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Influence of Degassing on Hot-Melt Extrusion Process

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Abstract

The present study aimed to evaluate the effect of degassing on an extrusion process, with respect to extrudate quality and drug release properties. Processed formulations were extruded with and without a degassing vent port at various locations along the barrel. All the experiments were performed under constant processing temperature, feeding rate, and screw speed. During the extrusion process, torque and pressure were monitored and recorded. The degassing process was beneficial when used over a conveying section after a mixing section. This is attributed to the large surface area available on the conveying elements, which minimizes the internal volume of the processed material, thereby facilitating the escape of entrapped gases. Degassing enhanced the homogeneity, physical appearance, and drug release properties of all the formulations. Furthermore, the degassing process also enhanced the cross-sectional uniformity of the extruded material, which is beneficial for visual monitoring during processing. Degassing considerably reduced the post-extrusion moisture content of Formula D3, which contains the highly hygroscopic polymer Kollidon® 17 PF, suggesting that the greatest influence of this process is on hygroscopic materials. The reduction in post-extrusion moisture content resulting from the inclusion of a degassing vent port, reduced fluctuations in the values of in-line monitoring parameters such as pressure and torque. Employing a degassing unit during hot-melt extrusion processing could help increase process efficacy and product quality.

Graphical Abstract

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Keywords

Hot-melt extrusion (HME); Degassing; Carbamazepine; Chemical imaging

1. Introduction

Hot-melt extrusion (HME) is a well-investigated technology in both the food and plastic industries and involves a continuous process where molten materials under elevated temperature and pressure, are pumped along a rotating screw and out through an orifice (Crowley et al., 2007). Over the last thirty years, HME has emerged as a promising cost-effective technology for the pharmaceutical industry. The advantages of this process are that it has high throughput and relatively few processing steps compared to more conventional pharmaceutical processing technologies, and is both solvent free and potentially continuous (Repka et al., 2007). Currently, HME is widely used in the production of solid dispersions and controlled release formulations (Repka et al., 2008). Various dosage forms, such as pellets, tablets, and mucoadhesive films for transmucosal products, can be easily prepared from hot-melt extrudates (Repka et al., 2008). However, the potential for HME applications in pharmaceutical research and development has not yet been fully realized, mainly owing to the complexity of HME design and the non-Newtonian behavior of the extruded materials (Thomas and Yang, 2009). This makes it somewhat difficult to predict the behavior of materials processed by HME using mathematical modeling (Douroumis, 2012).

HME technology has been adopted primarily from the plastics industry, and therefore monitoring of the process and product quality may require adaptation to the requirements of the pharmaceutical industry. For example, the materials used in the production of plastic or food products are usually less valuable and/or sensitive than pharmaceutical products. In addition, the physicochemical properties of pharmaceutical constituents may not require the same considerations as those processed in other industries (i.e. water solubility, molecular weight, polar surface area, partition coefficient, etc.). As a continuous process, the starting materials and processing parameters have important role in controlling the quality of the hot-melt extrudates (Crowley et al., 2004; Sarode et al., 2013). Several reports have illustrated the significant impact of processing parameters on the physicochemical properties of the extruded drug (Verreck et al., 2003). In a study presented by Liu, Wang et al. 2010, demonstrated the influence of extrusion temperature, screw speed, and residence time on the dissolution rate (Liu et al., 2010). The dissolution rate was significantly increased with increasing extrusion temperature and screw speed, an observation that can be explained by

the enhancement of distributive mixing. The processing parameters that are of primary importance to the pharmaceutical industry are temperature, feeding rate, and screw speed; however, additional factors that may also affect both the process and the final product include degassing, torque, and pressure (Kolter et al., 2012). Effective degassing has been shown to have multiple effects on products in the plastic and food industries, including an increase in the free volume, reduction in the residual moisture content, improvements in odor, changes in the visual appearance, alterations in mechanical properties, prevention of bubbling or foaming, and homogeneity of mixing (Kohlgrüber, 2012). Kohlgrüber in 2012 demonstrated that proper degassing could easily be attained by changing the number, location, and geometry of the degassing vent port openings. Although the pharmaceutical literature strongly suggests that there is a definite need to investigate the influences of screw torque and degassing (Rauwendaal, 1998), pertinent studies relating to the impact of the degassing process on pharmaceutical applications are limited. Degassing is generally regarded in the pharmaceutical industry as merely an additional step in the manufacturing process (Douroumis, 2012). In the production of plastics and food, degassing has been intensely investigated and several studies have shown it to have a considerable influence on the properties of the final product (Kohlgrüber, 2008). Multiple protocols have been developed to enhance the degassing process, including the use of vacuum equipment, addition of a stripping agent, and designing screws specifically for degassing (Kühnle, 1986).

Degassing or venting is the process of removing gas and other volatile substance from extruded materials (Kohlgrüber, 2008) and should be considered one of the most important steps for any extrusion processes. Generally, gases may arise from the air trapped during the feeding process, or from the processed materials (Repka et al., 2013). Materials extruded with either polymers or active pharmaceutical ingredients (API) can have air trapped in the pores or adherent to their surfaces (Douroumis, 2012). The entrapped molecules may affect other processing parameters as well as the quality of the product. Under conditions of elevated temperature and pressure, melted materials are compressed and consequently, degassing is necessary to remove any residual moisture, air, polymer monomers, oligomers, solvents, reaction products, and decomposed materials, which could interfere if released during the extrusion process.

The main objective of this study was to determine the influence of extrusion degassing on the properties of the extrudate such as dissolution rate, physical stability, and chemical stability as well as to monitor other parameters while evaluating the visible effects on the product. In this study, the effect of a vent port open to the atmosphere, with a large opening to release gas while retaining molten materials was evaluated.

2. Materials and Methods

2.1. Materials

Carbamazepine was purchased from Afine Chemicals Limited, Zhejiang, China. Polyvinylpyrrolidone (Kollidon® 17 PF) was received as a gift sample from BASF Chemical Co. (Ludwigshafen, Germany). Hydroxypropylcellulose (Klucel™ ELF) was received as a gift sample from Ashland Inc (Wilmington, DW 19808 USA). All other

chemicals used were of analytical grade and obtained from Fisher Scientific (Fair Lawn, NJ 07410 USA).

2.2. Methods

2.2.1. Thermal Characterization Studies

2.2.1.1. Thermogravimetric Analysis: A Perkin Elmer Pyris 1 thermogravimetric analyzer (TGA) equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., Connecticut, USA) was used for thermogravimetric analyses of the samples. Each sample was weighed and heated from 20–220°C at a heating rate of 10°C/min under an inert nitrogen atmosphere and monitored for the percent weight loss with temperature increase.

2.2.1.2. Differential Scanning Calorimetry: A Perkin Elmer Diamond Differential Scanning Calorimeter (DSC) (Perkin Elmer Life and Analytical Sciences, 710 Bridgeport Ave., Connecticut, USA) equipped with Pyris manager software (Shelton, CT, USA) was used to perform polymer-drug miscibility studies. Each test formulation in this study was weighed (approximately 2–5 mg) and was hermetically sealed in an aluminum pan. The samples were then heated from 20°C to 220°C at a linear heating rate of 10°C/min under an inert nitrogen atmosphere. The extrudates were also evaluated in a similar manner to assess the morphology of the API.

2.2.1.3. Moisture content: Moisture content was examined by measuring loss on drying (LOD) using a halogen moisture analyzer balance (MB45 moisture analyzer, Ohaus, USA). Each formulation was analyzed before and after extrusion. The percentage of moisture was estimated by drying five to eight grams of each mixture at 105°C for 15 min.

2.2.2. Non-Thermal Characterization Studies

2.2.2.1. Chromatography system and conditions: The drug content was determined on a Waters high-performance liquid chromatography (HPLC) system consisting of a Water 600 binary pump, Waters 2489 UV/detector, and Waters 717plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157). Empower 2 software was used to analyze the data. A Phenomenex Luna[®] C18 reverse phase column (5 µm 100 Å, 250 × 4.6 mm) was used as the stationary phase. The mobile phase was water, methanol, and acetic acid (34:65:1% v/v/v), and the UV detector was set at a wavelength of 285 nm. The flow rate was maintained at 1.0 mL/min, and 20 µL of each sample was injected. The uniformity of the drug content was assessed by dissolving a weighed quantity of the carbamazepine extrudate in methanol with subsequent analysis by the HPLC procedure outlined above. All studies were performed in triplicate. Samples from the dissolution studies (section 2.2.2.3) were filtered and 20 µL was injected for analysis by the same protocol.

2.2.2.2. Fourier transform infrared spectroscopy (FTIR) and Chemical imaging: Mid-infrared spectra from 4000–650 cm⁻¹ were collected on an FTIR (Agilent Technologies, Cary 660 & 620IR) apparatus equipped with a sampling accessory (MIRacle ATR, Pike Technologies), fitted with a single bounce diamond coated ZnSe internal reflection element. Chemical images were collected using an infrared microscope, which was equipped with a

Ge micro ATR. The spectra were analyzed using Agilent's software suite (Resolutions Pro Version 5.2.0).

2.2.2.3. *In-vitro* dissolution study: Extruded samples were accurately weighed (100 mg carbamazepine) and put into hydroxypropyl methylcellulose (HPMC) capsules. *In-vitro* release studies (n=3) were carried out at $37 \pm 0.5^\circ\text{C}$ using a Hanson SR8-plusTM dissolution test station (Chatsworth, CA) operated at 100 rpm paddle speed with 900 ml of distilled water as the dissolution medium (Alshahrani et al., 2015). Samples were collected at 10-, 20-, 30-, 45-, 60-, 90-, and 120-min intervals and were then filtered and analyzed using the HPLC method described in section 2.2.2.1.

2.2.2.4. Stability Study: Extruded samples were stored in a stability chamber at 40°C and 75% relative humidity (RH) for three months. Stability studies were then performed to test the crystalline content (using DSC), chemical stability (HPLC), and *in-vitro* release parameters. The drug release profiles were compared using a mathematical approach for two factors, a similarity factor (f_2) and a dissimilarity factor (f_1). Both can be calculated using the following equations:

$$f_1 = \left\{ \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right\} \bullet 100$$

$$f_2 = 50 \bullet \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \bullet 100$$

The dissolution profiles can be considered similar when the value of the similarity factor (f_2) is greater than 50 and the dissimilarity factor (f_1) is less than 15 (FDA, 1997).

2.2.2.5. Preparation of solid dispersions: The polymers Kollidon[®] 17 PF and KlucelTM ELF were sieved through a USP mesh screen (#35) and stored in an oven (40°C) overnight to remove any residual moisture. They were then blended with carbamazepine (Table I) using a twin shell V-blender (GlobePharma, Maxiblend[®]) at 25 rpm for 10 min. Each formulation was subsequently melt extruded using a co-rotating twin-screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific; Standard screw design configuration, Figure 1a) employing the same processing conditions for each polymer (temperature, screw speed, and feeding rate; Table I). In this study, the vent port, which was utilized, has an opening to the atmosphere to allow the gases to escape outside the extruder without using any vacuum device (Figure 1b). Thus this insert is designed in such a way that it has an opposite direction opening for gas release (75 mm) and at the same time it prevents the flow of melted material outside of the extruder,. Furthermore, it also helps to prevent any blockage of the opening itself. After processing, the extrudates were cooled to ambient temperature and stored in sealed glass vials for further investigation.

3. Results and Discussion

3.1. Thermogravimetric Analysis (TGA)

TGA studies were performed on the carbamazepine formulation with Kollidon[®] 17 PF and KlucelTM ELF physical mixtures. TGA thermograms showed that each formulation was thermally stable when heated from 20°C to 220°C , which was above the extrusion

temperature (Figure 2). This data indicated that the formulations would not undergo degradation at the temperatures employed during the extrusion process.

3.2. Differential Scanning Calorimetry (DSC)

DSC thermograms confirmed the presence of the amorphous form of carbamazepine in all the freshly extruded formulations. Figure 3 illustrates the lack of the thermal events associated with the melting of crystalline carbamazepine (193°C) and demonstrates that carbamazepine was completely miscible at drug loading used in each polymer. DSC data indicated that CBZ is miscible with Kollidon® 17 PF and Klucel™ ELF, which is in agreement with earlier literature (Bühler, 2008; Patterson et al., 2008; Vaka et al., 2014). Additionally, the DSC data shows that the degassing process had no effect on the morphology of carbamazepine.

3.3. Moisture content

The moisture content of each formulation was measured to evaluate the impact of the degassing step on the moisture content of the final product. Prior to extrusion, the moisture content of the Kollidon® 17 PF and Klucel™ ELF mixtures was approximately 7.64% and 3.45%, respectively. This relatively high moisture content demonstrates that overnight oven drying was ineffective in terms of removing residual moisture, and that this commonly employed, preparatory step is unnecessary. This proved to be especially true for highly hygroscopic polymers including Kollidon® 17 PF. Furthermore, the formulations containing Kollidon® 17 PF and Klucel™ ELF extruded without the degassing step had a moisture content of 6.21% and 3.32%, respectively, after extrusion. These results demonstrate that the extrusion process (without a vent port) can remove a small portion of the adsorbed moisture content either through the feeding hopper, the die or during the post process cooling. In contrast, when a vent port was included, the moisture content of the extrudates was decreased to a mere 0.73% (Table I) and progressively decreased as the vent port was moved further downstream (i.e. toward the die of the extruder). As shown in Table I, the moisture content significantly decreased for both polymers when the vent port was located at zone nine (Formulation A3 and D3). This could be attributed to the pressure differences inside the barrel at each location. In any screw extruder, after the feeding section the materials are moved inside the barrel by the rotation of the screw(s). As the molten materials move forward, the extruder increases the pressure and temperature which reach a maximum at the mixing zone(s) due to the intense shearing force in this section (Kohlgrüber, 2012). The higher temperature and pressure the molten materials experience as they are transported through the barrel increase the volatility of the moisture content and permit water and/or other volatile materials to be released. For this reason, locating the vent port after the last mixing zone (as for Formulation A3 and D3) will increase the efficiency of degassing more than if it was located at zone four or zone six (Figure 1a).

In this study, the vent port was inserted after the mixing zones where conveying elements begin. Conveying elements have a larger pitch than other elements, which determine the contact and surface area of the molten materials. Maximizing the surface area exposed to atmospheric pressure, and minimizing the internal volume, which kinetically entraps adsorbed moisture, promotes the release of more vapor from the molten materials.

Moreover, the higher pitch of the conveying elements translates into a higher free screw volume, which provides a greater opportunity for volatile materials to escape (Repka et al., 2013). For this reason, the conveying section after the mixing zone is the preferred location for insertion of the vent port. Furthermore, the pressure difference between mixing and conveying zones will facilitate the removal of any moisture or volatile substances, which can be easily evacuated through the vent port.

3.4. Drug Content

The uniformity of drug content was measured pre and post-extrusion to ensure uniformity of mixing, and to assess the chemical stability of carbamazepine. Each formulation was analyzed by HPLC for drug content. The average drug content ranged from 91.41 to 102.72 % (Table I). This indicates that carbamazepine was chemically stable with no trace of degradation or weight loss after extrusion in any of the tested formulations, and further confirms the TGA results. However, inclusion of a vent port did affect the uniformity of the drug content within each formulation. carbamazepine distribution was quantified between samples of each formulation using percent relative standard deviation (%RSD). A higher %RSD indicates a lower uniformity of drug content between the samples of the same formulation. From an analysis of the HPLC data, adding a vent port decreased the %RSD values for carbamazepine with Kollidon® 17 PF from 6.84 to 2.47. This difference indicates that the homogeneity of mixing inside the barrel was enhanced by the addition of the vent port. This improvement is due to a decrease in the moisture, or any other volatile substances, that may otherwise interfere with efficient mixing.

3.5. Chemical imaging

Only the Klucel™ ELF formulations were examined by chemical imaging since the Kollidon® 17 PF formulations were extremely brittle, which prevented the application of sufficient pressure for analysis. Figure 4 represents an infrared image of the carbonyl group present in the amorphous carbamazepine within the extrudates at wavenumber 1671. The photographs were taken at 5.5: μm spatial resolution in transmission mode with a total field of view (FOV) of 300×300 : μm . The false color images visually illustrate the location of carbamazepine within the extrudates as the color intensities are a function of the presence of a spectral band unique to carbamazepine in these formulations. The blue area indicates an absence of carbamazepine in that region, while red indicates relatively high carbamazepine concentrations. In Figure 4a, a large blue area indicates a lack of carbamazepine in that region, which translates to inhomogeneity. The images illustrate that adding a vent port resulted in an improvement in homogeneity, which was optimized by inserting the vent port at zone nine. Figures 4b, c, and d, illustrate differences in the distribution of carbamazepine as a function of the vent port location. During passage through the extruder, the temperature and pressure increase and the energy being transferred into the process materials also increases. As mentioned in section 3.3 (moisture content), inserting the vent port at zone 9 exhibited a lower moisture content. Thus, by reducing the moisture content (5–6 %) one can expect that this would impact the distribution of the CBZ within the molten polymer. Even though there was no mixing zone after zone 9, the conveying element still imparted adequate mixing (Patil et al., 2015). Therefore, the efficacy of degassing is related to the location of

the vent port. The results of the imaging were in agreement with the HPLC data, both of which confirm an improvement of mixing after adding the vent port.

3.6. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra (Figure 5) for pure carbamazepine demonstrated the characteristic peaks of crystalline carbamazepine form III at 3461 and 3154 cm^{-1} (Djuris et al., 2013). These peaks were also present, unchanged, in the physical mixtures of the formulations, which indicates that physical mixing did not result in inter-molecular interaction between carbamazepine and the polymers. However, these peaks disappeared in the FTIR spectra of the extruded formulations (Figure 5). This confirms that carbamazepine forms amorphous solid dispersions in the polymeric carrier. Degassing, however, did not affect the FTIR spectra further, indicating that degassing did not alter the chemical or physical state of the API.

3.7. *In-vitro* release studies

The results of the dissolution profiling varied among the tested formulations. Figure 6 shows that after degassing, the extruded formulations (A3 and D3) demonstrated faster drug release than the corresponding formulations (A0 and D0) without degassing. Drug release from the extruded matrices was found to vary substantially with the percentage of moisture as well as with the location of the vent port. However, the difference between the drug release profiles of the degassed and non-degassed formulations was significant for only the first 30 min of the study after which time they converged. For example, after 10 min, the percentage of drug release from formulations A0 (non-degassed) and A3 (degassed) were 8.48% and 54.1% respectively; however, after 90 min the values increased to 91.82% and 92.16% respectively. This may result from further mixing of the melt, which increases the dispersibility of carbamazepine in the polymeric carrier. As demonstrated above, degassing during processing enhanced the homogeneity of mixing and the resulting increased molecular dispersion will increase the wettability and solubilizing effect of the carrier. In the first few minutes of the test, the drug release is limited by the shell of the capsules, which then disintegrates so that the drug release becomes dependent on diffusion of carbamazepine from the surface of the capsule contents. The disintegration rate of the shell is common to all the formulations, but since degassing affects the distribution of carbamazepine, this could be expected to be reflected in variability of drug release. The standard deviation during the first 30 min was high for formulations A0 and D0, and reduced for A3 and D3. After this time, however, most of the contents of the capsule will be dispersed and all formulations would be predicted to exhibit similar dissolution rates. Another factor to consider is energy consumption that is energy applied in the form of temperature and shearing stress that can convert the crystalline form of carbamazepine into the amorphous form. This energy can also serve to mix and disperse the carbamazepine within the molten polymer. Molten materials with different levels of moisture content have different rheology and viscosity properties (Akdogan, 1996). In addition, the presence of moisture or other volatile substances such as monomers can interrupt the energy distribution and affect the mechanical properties of the product. Each material has its own heat capacity, which affects the heat distribution within the melt, including any adherent moisture and other volatile substances, which can partially absorb the energy and reduce the efficiency of solid dispersion. Differences in composition can therefore have an effect on the distribution of shear energy

and mix intensity. In this study, the morphological changes that were detected by DSC confirmed that carbamazepine was in the amorphous form in all the formulations. However, solid dispersions produced by HME can result in a variety of different forms including solid solutions, glass solutions or suspensions, and simple eutectic mixtures, as well as the amorphous form in a polymeric carrier. Most often, the resulting solid dispersion is a combination of a number of types (Ghebre-Selassie and Martin, 2003). Two different types of mixing can be applied using the mixing screw elements, distributive mixing and dispersive mixing. Distributive mixing aims mainly to distribute the carbamazepine throughout the molten polymer matrix while dispersive mixing results from the application of shear stresses on the extruded materials, which are sufficient to break any agglomerates down to a smaller particle (Gogos and Liu; Martin, 2008). Thus, degassing may enhance mixing which will affect the quality of solid dispersion and the subsequent homogeneity of processed materials.

3.8. Processing observations

In this study, the extrusion parameters were held constant for all formulations. Under constant parameters (feeding rate, temperature, screw speed) the main factor affecting the torque and the die pressure will be the movement of the materials (Baird and Collias, 2014). The software suite of the extruder recorded the changes in torque and die pressure, every five seconds. Screw torque can monitor by electric sensors on the motor and a pressure probe sensor was connected to the die to follow these during processing. The torque was recorded as a percentage (100% equals 24 Nm), and pressure was measured in bar (TM, 2006). It was reported that pressure and torque fluctuations change extrusion processing behavior (Abeykoon et al., 2011). In this study, different trends in torque and die pressure were observed. Monitoring the screw torque and extruder pressure demonstrated a correlation with the conveying, mixing, and melting of the extrudate. Understanding and adjusting the parameters involved in the process are necessary to improve the extrusion efficacy and achieve the desired quality in the product.

3.9. Torque

Torque is the amount of motor force required to move the material through an extruder (Goodrich and Porter, 1967). For most extruders, the torque applied is monitored during the process, and different parameter adjustments are applied based on this measurement. Unlike other industries, where a high torque is required to process hard materials such as ceramic powders, for pharmaceutical HME applications, a low torque is preferable to increase the free volume resulting in higher throughput and providing more intense mixing at lower extrusion temperatures (Repka et al., 2013). Analysis of the torque data showed that the average motor torque percentage changed as the location of the vent port moved. The torque averages for carbamazepine with Kollidon® 17 PF were 19.9, 25.5, 23.9 and 20.4% for A0, A1, A2, and A3 respectively. Location of the vent port at zone four (formulation A1) initially increased the torque which gradually decreased as the vent port was moved toward the die (Table I). This phenomenon is due to a combination of dilution and the plasticizing effect of adsorbed moisture, which has been reported to be associated with mechanical behavior changes that may affect the torque (Stubberud et al., 1996). Moisture may act as a diluent and decrease the total viscosity of the material inside the barrel resulting in an

increase in the flow rate of molten materials without increasing the torque (Cheremisinoff, 1993). This explains the decrease in torque when the vent location was changed from zone four to zone six. Formulation A1 showed a relatively higher torque than that shown by formulations A2 or A3, since the moisture was removed earlier during the process. Formulation A3 has the lowest torque value as the moisture was utilized as a plasticizer for a longer period than that during the processing of formulations A1 or A2. However, similar torque values were obtained, albeit with different standard deviations when comparing equivalent formulations without degassing (A0) and with degassing (A3). Degassing was able to reduce the fluctuations in the torque measurement even if the average values of A0 and A3 were very similar. Reducing the torque fluctuations will impact the die pressure and, consequently, the physicochemical properties of the final product (Köster and Thommes, 2010). Furthermore, the torque will affect the specific mechanical energy (SME) consumption, which is an important factor to consider for scaling up the process (Martin, 2008).

$$SME = \frac{\text{Consumed motor power}}{Q} = \frac{\tau \cdot N}{\tau_{\max} \cdot N_{\max}}$$

Where τ is torque (%), Q is the feeding rate in kg/h, and N is the screw speed (rpm).

Over the last ten years, HME has demonstrated relatively simple scalability, which is a considerable advantage with respect to the potential of the technology in pharmaceutical production. Process parameters play a significant role during scale up procedures and one of the most critical issues during the scale up process is torque limitation. For large scale production, the torque will affect several aspects including energy consumption, product quality, consistent flow, and maximum feeding rate (Kolter et al., 2012) and it is therefore critical to optimize this parameter. As already described, degassing represents an apparent advantage in terms of minimizing the variations in torque values as well as an overall control of torque during processing. The scale up of melt extrusion processes, however, is still challenging due to a limited insight into the process (Singhal et al., 2011). A recent survey of the literature revealed that no significant progress has yet been reported regarding the implications of degassing on pharmaceutical processing operations. A deeper understanding of the parameters affecting the process may be utilized to develop monitoring tools for quality management systems and, as such, can assist in the application of quality by design (QbD) principles.

3.10. Pressure

The second parameter analyzed in this study was die pressure which is the force exerted on the materials within the die, responsible for compression/densification as the molten material is forced through (Repka et al., 2013). Die pressure is dependent on the extruder temperature, screw speed, material properties, and feeding rate (Akdogan, 1996). In this study, the addition of the vent port had no significant effect on the absolute value of die pressure. However, pressure fluctuations dramatically decreased and a relatively constant value for die pressure was maintained after adding the vent port (Table I), which is

indicative of process stability and a steady state. The die plays an essential role in forming and shaping the extrudate, as well as in determining the physical appearance of the final product (Stevens and Covas, 1995). The last zone of the extruder (just prior to the die) is responsible for moving the materials to the die and is the site of maximum backpressure. If the pressure is constant, the movement of the in-process materials will be more uniform, which will be reflected in the shape of the product and an overall uniformity in physical appearance.

A constant pressure and torque are also necessary for effective and homogeneous mixing. Also, Minimizing fluctuations in pressure is beneficial for in-line quality prediction tools as shown in a recent study, where the researchers used NMR as a prediction tool, following the influence of die pressure on in-line Raman spectroscopy monitoring of the solid state of the final product (Saerens et al., 2011). Different die pressures affected the quality of the NMR results with lower variations in die pressure associated with improved output, which will facilitate QbD studies. Larger extruders have larger screw diameters and, thus, an increased volume inside the barrel. As a result, it is expected that with larger extruders (relative to the 16 mm used in this study) the effects of degassing will be more pronounced as there is more moisture retaining material in process per unit time and proportionally more internal volume within the polymer melt to trap any volatile materials. After degassing, more of the total energy applied to the system, including barrel temperature, will be imparted to the constituents of interest, namely the API and carrier. Thus, degassing should effectively enhance the output while potentially decreasing the cost of production through enhanced energy utilization.

3.11. Shape

Figure 7 illustrates the difference in appearance between extrudates formed with or without degassing. The decrease in moisture content was associated with an improved physical appearance of the extrudates. Extrudates that were produced without a vent port appeared visually obstructed with irregularities on both the surface and the interior. In contrast, the degassed extrudates appeared clear and consistent with few abnormalities; however, it should be noted that this was partially because of the location of the vent port. The physical appearance and hardness were altered by the addition of the vent port. Formulation A0 could be described as brittle and irregular, while formulation A3 was hard, clear and consistent, bearing no trace of entrapped gas pockets. The appearance of gas pockets within an extruded material is due to the moisture flash-off, which occurs after the material leaves the pressurized die and is exposed to a sudden decrease in pressure (Akdogan, 1996). This flash-off occurs very rapidly, and can be detrimental to the shape of the final product. In the last zone of the extruder, there are discharging elements with single flight geometry, designed to push the material into the die, ensure a uniform delivery rate through the die cavity, and to generate the required extrusion pressure. It is important that the extruder screw at this zone should be filled with molten materials to maintain a constant shape and uniform product production, and to prevent foaming of the extrudates or inclusion of air bubbles which are primarily the result of moisture and/or air entrapment in the feeder zone (Stevens and Covas, 1995). The presence of any volatile materials can alter the pressure and the free volume at the discharging zone, which may subsequently affect the uniformity and the shape of the

product. Constant pressure, resulting from the absence of entrapped gasses, should facilitate the extrusion of a product with uniform appearance from the discharging elements. After degassing, the extrudates became uniform and consistent in shape than the extrudates without degassing (Figure 7). Additionally, the appearance of gas bubbles in the extrudates decreased in the formulation A3, with a corresponding reduction in the moisture content.

3.12. Stability Study

After three months of storage at 40°C and 75% RH, the *in vitro* release was compared to freshly produced extrudates. The release profiles of carbamazepine varied between the formulations, with a general trend to a decrease in the release over time. This was particularly noticeable in the formulations processed without degassing, and with a dependency on the location of the vent port at the time of processing. The similarity factor for each formulation increased as the vent port was moved from zone 4 to zone 9, with the opposite true for the dissimilarity factor (Table II). These differences are attributed to the percentage of moisture content in each formulation, which as discussed previously, is dependent on the location of the vent port. Moisture is a prime enabler of re-crystallization processes for most thermodynamically unstable solid dispersion systems although intense mixing could help retard any nucleation and crystal growth of carbamazepine polymorphs from the amorphous phase. Moreover, as previously indicated, degassing improved the uniformity of mixing which was also enhanced by removing air, moisture and other volatile substances. Inserting the vent port at zone nine permits the utilization of entrapped moisture as a plasticizer but then facilitates its removal just prior to the material exiting the die, thereby effectively utilizing the advantages of entrapped moisture and then subsequent purging the system of entrapped gas before deleterious effects can be imparted to the extruded material.

4. Conclusion

The novel findings of this study lead to the recommendation that proper degassing, placing at least one vent port after the last mixing zone (wherever applicable) should be a part of many hot melt extrusion processes. Degassing can enhance the properties of the final product by removing residual moisture, volatile substances and subsequent air bubbles, thereby facilitating the production of consistent, smooth uniform extrudates. Additionally, venting of entrapped gasses will reduce the torque and pressure variations, and have a positive impact on the homogeneity and efficiency of the process. The consideration of the devolatilization process and its influence is of particular significance during scaling up of the process. The degassing process should be evaluated on a case by case basis, dependent primarily on the nature of the properties (i.e. low molecular weight polymers, solvent usage, volatile materials, hygroscopic materials, etc.) of the materials (API, stabilizers, antioxidant, plasticizers, pigments and other additive) being utilized.

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a) Schematic representation of screw design configuration of 16-mm extruder and b) Vent port.

Figure 2.
TGA data for pre-extrusion for different polymers and pure carbamazepine.

Figure 3.
DSC data for pure carbamazepine and all the extruded formulations.

Figure 4.

a) Chemical image (5.5: m spatial resolution) of non-degassed formulation (extrudates A0) highlighting the intensity of the carbonyl present in amorphous carbamazepine. b) Chemical image (5.5: m spatial resolution) of formulation degassed at zone four (extrudate A1) highlighting the intensity of the carbonyl present in amorphous carbamazepine. c) Chemical image (5.5: m spatial resolution) of formulation degassed at zone six (extrudate A2) highlighting the intensity of the carbonyl present in amorphous carbamazepine. d) Chemical image (5.5: m spatial resolution) of formulation degassed at zone nine (extrudate A3) highlighting the intensity of the carbonyl present in amorphous carbamazepine.

Figure 5.

FTIR spectra a) pure carbamazepine, b) physical mixture of carbamazepine:Kollidon[®] 17 PF (25:75), c) physical mixture of carbamazepine:Klucel[™] ELF (25:75), d) extrudates of carbamazepine:Kollidon[®] 17 PF (25:75), e) extrudates of carbamazepine:Klucel[™] ELF (25:75).

Figure 6.

a) *In vitro* release profiles of pure carbamazepine, degassed and non-degassed Kollidon® 17 PF formulation extrudates. b) *In vitro* release profiles of pure carbamazepine, degassed and non-degassed Klucel™ ELF formulation extrudates.

Figure 7.
Optical microscope photographs of fresh extrudates of Kollidon® 17 PF with carbamazepine.

Table I

Formulation processing conditions.

Formulation	Polymer	carbamazepine % (w/w)	Polymer % (w/w)	Vent port	Torque%	Pressure (Bar)	Moisture Content %	Drug Content %	Screw speed (rpm)	Temperature (°C)
A0	Kollidon® 17 PF	25	75	None	19.89 (7.48)	2.35 (2.31)	6.21 (1.28)	91.79 (6.84)	100	145
A1	Kollidon® 17 PF	25	75	Zone 4	25.52 (6.02)	2.47 (0.03)	2.48 (0.74)	94.84 (4.99)	100	145
A2	Kollidon® 17 PF	25	75	Zone 6	23.91 (2.69)	2.52 (0.00)	1.02 (0.84)	99.38 (3.65)	100	145
A3	Kollidon® 17 PF	25	75	Zone 9	20.40 (1.38)	2.01 (0.00)	0.73 (0.21)	102.72 (2.47)	100	145
A-PM	Kollidon® 17 PF	25	75	NA	NA	NA	7.64 (0.92)	101.31 (2.61)	NA	NA
D0	KluceI™ ELF	25	75	None	46.61 (4.22)	2 (0)	3.32 (2.4)	91.41 (1.9)	100	140
D1	KluceI™ ELF	25	75	Zone 4	73.59 (2.30)	2 (0)	2.71 (2.08)	93.14 (1.51)	100	140
D2	KluceI™ ELF	25	75	Zone 6	73.76 (1.67)	2 (0)	2.34 (1.29)	95.41 (1.44)	100	140
D3	KluceI™ ELF	25	75	Zone 9	55.95 (1.56)	2 (0)	1.8 (0.89)	99.05 (1.12)	100	140
D-PM	KluceI™ ELF	25	75	NA	NA	NA	3.45 (0.77)	99.64 (1.72)	NA	NA

Parentheses represent relative standard deviation, PM- physical mixture.

Table II

Stability study data for all the formulations after three months.

Formulation	Similarity factor f_2	Dissimilarity factor f_1
A0-3M	36.50	22.90
A1-3M	45.95	13.62
A2-3M	71.67	3.93
A3-3M	68.24	4.17
D0-3M	50.36	16.03
D1-3M	53.64	12.80
D2-3M	66.82	5.97
D3-3M	66.47	6.38