragit[®] E PO displayed a lower T_g value as compared to linear copolymers such as Eudragit[®] L 100 or Eudragit[®] S 100. These results agree with the literature, where it was reported that the branch copolymers

have increased flexibility in their structures and thus require less energy for material flow (9). Differences in monomer ratios affected T_g as observed for Eudragit[®] L 100 and Eudragit[®] S 100. Although these polymers had similar chemical composition, the differences in monomer ratios, i.e. 1:1 or 1:2 between methacrylic acid and methacrylate, resulted in differences in T_g , as shown in Table 2. The effect of molecular weight on T_g of copolymers was also compared, however, it appeared to have no significant impact on T_g . Among the polymers used, Eudragit[®] L 100-55 had the highest molecular weight (320000 Da) but its T_g was low (111°C). Eudragit[®] RS 100 and Eudragit[®] RL 100, which on the other hand had similar molecular weights and somewhat similar chemical composition, exhibited similar T_g of 63-64°C.

The TGA analysis was carried out to determine moisture content and polymer stability upon heating. The results are presented in Table 2. The moisture loss was obtained by calculating percent weight change between 25-120°C, which was below 2% for all polymers used. Percent weight loss from 150-300°C was attributed to material degradation. As shown in Table 2, Eudragit[®] E PO displayed low T_g and high T_d values and, therefore, higher window of temperatures for their processing. In comparison, the range of processing temperature of Eudragit[®] L 100-55 based on the difference in T_g and T_d was narrow. These results agree with the observations by

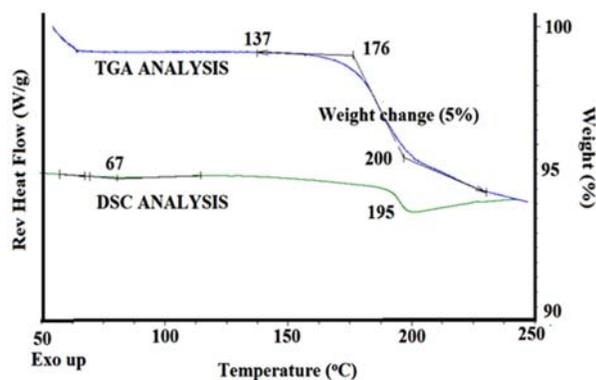


Figure 3 Overlay of DSC and TGA analysis for Eudragit[®] L 100. The Y-axis, left side of the graph represents, rev. heat flow (W/g) obtained from modulated DSC analysis and is plotted against change in temperature (°C) on X-axis, Y-axis (right side of the graph) represents percentage sample weight (%) with change in temperature. In the DSC analysis a T_g event was observed at 195°C. In the TGA analysis, sample weight loss (5%) was observed starting at 176°C, representing material degradation.

DiNunzio *et al.* (13) in the production of amorphous solid dispersions of itraconazole in Eudragit[®] L 100-55. Lin *et al.* (14) studied the thermal stability of Eudragit[®] L 100 and showed that methacrylic acids form anhydrides through structural rearrangement and loss of water at 170°C.

A representative example of the TGA analysis for Eudragit[®] L 100 is shown in Figure 3, where there was 5% weight loss initiated at 137°C with a major weight change at 176°C. This weight loss could be due to the loss of water produced by the conversion of methacrylic acids to anhydrides as discussed earlier. Similar results were also found for Eudragit[®] S 100. Thus, some polyacrylates are prone to degradation during melt extrusion. If they are used, suitable attempts should be made to process these materials at lower temperatures by adding other additives such as plasticizers. It should be noted that a polymer may degrade through other changes during processing that may not be accompanied by weight loss. However, in this study, the aim was to establish conditions relevant to hot melt extrusion processing and therefore only thermal degradation was considered. It should also be noted that the onset of degradation could vary

depending upon the heating rate and the applied shear and therefore these values should be carefully considered before applying them in a melt extrusion experiment.

Various literature reports indicate a disconnect between T_g and melt extrusion processing temperature. For example, Sathagiri *et al.* (15) processed Eudragit[®] E PO, despite a low T_g of 52°C at a temperature as high as 120°C, even after the addition of a 50% drug load to the polymer matrix. Chokshi *et al.* (10) found that rheological parameters, rather than the T_g , were good predictors of melt extrusion temperatures. Wu *et al.* (16) found that the torque generated during HME was directly related to viscosity and thus was a good parameter in identifying the processing temperature. Viscoelastic studies were conducted in the present study using an oscillatory rheometer by parallel plate method and the results are presented in Figure 4 and also summarized in Table 2. The dynamic temperature sweep of one representative polymer, Eudragit[®] E PO, is shown in Figure 5. This figure serves as a reference to understand the relationships between various rheological parameters. The diagrams display complex viscosity, η^* , storage modulus, G' , loss modulus, G'' and $\tan \delta$. A previous study (6) showed that the $\tan \delta$ is the

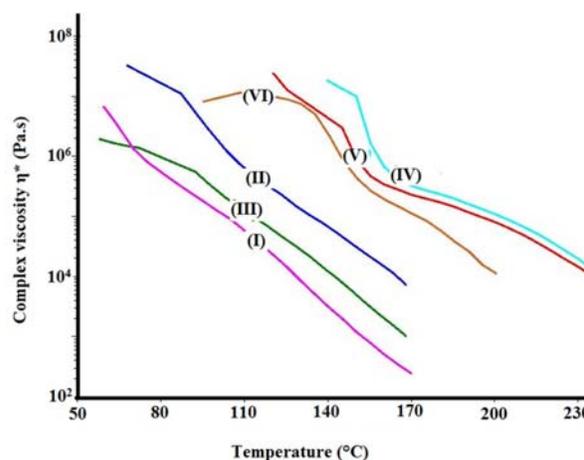


Figure 4 Complex viscoelastic properties of methacrylate polymers were obtained using dynamic temperature sweep using oscillatory rheometer and plotted against temperature. (I) Eudragit[®] E PO, (II) Eudragit[®] RL PO, (III) Eudragit[®] RS PO, (IV) Eudragit[®] L 100, (V) Eudragit[®] S 100, (VI) Eudragit[®] L 100-55.

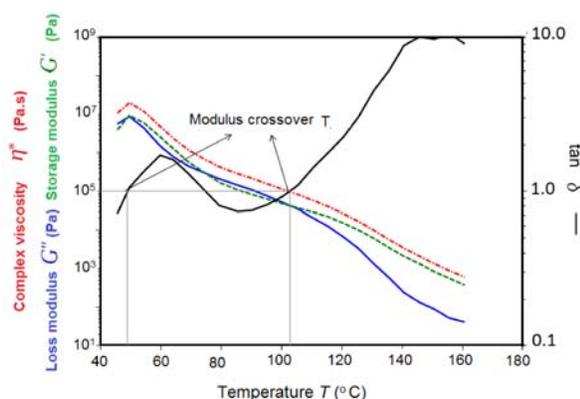


Figure 5 Viscoelastic properties of Eudragit® E PO sample is shown as obtained by dynamic temperature sweep method using oscillatory rheometer. The graph displays complex viscosity, η^* , storage modulus, G' and loss modulus, G'' (Y-axis, left side bar) plotted against temperature (X- axis). Y-axis on right side bar represents $\tan \delta$, i.e. ratio between storage modulus and loss modulus at varying temperature. At $\tan \delta = 1$, the loss modulus increases with change in temperature and is equivalent to storage modulus, this represents a “cross over temperature” at which the flow properties of material predominates the behavior of material.

ratio between the storage modulus and the loss modulus at varying temperatures. At $\tan \delta = 1$ the loss modulus increased with the change in temperature and was equivalent to storage modulus. This temperature represents a “crossover temperature” above which the material starts to flow.

As shown in Figure 5, two crossover temperature events were observed when $\tan \delta$ was equivalent to 1 for Eudragit® E PO at 49°C and 105°C. The first event at 49°C corresponded to T_g value on the DSC plot and represented the relaxation of branch monomers attached to the main linear copolymer chain. The second event at 105°C represented the relaxation and flow of main block chain of copolymers. Figure 5 shows that the complex viscosity plot also agreed with the above hypothesis that after the first event of crossover, the polymer transitioned from a rigid state to the rubbery state. For the purpose of melt extrusion, the second event was of greater relevance as it represented the conversion of polymer from the rubbery state to the flowable state. This phenomenon with multiple crossover

temperature was found to be relevant with other branched co-polymers like Eudragit® RL PO and Eudragit® RS PO as well.

The cross-over temperature for all the polymers are summarized in Table 2. For linear co-block copolymers, such as Eudragit® L 100, Eudragit® S 100, and Eudragit® L 100-55, a single crossover event was observed which was followed by an exponential drop in viscosity. In most cases the polymer flowed after its T_g , which resulted in high $\tan \delta$ value as compared to T_g . However, as discussed earlier, Eudragit® L 100 and Eudragit® S 100 degraded at 136°C with the formation of an anhydride and, as a result, released water as a byproduct. Since it was a non-reversible change, this phenomenon was not observed in the DSC analysis. During the temperature ramp up rheology study, the moisture loss resulted in a relaxation of the polymer chains as shown by cross-over of storage modulus and loss modulus ($\tan \delta = 1$) at 145°C for Eudragit® L 100 and 140°C for Eudragit® S 100.

Being thermoplastic in nature, polyacrylates showed reduced viscosity with increased temperature. Below the crossover temperature, i.e., $\tan \delta = 1$, the viscosity was very high indicating a stiff material. At higher temperatures, the polymer chains disentangled and arranged linearly, thereby facilitating flow and thus decreasing viscosity. The complex viscosities of all polymers are summarized in Figure 4. Eudragit® RS PO, Eudragit® RL PO and Eudragit® E PO with average molecular weights between 30000 - 50000 Da displayed lower viscosity compared with Eudragit® S 100, Eudragit® L 100 and Eudragit® L 100-55 with higher molecular weights of 125000, 125000 and 320000 Da, respectively, indicating increased viscosity for the higher molecular weight polymers.

The relevance of rheology to melt extrusion has been shown in a previous study (5), where viscoelastic measurements were compared with torque analysis during melt extrusion and it was observed that the polymer was extrudable between the viscosity range from 1000 to 10000

Pa.s, where the torque exerted on the melt extruder screws was between 20 and 60%. Below 1000 Pa.s, the material was free flowing and non-extrudable, whereas, above 10000 Pa.s, the melt extruder could not withstand torque and stopped. Thus, based on these observations, a predicted extrudable temperature range was determined as 1000 - 10000 Pa.s (5). Kolter *et al.* (17) have reported similar viscosity ranges for melt extrusion. Based on these values, the predicted extrusion temperature ranges for various polyacrylates are provided in Table 2. These values indicate the approximate temperature range at which the complex viscosity of the analyzed polymer was within 1000- 10000 Pa.s. It should be noted that these predicted ranges serve only as a guidance to begin the melt extrusion work. The actual temperature for extrusion may vary with the shear exerted on the polymer and the capacity of the melt extruder to withhold the generated torque. As shown in Table 2, Eudragit® L 100, Eudragit® L 100-55 and Eudragit® S 100 which had a viscosity above 10000 Pa.s at 200°C and a degradation temperature around 170°C could not be extruded. Other polyacrylates were extrudable at an extrusion temperature range between 120°C - 170°C.

Thus, in summary, all polymers used in the present study were amorphous in nature with distinct single or dual halos in their powder XRD patterns. Thermal studies provided glass transition temperatures, moisture contents as well as the temperatures at which the polymers degrade accompanied by weight loss. The conversion of rigid polymers to their viscous liquid forms with the increase in temperature was established by thermomechanical analysis and importance of G'' , G' , $\tan \delta$ and η^* were highlighted.

CONCLUSION

A database for physical, thermal and rheological properties of polyacrylate based polymers that can support hot melt extrusion has been generated. The thermal and viscoelastic properties were affected by various structural

contributes such as branched chain, molecular weight differences, and ratios of individual monomers in block copolymers. Based on thermal and viscoelastic properties of various homoblock copolymers, Eudragit® E PO should be easily extrudable, whereas Eudragit® RL PO and Eudragit® RS PO, based on their differences between crossover temperatures and T_d and based on the predicted extrusion range showed a narrow temperature window for extrusion. Heteroblock copolymers of polymethacrylates and polymethacrylic acid such as Eudragit® L 100, Eudragit® L 100-55 and Eudragit® S 100 were stiffer than homoblock copolymers and were found non-extrudable based on various thermal and viscoelastic properties and should be used with suitable plasticizers.

REFERENCES

- 1 Serajuddin ATM. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. *J Pharm Sci*, 88(10): 1058-1066, 1999.
- 2 Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm*, 50(1): 47-60, 2000.
- 3 Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, Martin C. Pharmaceutical applications of hot-melt extrusion: part I. *Drug Dev Ind Pharm*, 33(9): 909-926, 2007.
- 4 Repka MA, Shah S, Lu J, Maddineni S, Morott J, Patwardhan K, Mohammed N. Melt extrusion: process to product. *Expert Opin Drug Deliv*, 9(1): 105-125, 2012.
- 5 Gupta SS, Meena A, Parikh T, Serajuddin ATM. Investigation of Thermal and Viscoelastic properties of polymers relevant to hot melt extrusion, I: Polyvinyl based copolymers. *J Excip Food Chem*, 5(1):32-45, 2014.
- 6 Meena A, Parikh T, Gupta SS, Serajuddin ATM. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion, II: Cellulosic polymers. *J Excip Food Chem*, 5(1):46-55, 2014.
- 7 Barnes HA, Hutton JF, Walters K. An introduction to rheology. *Elsevier*, Amsterdam, 1989.
- 8 <http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products> (accessed on January 21, 2014).
- 9 Yang R, Wang Y, Zheng X, Tang X, Zhang X. Preparation and evaluation of ketoprofen hot-melt

- extruded enteric and sustained-release tablets. *Drug Dev Ind Pharm*, 34(1): 83-89, 2008.
- 10 Chokshi R, Sandhu H, Iyer R, Shah N, Malick A, Zia H. Characterization of physico-mechanical properties of indomethacin and polymers to assess their suitability for hot-melt extrusion process as a means to manufacture solid dispersion solution. *J Pharm Sci*, 94(11): 2463-2474, 2005.
- 11 Zheng X, Yang R, Tang X, Zheng L. Part I: characterization of solid dispersions of nimodipine prepared by hot-melt extrusion. *Drug Dev Ind Pharm*, 33(7): 791- 802, 2007.
- 12 Turi, E., Thermal characterization of polymeric materials, chapter 3, *Academic press*, New York, pp 248, 1981.
- 13 Hughey J, DiNunzio J, Bennett R, Brough C, Miller D, Ma H, Williams R, McGinity J. Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: A comparative study of hot melt extrusion and KinetiSol® dispersing. *AAPS PharmSciTech*, 11(2): 760-774, 2010.
- 14 Lin S, Liao C, Hsiue G. A reflectance FTIR/ DSC microspectroscopic study of the nonisothermal kinetics of anhydride formation in Eudragit L- 100 films. *Polymer Deg and Stab*, 47(2): 299-303, 1995.
- 15 Sathigari SK, Radhakrishnan VK, Davis VA, Parsons DL, Babu RJ. Amorphous-state characterization of efavirenz-polymer hot-melt extrusion systems for dissolution enhancement. *J Pharm Sci*, 101(9): 3456–64, 2012.
- 16 Wu C, McGinity J. Influence of methylparaben as a solid-state plasticizer on the physicochemical properties of Eudragit® RS PO hot-melt extrudates. *Eur J Pharm Biopharm*, 56(1): 95–100, 2003.
- 17 Kolter K, Karl M, Nalawade S, Rottmann N. Hot-melt extrusion with BASF pharma polymers, *Extrusion compendium*. 2nd ed., BASF SE, Ludwigshafen, Germany, 2010.