Journal of
Manufacturing and Materials Processing

MDPI

Article

Processing Stability and the Significance of Variation in Extrusion Speeds and Temperatures on SSB® 55 Pharma Grade Shellac for Oral Drug Delivery

Noel M. Gately [1,*] and James E. Kennedy [1,2]

[1] Materials Research Institute, Athlone Institute of Technology, Co., Westmeath N37 HD68, Ireland; james.kennedy@kastus.com

[2] Centre for Industrial Services and Design (CISD), Department of Mechanical and Polymer Engineering, School of Engineering, Athlone Institute of Technology, Co., Westmeath N37 HD68, Ireland

* Correspondence: n.gately@ait.ie; Tel.: +353-(0)9064-42588

Received: 18 July 2017; Accepted: 30 August 2017; Published: 6 September 2017

Abstract: The melt-extrusion process is utilized in the pharmaceutical arena for the manufacturing of a variety of dosage forms and formulations, including solid dispersions. This technology is considered an efficient and continuous dosage form manufacturing method. However, there are potential challenges mainly because, during hot-melt extrusion, polymers are subject to mechanical and thermal degradation. Mechanical degradation may be induced by the shear effects imposed by the rotating screw. Thermal degradation results from high temperatures and includes random scission, scission from the ends of the polymer and unzipping of substitute groups. This paper endeavors to understand the impact of thermal and/or mechanical components of the melt-extrusion process on the stability of a pH sensitive polymer, namely Shellac. Correlation between the screw speeds and processing temperature profile was examined in the context of the overall degradation profile of the polymer. The results suggest that the processing stability of Shellac was reliant on optimization of screw speed (rpm) and process temperature.

Keywords: melt extrusion; process stability; Shellac; oral drug delivery

1. Introduction

Few studies have been reported in the literature concerning the stability of polymers in tablet matrices prepared by hot-melt extrusion. Shellac is the purified product of lac, a natural resinous oligomer (MW $\approx$ 1000 D) secreted by the parasitic insect Kerria lacca on various host trees in India, Thailand, and Myanmar. Shellac consists of polyesters of mainly aleuritic acid, shellolic acid, and a small amount of free aliphatic acids. The composition varies depending on the insect species as well as the host tree from which the raw material is obtained [1,2]. Shellac for pharmaceutical applications is usually dewaxed Shellac that is refined by the solvent extraction method and is a food grade material whereby the Food and Drugs Administration (FDA) classes it as 'Generally Recognized as Safe' (GRAS). Shellac has traditionally and extensively been used as a coating polymer, but a novel application for SSB® 55 Pharma grade Shellac is the preparation of monolithic matrices using hot melt extrusion. Therefore, an initial study into the process ability of the polymer was undertaken. Crowley et al. [3] investigated the thermal stability of polyethylene oxide (PEO) during the hot melt extrusion process. The degradation of polymer is sensitive to both process temperature and screw speed and the mechanism of degradation during the extrusion process is attributed to both thermal and mechanical energy. Variables such as processing temperature and screw speed could potentially have an effect on the properties of the blends produced via hot melt extrusion [4].

2. Materials and Methods

2.1. Hot Melt Extrusion Conditions

All of the melt compounding detailed herein was carried out on a bench-top APV Baker twin screw extruder (MP19 TC25, APV Baker, Newcastle-under-Lyme, United Kingdom) with 19 mm diameter screws and a 35/1 length to diameter ratio. APV co-rotating extruder screws are designed and manufactured in a modular construction. The screws are made up of individual sections that slide onto a keyed or splined shaft. Therefore, different screw configurations using narrow disk bi-lobal kneading elements can be arranged at any location along the shaft to generate controlled shear or mixing effects. The design of the screw assemblies has a significant impact on the degradation of drugs or excipients [5]. In the case of the compounding detailed in this work, the screws were assembled in the co-rotating intermeshing mode. The material to be compounded was fed at a constant speed into the hopper of the APV twin screw extruder by means of a screw feed system. In all cases, the speed of the delivery screws was maintained at such a rate as to ensure that the materials were starve fed into the mixing screws. This ensured that in all cases, output was independent of screw speed. The resultant homogeneous melt was extruded through a cylindrical die to form a strand. Extrudate samples were collected 10 min after the start of the process in order to allow the extruder to purge and ensure any remaining materials inside the barrel were eliminated. The extrudates were cooled down to room temperature before granulation was carried out using a granulator. In this work, SSB® 55 Pharma grade Shellac was subjected to five subsequent extrusion cycles and the effect of prolonged exposure to heat and shear stresses on the polymer's structural and performance properties were investigated. The screw speed and the extrusion temperature profile were constant, as outlined in Table 1. To investigate the significance of extrusion temperatures on the Shellac polymer, samples were processed and collected using the two different sets of extrusion temperatures as outlined in Table 2, keeping the screw speed constant at 50 rpm. In order to investigate the effect of screw speed variability on the properties of a novel SSB® 55 Pharma grade Shellac, virgin material was compounded using the bench-top APV twin screw extruder over a range of screw speeds, namely 25, 50, 100, 150 and 200 rpm. In this extrusion process, the temperature profile was consistent, as per Table 2 temperature 1.

Table 1. Extrusion conditions used to compound SSB® 55 Pharma grade Shellac.

Screw Speed (RPM)	Temperature (°C)						
	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Die
100	30	35	40	50	60	65	70

Table 2. Extrusion conditions used to examine the effect of temperature variations in processing of a novel SSB® 55 Pharma grade Shellac.

Screw Speed (RPM)		Temperature (°C)						
		Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Die
50	Temp. 1	30	35	40	50	60	65	70
50	Temp. 2	40	45	50	60	70	80	90

2.2. Differential Scanning Calorimetry (DSC)

A TA instruments 2010 DSC was used throughout the course of the work to date. Samples of between 9.0 and 12 mg were weighed out using a Sartorius scales having a resolution of 1×10^{-5} g. Samples were then placed in non-perforated aluminium pans which were crimped before testing, with an empty crimped aluminium pan being used as the reference cell. Volatiles were removed from the purging head with nitrogen at a rate of 30 mL/min. Calorimetry scans were carried out over varying temperature ranges between −50 °C and 250 °C at a rate of 10 °C per minute. Calibration of the

instrument was performed using indium as standard. Sub-ambient DSC was carried out exclusively on the TA instrument 2010 DSC, with the test cell brought to low temperature with the aid of liquid nitrogen. After each scan was completed, the melting points were analyzed to determine heats of fusion (ΔH) and melting point (Tm) of each batch.

2.3. Rheological Analysis

In all cases throughout this study, oscillatory parallel plate rheological measurements were carried out on samples using an Advanced Rheometer AR1000 (TA Instruments, Hüllhorst, Germany) fitted with a Peltier temperature control (set to 70 °C) and a 40 mm diameter parallel steel plate. Samples were tested in triplicate (using individual samples) and the samples were subjected to a low strain range sweep from 1.88×10^{-4} to 1×10^{-3} at a frequency of 1 Hz, while a constant gap of 2000 μm was utilized on the samples to ensure proper contact between the polymer and the surface plates of the instrument. The shear storage (elastic) modulus G′ and the shear loss (viscous) modulus G″ were noted for determining the comparative strength of the Shellac. The following is the procedure used in all of the rheological studies detailed herein. The air and nitrogen supplies were turned on and the air bearing guard was removed. The instrument was calibrated for inertia and the geometry was set for the 40 mm steel parallel plates being used. The instrument was mapped and the rheometer was brought to the test temperature of 70 °C. The gap between the plates was zeroed and the plates were returned to the default back off distance before the sample was loaded. The amount of sample loaded has an effect, and so extreme care was taken during sample loading to ensure the correct fill. The apparatus was set to take 10 points per decade with 5% tolerance. After each test, a bronze scraper was used to remove the sample from the plates before the machine.

2.4. Swelling/Degradation Studies

The swelling characteristics of the samples were investigated in triplicate at 37 °C. Samples with a mass of 5.0 ± 0.5 g were placed in a dissolution vessel containing 150 mL of buffer. Samples were initially dried under vacuum at 200 mmHg for 24 h at 37 °C to a consistent weight. Periodically, the samples were removed, then blotted free of surface water with filter paper, and the swollen weight of the sample was measured using a Sartorius scales at room temperature. The samples were re-submerged in buffer and the percentage that the samples swelled was calculated using the formula as presented in the following equation:

$$\text{Swelling } (\%) = \frac{(Wt - Wo)}{Wo} * 100 \quad (1)$$

where Wt is the mass of the sample at a predetermined time and Wo is the initial weight of the sample.

3. Results

3.1. Hot Melt Extrusion

On exiting the extruder die, the extrudate did not experience any color change on going from the first pass to the fifth pass. Extruder torque is basically the torsional force of the extruder and is a measure of the resistance that the drive motor experiences as a consequence of the melt viscosity of the polymer inside the barrel. It is measured in ft-lb or Newton-meters (Nm) and is often expressed as percentage torque on the equipment. In this study, the extruder torque reading was recorded and higher viscosity melts will exert more pressure than melts with lower viscosities.

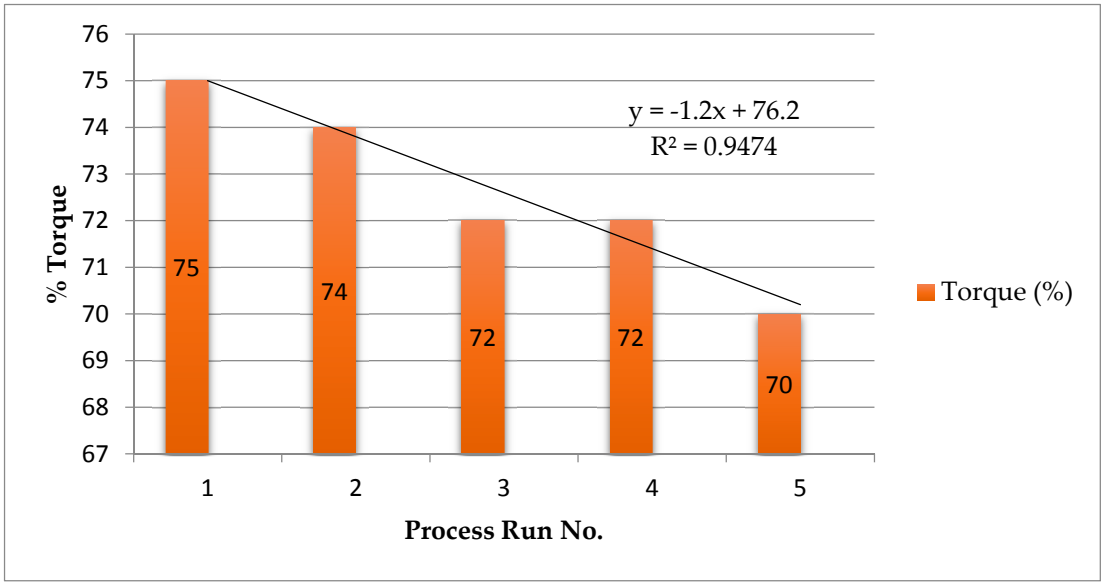
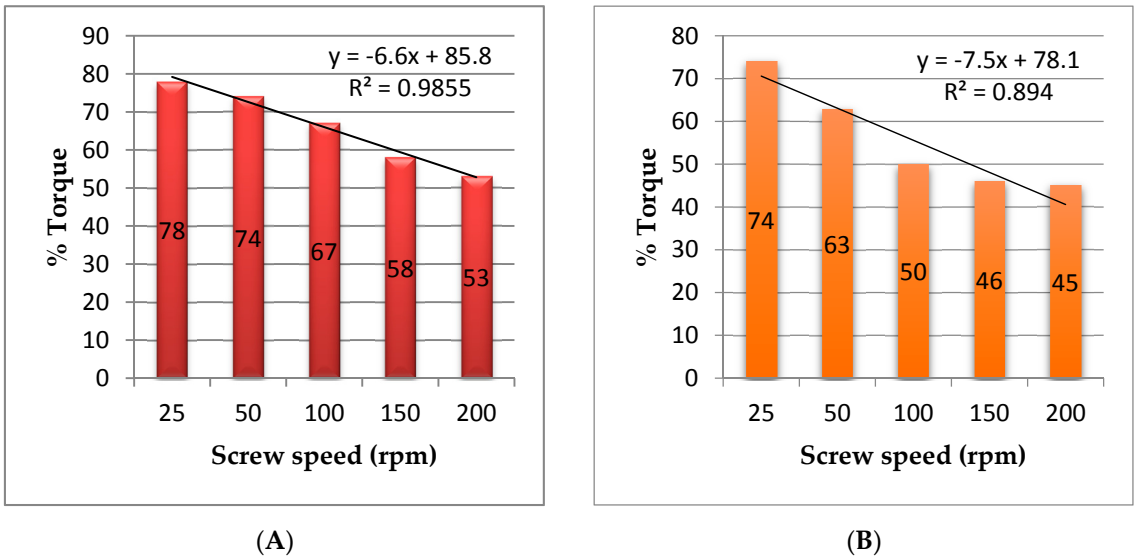


Figure 1. Extruder torque readings observed during re-processing of novel SSB® 55 Pharma grade Shellac.

Figure 1 illustrates a decrease in percentage torque of the polymer after each processing run was observed. This decrease in percentage torque is most likely due to a decrease in viscosity of the polymer, which is probably an effect of chain scission, leading to a reduction in the molecular weight of the polymer. Figure 2 shows the torque readings recorded during processing of the novel SSB® 55 Pharma grade Shellac over two temperature ranges as outlined above, and also over a range of screw speeds. For temperature profile 1 (lower process temperatures), torque values decreased linearly from 78% to 53% as compared to temperature profile 2 (higher process temperatures) which started at 74% and decreased linearly to 45%. At the higher processing temperatures, lower values of torque are noted as a result of the temperature dependency of polymer melts. Melt viscosity is inversely related to the fractional free volume in the polymer melt, which increases from a small value at the glass transition temperature (Tg) linearly with increasing temperature [6]. In all cases, the higher screw speeds result in lower values of torque; however, this would not be expected due to the higher volumes of material being processed per unit time. It was also observed that when processing at the higher screw speeds, the exiting die material was much more liquefied in texture, as discussed in the previous section and it is hypothesized that the higher processing screw speeds would generate much higher shear intensity and therefore an increase in internal barrel temperature, which would contribute to lower values for torque. This viscosity reduction may facilitate the drugs' possible dispersion among polymer chains, and SSB® 55 Shellac could possibly be a good candidate for a hot melt extruded drug delivery device. As a constant starve feed feeding rate was used, it transpired that torque values decreased from 78% at 25 RPM to 53% when the screw speed increased to 200 RPM. As screw material filling was reduced by using higher screw speed, it could lead to higher shear being transferred to the material inside the barrel. Thus, the matter in the extruder was fluidized, due to the polymer's thermoplastic behavior, and this could explain the torque decreases. It was also noted that when processing at the higher screw speeds, the exiting die material was much more liquefied in texture and proved difficult to collect good defined strands. Screw speeds of between 50 and 100 rpm were deemed optimal for reliable extrusion of virgin SSB® 55 Pharma grade Shellac at these processing temperatures, as the material was easier to collect exiting the die.



(**A**) (**B**)

Figure 2. Extruder torque readings observed during processing of novel SSB® 55 Pharma grade Shellac with (**A**) temperature profile 1, and (**B**) temperature profile 2.

3.2. *Differential Scanning Calorimetry*

SSB® 55 Shellac was reprocessed five times with samples removed after each processing run for DSC analysis. The thermo-gram displayed in Figure 3 shows the collated results. Inconsequential change in the melting point is detected after the multiple processing steps. However, a slight variation in the area under the curve between the samples taken after the first processing run and after the last processing run is noted. Polymer crystallinity can be determined with DSC by quantifying the heat associated with melting (fusion) of the polymer; these values are determined by the area under the curve, whereby the heat of fusion after first run was determined to be 6.938 J/g, falling to 4.117 J/g. It is apparent that there is a marginal decrease in the degree of crystallinity in samples reprocessed five times, with the thermodynamic heat of fusion at the equilibrium melting temperature decreasing by 42%. This reduction could be due to polymer chain breakages due to mechanical shear effects and may also be a result of previous processing thermal history. When these findings are coupled with the torque values recorded above, the former theory is more likely than the latter. Samples were analyzed to examine the effect of screw speed on crystallinity. Although the areas under the curves of DSC graphs and ΔH values (a parameter that can be used for defining crystallinity) fluctuate, they exhibit a slightly increasing trend. As the screw speed increased during the process, the relative crystallinity of the polymer increased from 208% at 25 rpm to 251% at 200 rpm, as shown in Figure 4 and Table 3. It is possible that the observed increase in relative crystallinity in this study occurred as a result of the shearing of large polymer chains and subsequent creation of smaller polymer chains with higher mobility with which to crystallize. The screw channels become less filled during processing at higher screw RPM rates and a constant feeding rate. As a consequence, the pressure to transport the melted blend through the screws becomes lower, causing the material to remain for a longer residence time in the extruder barrel, which would lead to the material remaining longer inside the extruder where it almost certainly is subjected to higher shear. Those processing conditions could lead to the polymer molecular degradation, which usually occurs by chain scission [7]. Therefore, Shellac short chains would have higher mobility to crystallize at higher crystallinity content. When the polymer chains are degraded, they become shorter with higher mobility, which becomes easier to adjust them in the crystalline pattern structure which could be the main reason to allow higher heat of fusion during melting in the DSC. Shorter chains would also result in the observed reduced viscosity and operational torque values which are in agreement with the observations made above. The Tm reduced initially from 56.47 °C for virgin base material to 44.32 °C following the first process run at 25 rpm, most likely

due to a relaxation of polymer chains and the formation of shorter chains following its first thermal run. Thereafter, all the melt temperatures remained relatively constant between 44.32 °C and 45.63 °C, further reinforcing the processing stability of the polymer.

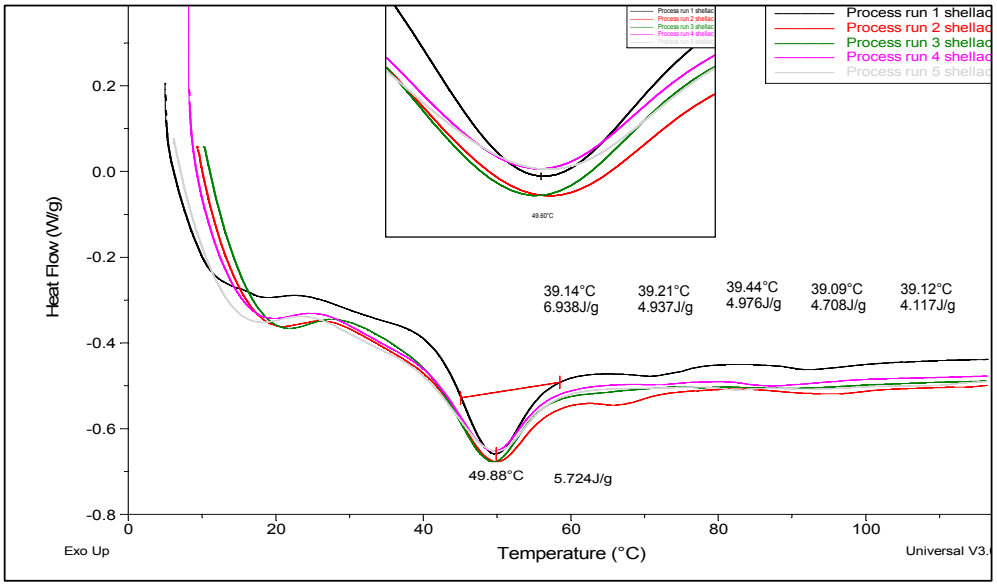


Figure 3. Overlay differential scanning calometry (DSC) thermogram of samples from each process run number.

Table 3. Effect of various screw speeds on SSB® 55 Pharma grade Shellac endothermic peak and enthalpy.

Sample	Peak Temperature (°C)	Enthalpy (J/g)	Relative Crystallinity (%)
Base Material	56.47	3.61	100.00
25 rpm	44.32	7.55	208.88
50 rpm	45.63	8.28	229.09
100 rpm	45.30	8.60	237.95
150 rpm	44.48	8.31	229.98
200 rpm	44.56	9.07	250.93

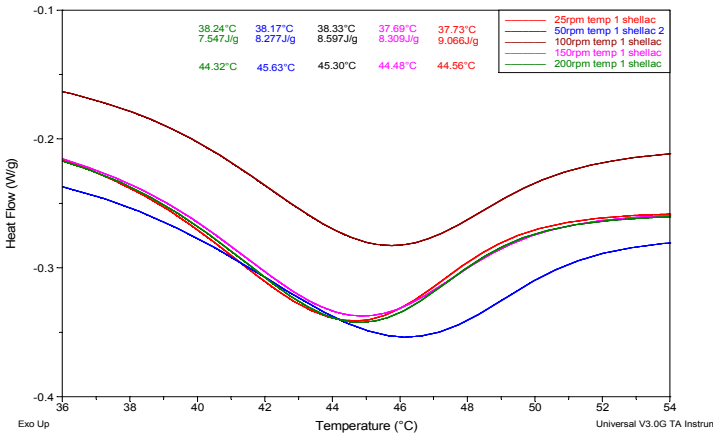


Figure 4. Overlay of DSC thermograms of samples from SSB® 55 Pharma grade Shellac with increased screw speeds.

The processing temperatures used in this study are not seen to have any significant impact on the melting points of the resultant matrices, with all samples remaining in the region of 44.3 °C to 45.6 °C. However, it is shown in Table 4 that there is a marginal decrease of approximately 5% in the degree of relative crystallinity in samples processed using the higher temperatures at 100 rpm screw speeds. In each run, the specific enthalpy needed for melting the polymer samples decreases as the processing temperature increases. It is possible that the observed decrease in crystallinity in this study occurred as a result of much higher shear intensity, and therefore, an increase in internal barrel temperature which would contribute to lowering of crystallinity. The melting peaks are also slightly broader than virgin Shellac, indicating that there are more amorphous regions in these samples. Since the melting points of all samples did not change much, it was concluded that the change of the crystal thickness was negligible.

Table 4. Endothermic peak (melting point) and enthalpy values for each sample.

Sample	Temp Profile 1 (Tm °C)	Temp Profile 2 (Tm °C)	Temp. Profile 1 Enthalpy (J/g)	Temp. Profile 2 Enthalpy (J/g)
25 rpm	44.32	44.57	9.47	8.99
50 rpm	45.63	45.34	7.09	6.64
100 rpm	45.30	45.17	9.42	8.99
150 rpm	44.48	45.37	8.25	8.81

3.3. Rheological Analysis

The effect of reprocessing yielded a significant drop in complex viscosity of the material, and by inference, has shown a decrease in the molecular weight of the material after the first processing run, as depicted in the rheological data displayed in Figure 5. This is consistent with the data obtained during processing and thermal analysis of the samples from each run. This decrease in viscosity is likely an effect of chain scission, as a result of the mechanical shearing of polymer chains leading to a reduction in the molecular weight of the polymer. This drop in viscosity is not seen to be significant enough to adversely affect the material, as no corresponding drop in the melting point of all the process run samples was recorded during thermal analysis. Figure 6 shows that there is a higher viscosity at low shear rates for all of the samples tested, but that a reduction in viscosity is observed following each process run. It can be seen that all samples exhibited shear thinning properties with the viscosity decreasing rapidly beyond a shear rate of 1 S^{-1} and a levelling off beyond a shear rate of 50 S^{-1}. All runs show pseudoplastic behavior at high shears, whereby the viscosity decreases with an increasing rate of shear stress and are Newtonian at low shears. These results are in agreement with the observed changes in torque during processing.

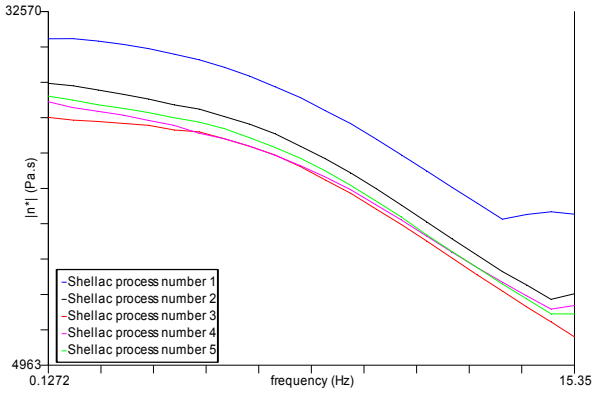


Figure 5. Complex viscosity (η*) versus frequency (Hz) for each process run.

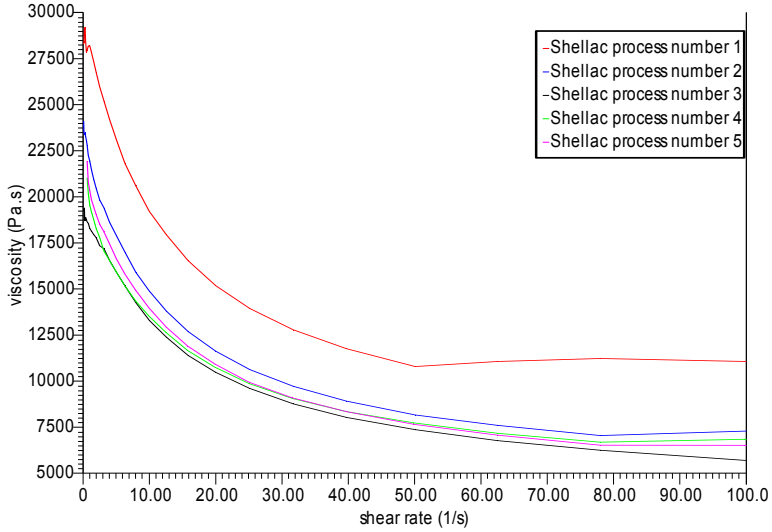


Figure 6. Viscosity (η) versus shear rate (1/s) for each process run.

The effect of processing at different screw speeds is seen to have a slight effect on the flow behavior of the matrices. Figure 7 displays complex viscosity as a function of frequency (Hz) for novel SSB® 55 Pharma grade Shellac at various screw speeds using temperature profile 1 (Table 2). It can be seen from the data presented that processing at higher screw speeds produces a slight drop in the viscosity of the polymer matrix. This is likely to be as a result of the mechanical shearing of polymer chains at the higher screw speed. This slight drop in viscosity is not seen to be significant enough to adversely affect the matrices, as no corresponding drop in the melting point of the matrices processed was noted during thermal analysis. For the same barrel temperatures, the torque decreases as the screw speed increases. There are two reasons for this observation; on the one hand, the higher screw speeds correspond to a higher shear rate, which leads to a more pronounced shear thinning effect (Figure 8), causing lower viscosity and lower torque. On the other hand, a more viscous dissipation heat generated at higher screw speeds results in increasing the melt temperature and lowering the torque, as observed above.

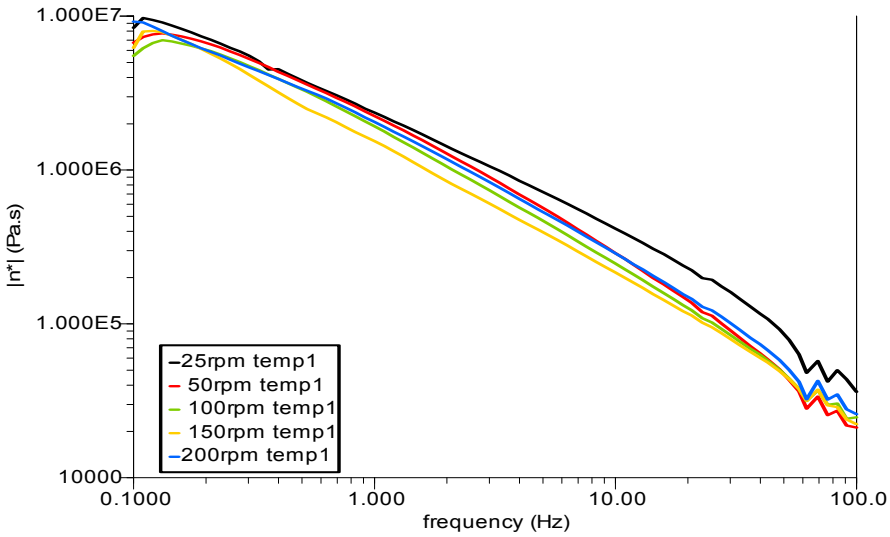


Figure 7. Complex viscosity (η*) versus frequency (Hz) for novel SSB® 55 Pharma grade Shellac at various screw speeds.

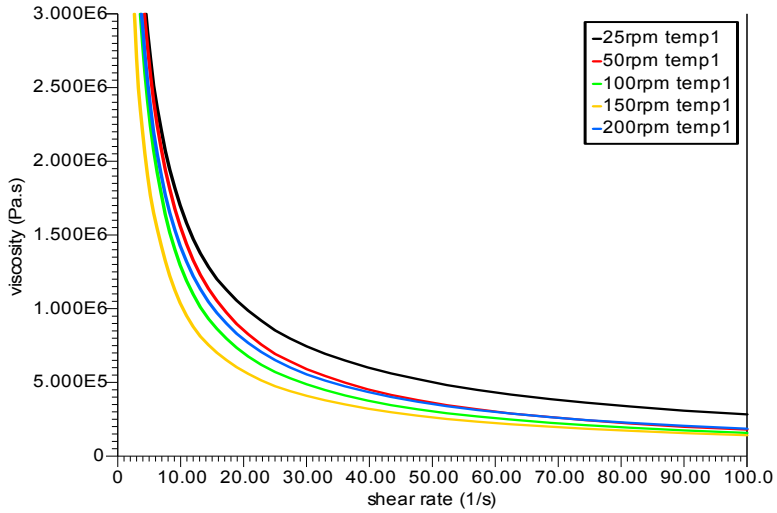


Figure 8. Viscosity (η) versus shear rate (1/s) for novel SSB® 55 Pharma grade Shellac at various screw speeds.

The effect of processing at different temperatures and screw speeds is seen to have a slight effect on the flow behavior of the matrices. Figure 9 depicts complex viscosity, η*, plots as a function of frequency for samples taken at various screw speeds in conjunction with processing at two different temperature profiles. At the lower screw speeds, the polymer samples taken using temperature profile 2, yields a lower viscosity than those produced under profile 1. A change-over point can be seen from 100 rpm upwards, whereby the reverse is apparent; the polymer samples produced using temperature profile 1 yield a lower viscosity than those produced under profile 2. A similar trend is observed, along with a cross over region in the viscosity curves in Figure 10, which also illustrates that, as the shear rate is increased, a more pronounced shear-thinning behavior is observed. Generally, two regions of flow profiles, low shear and high-shear regions can be identified. In the low-shear region, the shear-rate-dependent viscosity decreased dramatically, suggesting shear thinning behavior (non-Newtonian behavior). At the lower shear rates of between 0 and 25 S^{-1}, the starting values for viscosity were greater with increased screw speeds; for example, at 25 RPM, a starting viscosity of 3.0E6 Pa·S was found, compared to the sample prepared at 100 RPM, where above 4.0E6 Pa·S was evident. In addition, lower shear thinning and higher viscosity was observed at both higher temperatures and screw speeds and this could possibly be due to the higher volumes of material being processed per unit time. However, the shear-rate-dependent viscosity was found to be nearly independent of shear rate at high shear rates. These findings concur with those reported in processing observations with extruder torque values and thermal analysis above. Goswami et al. [8] reported a sharp decrease of the melt-viscosity of Shellac with the increase in temperature, and this suggests conformational changes of Shellac molecules as a result of the rise in temperature. For polymer fluids at temperatures far above the glass transition temperature or the melting point, the viscosity follows the Andrade or Arrhenius equation:

$$\eta \cong K\, e^{E/RT} \quad (2)$$

where η is the melt viscosity of material, K is a constant at a given shear stress for a given polymer, E is the activation energy, R is the gas constant and T is the temperature in degrees Kelvin [9]. Clearly, increasing temperature is an effective means of decreasing melt viscosity in processing operations. Although the melt viscosity decreases with increasing temperature, two drawbacks are related to the increases in temperature. First, it takes time and costs money to put in and take out thermal energy. Second, excessive temperatures can lead to degradation of the polymer. There is certainly an upper limit to the processing temperature we can use for a particular polymer, which depends upon the degradation temperature.

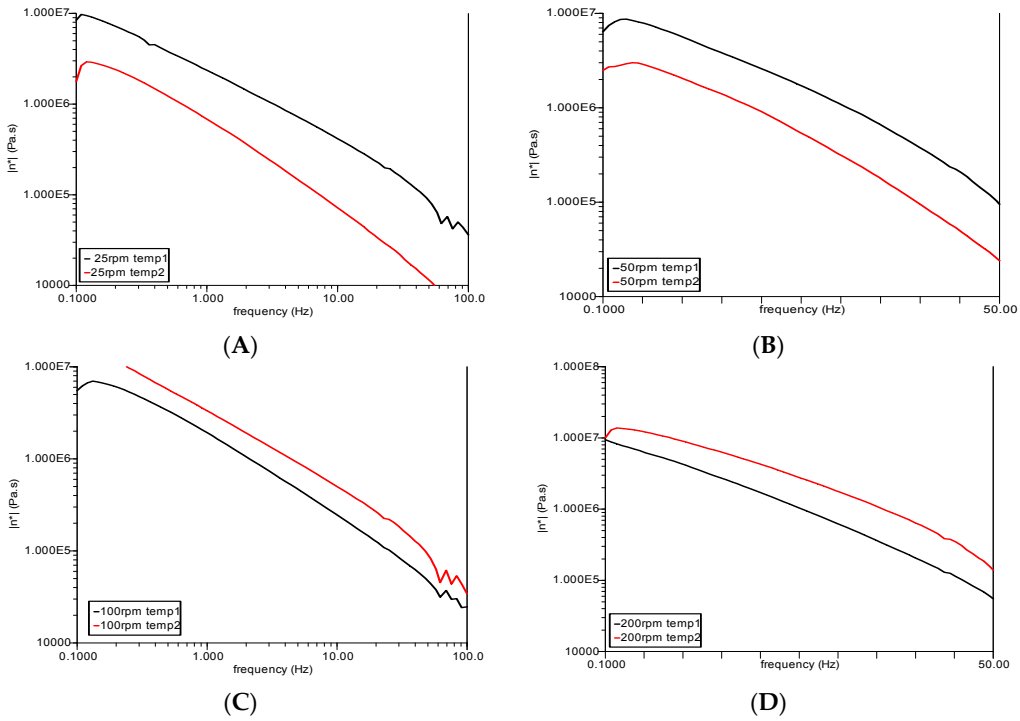


Figure 9. Complex viscosity (η*) of Shellac samples produced by different temperature profiles and screw speeds: (**A**) 25 rpm; (**B**) 50 rpm; (**C**) 100 rpm and (**D**) 200 rpm.

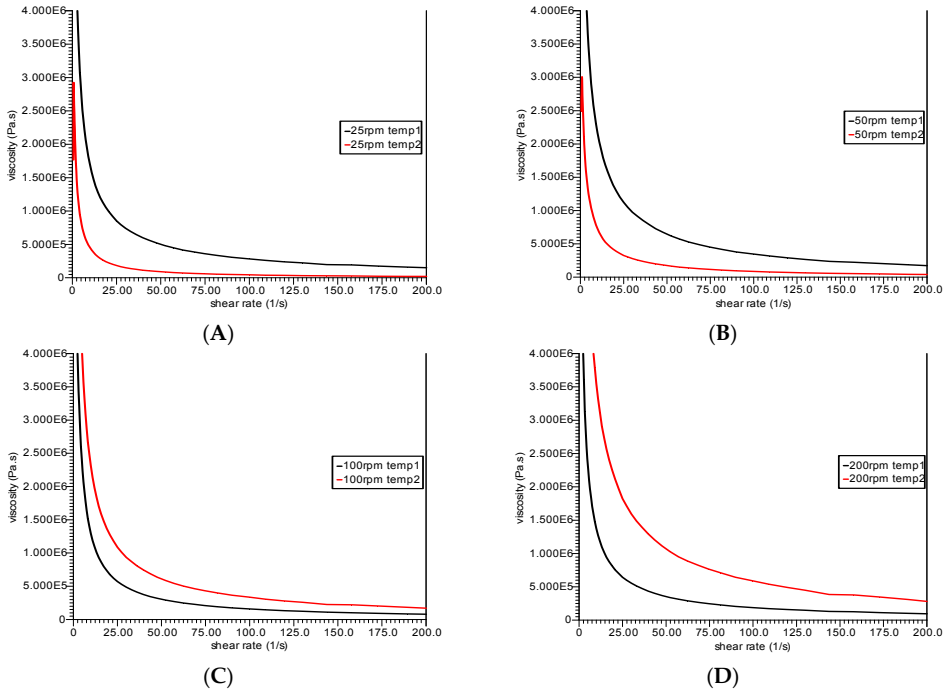


Figure 10. Viscosity (η) versus shear rate of Shellac samples produced by different temperature profiles and screw speeds: (**A**) 25 rpm; (**B**) 50 rpm; (**C**) 100 rpm and (**D**) 200 rpm.

3.4. Swelling Studies of Variation in Screw Speed and Extrusion Temperature on a Novel SSB® 55 Pharma Grade Shellac

Shellac is comprised of aliphatic, aleuritic, shelloic, and jalaric alicyclic hydroxy acids and their polyesters. It is not water soluble, but is soluble in alcohol and alkaline solutions [10]. Figure 11 illustrates the structure of Shellac and its polyester chains [11]. Alkali treatment of Shellac causes an increase in acid value (AV) and a reduction of ester value (EV), indicating that the polyester chains of Shellac are broken down and free carboxylic acid and free hydroxyl groups are produced. Therefore, dissolution occurs by hydrolysis of the backbone polyester chain [12]. Swelling may be a very important characteristic of polymers that control the drug release from the matrix via a diffusion mechanism that depends on the rate of penetrant entry into the matrix. The effect of swelling behavior of various SSB® 55 Pharma grade Shellac samples are recorded in Figure 11. Samples extruded were placed in physiological type buffer at pH 7.4, 6.8 and 1.2, respectively, at 37 °C and their rate of swelling/degradation was investigated. Due to its acidic character, Shellac is used primarily as an enteric coating. Because Shellac is a weak acid, the dissolution profiles were expected to be pH-dependent [1]. The weight loss or gain of films represents their solubility or insolubility, respectively, in different media. Investigation of the solubility of SSB® 55 Pharma grade Shellac showed the insolubility of these tablets at acidic pH (1.2) and modestly acidic pH (6.8) and their complete solubility at pH 7.4. This pH dependence was confirmed for all samples, as presented in Figure 12.

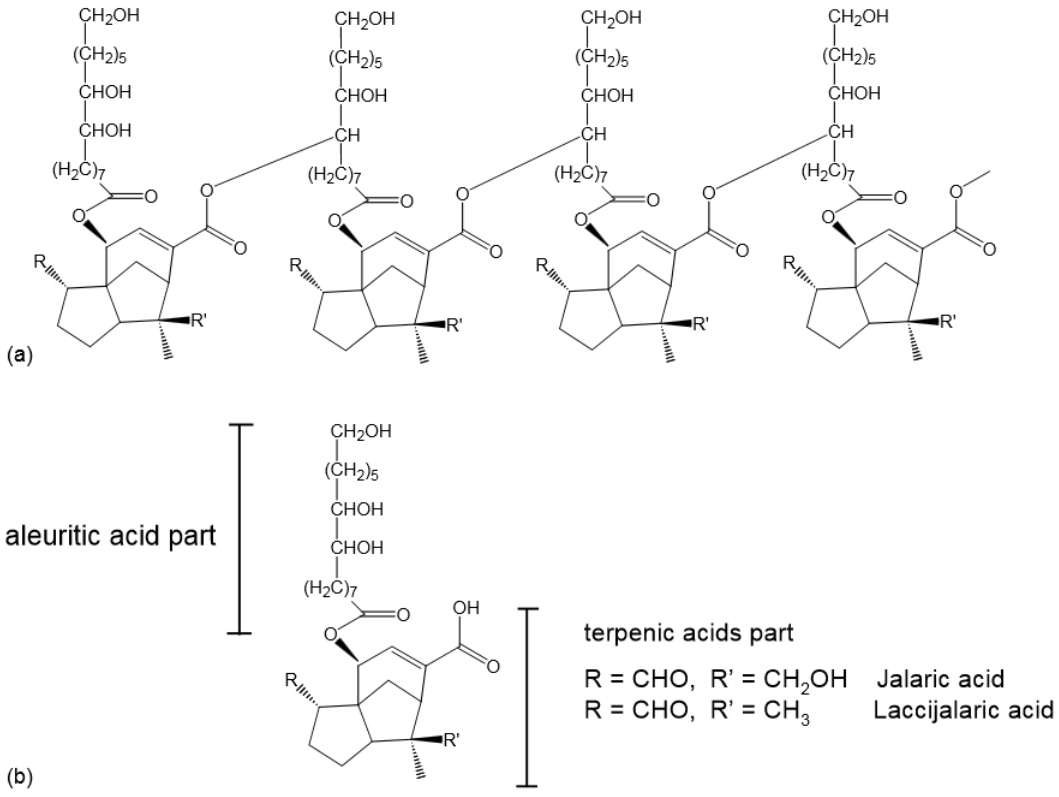
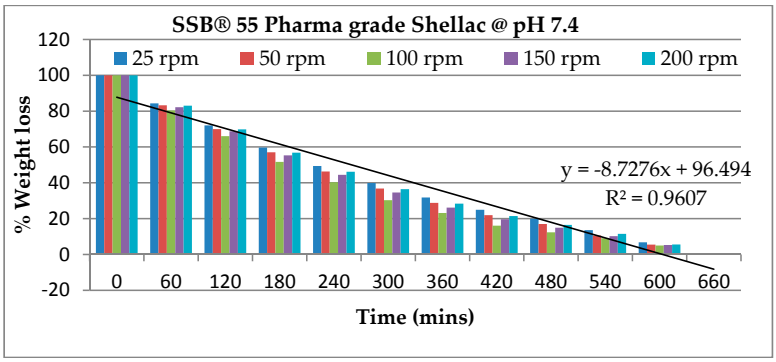


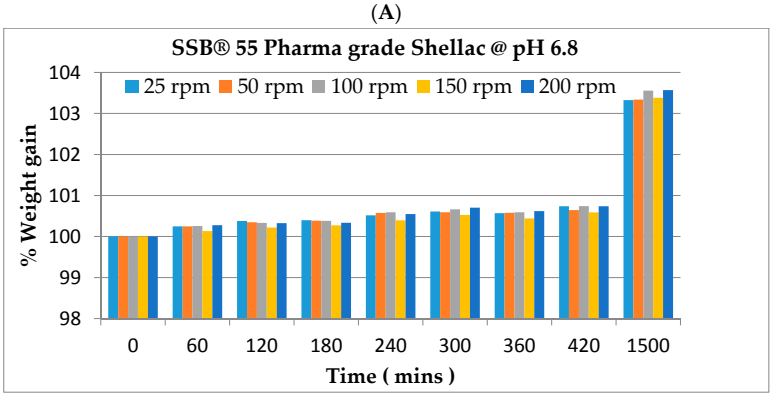
Figure 11. Chemical structure of shellac. Polyesters (**a**), single esters (**b**) [11].

At pH 7.4 (Figure 12A), approximately 90% weight loss was observed following 10 h of exposure to the slightly basic pH, and this dissolution occurred in a linear fashion suggesting a constant controlled rate of breakdown over time. Interestingly, there appears to be a slight increase in breakdown rate with increasing screw speeds over time, which could possibly be caused by mechanical shearing of the backbone polyester chain due to the increased shear inside the barrel as discussed above.

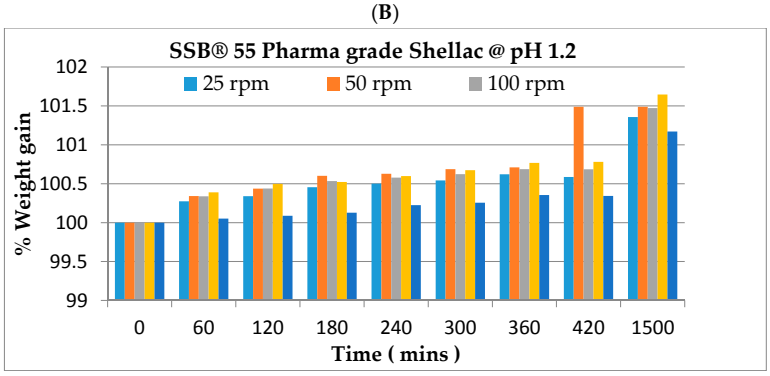
Smaller polyester backbone chains would be more susceptible to greater hydrolysis over time at this pH; Figure 12B shows that following 25 h (1500 min) of exposure at pH 6.8, only a modest average weight gain of approximately 3.5% was observed while the integrity of the sample was maintained. Again, there appears to be a slight increase in swelling with increasing screw speeds over time, which could possibly be caused by mechanical shearing of the backbone polyester chain due to the increased shear inside the barrel, as mentioned above. Limmatvapirat et al. [12] postulated that a higher number of polar groups (OH, COOH) of hydrolyzed Shellac enables intermolecular interaction through hydrogen bonding and the formation of highly structured matrix, thereby impeding diffusion of water. A similar trend was observed for pH 1.2, with only a slight average weight gain of 1.5% after 25 h exposure (Figure 12C). It is hypothesized that the addition of water-soluble polymers or Active Pharmaceutical Ingredient (API) to Shellac may have desired effects on the solubility, swelling and dissolution rate of the polymer [13]. The addition of 10% (w/w) water-soluble polymer to Shellac had a negligible effect on the solubility of films at pH 1.2, but resulted in improved solubility of the polymer at pH 6.8.



(A)



(B)



(C)

Figure 12. Plots of % weight gain/loss over time in (**A**) pH 7.4; (**B**) pH 6.8 and (**C**) pH 1.2.

4. Discussion

The stability of novel SSB® 55 Pharma grade Shellac when subjected to multiple extrusion operations was investigated. A loss in mechanical properties can occur by degradation during multiple extrusion processes by a combination of thermal, mechanical, and chemical degradation. It was verified that multiple processing cycle conditions change the rheological properties of SSB® 55 Shellac, and, not only does viscosity decrease, but there is also a marginal increase in the degree of crystallinity in samples reprocessed five times, as shown using DSC. A significant drop in the viscosity of the material, and, by inference, a decrease in the molecular weight of the material after the first processing run was observed. This decrease in viscosity is likely an effect of chain scission, leading to a reduction in the molecular weight of the polymer. This slight drop in viscosity is not seen to be significant enough to adversely affect the material, as no corresponding drop in the melting point of all the process run samples was recorded during thermal analysis. Hence, the control of the extrusion process, such as screw speeds and extrusion temperature profiles, are important steps in thermoplastics extrusion.

Higher screw speeds resulted in lower observed values of torque, possibly due to higher shear intensity, and therefore an increase in internal barrel temperature which would contribute to lower values for torque. Thermal analysis of the blends indicated that, as the blend composition varied, so too did the melting behavior. No adverse thermal effects were associated with varying the processing conditions. Steady state rheometry of the matrices indicated that higher screw speed was observed to result in slightly lower matrix melt viscosity when compared with matrices compounded using lower screw speeds. Also, a shear thinning behavior was observed for all samples at all temperatures studied. The results obtained indicate that careful processing of SSB® 55 Pharma grade Shellac matrices is necessary in order to ensure that the extruded material produced is suitable for use as an oral drug delivery device. It is also hypothesized that the addition of water-soluble polymers or APIs to the Shellac matrix may have desired effects on the solubility, swelling and dissolution rate of the polymer.

Acknowledgments: The Authors wish to acknowledge the support of Science Foundation Ireland (SFI) Technology Innovation Development Award (TIDA) for the funding support for this work.

Author Contributions: Noel Gately and James E. Kennedy conceived and designed the experiments; Noel Gately performed the experiments; Noel Gately and James E. Kennedy analyzed the data and Noel Gately wrote the paper.

Conflicts of Interest: The authors declare no conflicts of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

References

1. Farag, Y.; Leopold, C.S. Physicochemical Properties of Various Shellac Types. *Dissolut. Technol.* **2009**, *16*, 33–39. [CrossRef]
2. Rowe, R.C.; Sheskey, P.J.; Quinn, M.E. *Handbook of Pharmaceutical Excipients*; Pharmaceutical Press: London, UK, 2009.
3. Crowley, M.M.; Zhang, F.; Koleng, J.J.; Mcginity, J.W. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. *Biomaterials* **2002**, *23*, 4241–4248. [CrossRef]
4. Lyons, J.G.; Blackie, P.; Higginbotham, C.L. The significance of variation in extrusion speeds and temperatures on a PEO/PCL blend based matrix for oral drug delivery. *Int. J. Pharm.* **2008**, *351*, 201–208. [CrossRef] [PubMed]
5. Breitenbach, J. Melt extrusion: From process to drug delivery technology. *Eur. J. Pharm. Biopharm.* **2002**, *54*, 107–117. [CrossRef]
6. Brydson, J.A. *Plastics Materials*; Elsevier Science: Amsterdam, The Netherlands, 1999.
7. Ambrósio, J.D.; Pessan, L.A.; Otaguro, H.; Chinelatto, M.A.; Junior, E.H. The effect of extrusion conditions and the use of a compatibilizer in the crystallization of PBT/ABS blends. *Mater. Res.* **2013**, *16*, 1220–1228. [CrossRef]
8. Goswami, D.N.; Jha, P.C.; Mahato, K. Rheological studies of shellac. *Pigment Resin Technol.* **2003**, *32*, 107–112. [CrossRef]

9. Rosen, S.L. *Fundamental Principles of Polymeric Materials*; Wiley: Hoboken, NJ, USA, 1971.
10. Alzahrani, H.; Bedir, Y.; Al-Hayani, A. Efficacy of shellac, a natural product, for the prevention of wet gangrene. *J. Int. Med. Res.* **2013**, *41*, 795–803. [CrossRef] [PubMed]
11. Limmatvapirat, S.; Limmatvapirat, C.; Luangtana-anan, M.; Nunthanid, J.; Oguchi, T.; Tozuka, Y.; Yamamoto, K.; Puttipipatkhachorn, S. Modification of physicochemical and mechanical properties of shellac by partial hydrolysis. *Int. J. Pharm.* **2004**, *278*, 41–49. [CrossRef] [PubMed]
12. Limmatvapirat, S.; Nunthanid, J.; Luangtana-Anan, M.; Puttipipatkhachorn, S. Effect of alkali treatment on properties of native shellac and stability of hydrolyzed shellac. *Pharm. Dev. Technol.* **2005**, *10*, 41–46. [CrossRef] [PubMed]
13. Stummer, S.; Salar-Behzadi, S.; Unger, F.M.; Oelzant, S.; Penning, M.; Viernstein, H. Application of shellac for the development of probiotic formulations. *Food Res. Int.* **2010**, *43*, 1312–1320. [CrossRef]

© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).