The impact of the hot-melt extrusion process on polymer choice of Glyburide solid dispersions: The effect of wettability and dissolution

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Highlights

Abstract

Keywords: solid dispersion; glibenclamide; hot-melt extrusion; Soluplus®; Kollidon® VA64: PVP VA64

Abbreviations: GLY, glibenclamide or glyburide; DSC, differential scanning calorimetry; XRPD, x-ray powder diffraction; API, active pharmaceutical ingredient; BCS, biopharmaceutical classification system; SOL, Soluplus®; XμT, x-ray microtomography; FASSIF, fasted simulated intestinal fluid; ASD, amorphous solid dispersions; Kollidon® VA 64, polyvinylpyrrolidone-vinyl acetate copolymer; DE, dissolution efficiency; MDT, mean dissolution time;

Introduction:

The utilising of innovative combinatorial chemistry and high-throughput screening tools in drug discovery has led to more active pharmaceutical ingredients with poorly soluble properties reaching clinical stages of drug development processes. It is estimated that two out of five pharmaceutical compounds in the US market are considered poorly soluble (Fahr & Liu, 2007). Poorly soluble drugs are very challenging during pharmaceutical development as solubility, and further dissolution tends to be the rate-limiting step for these compounds entering the systemic circulations and giving the desired therapeutic response (Conway and Asare-Addo, 2016). To overcome this issue, several techniques are used. These techniques can be classified into three main categories (Savjani, Gajjar, & Savjani, 2012) : I: physical modification such as particle size reduction or crystal habit (polymorphs and amorphous forms) II: Chemical modification such as salt formation. III: Miscellaneous techniques such as supercritical fluids,

use of buffers or novel excipients (Asare-Addo et al., 2018; Adebisi et al., 2016; Adebisi et al., 2016; Al-Hamidi et al., 2014, 2013, 2010a, 2010b; Asare-Addo et al., 2015; Nokhodchi et al., 2017, 2015, 2005; Rabinow, 2004; Stahl et al., 2008; He at al., 2017; Ramirez et al., 2017; Šupuk et al., 2013).

Each technique has its drawbacks. For example, the enhancement of solubility of a neutral, weakly acidic or weakly basic drug using salt formation cannot always be feasible. Furthermore, the size reduction technique can also be limited to the extent of reduction as generating very fine particles can pose safety issues during handling (Serajuddin, 1999). One of the attractive routes to overcoming these problems is by manufacturing amorphous solid dispersions (ASD). ASD systems are composed of amorphous drug stabilised by the presence of a polymer (Newman, Nagapudi, & Wenslow, 2015). Solid dispersions can be classified into three main categories: first generation solid dispersions where an amorphous drug is dispersed in a crystalline carrier, second generation where an amorphous carrier such as polymers is used and third generation solid dispersions where the polymer used has self-emulsifying properties to maximise the solubility of the amorphous drug (Vasconcelos, Sarmento, & Costa, 2007). Solid dispersions can be manufactured by either solvent evaporation techniques or melting methods. In the solvent evaporation technique the drug and polymer are dissolved in a solvent followed by the evaporation of the solvent using spray drying (Paudel, Worku, Meeus, Guns, & Van den Mooter, 2013) or freeze drying methods (G. V. Betageri & Makarla, 1995). Melting methods especially hot-melt have many advantages including scalability, being a solvent and dust free method and has industrial applicability. The drug-polymer is blended then fed using a designated hopper to a heated barrel with a twin screw. The formulation is then mixed in the liquid state and moved toward a die that shapes the melts. The physical properties and ultimately the performance of filaments can be controlled by either changing either processing

parameters such as temperature, speed or twin-screw configuration or using different polymers (Van den Mooter, 2012).

Polyethyleneglycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer (PEG6000/vinylcaprolactam/vinyl acetate copolymer, Soluplus®, BASF, Germany) is a promising polymer that has attracted a lot of attention over the last decade. Soluplus® possesses the advantages of improving both the process (Djuris, Nikolakakis, Ibric, Djuric, & Kachrimanis, 2013) and the dissolution rate of poorly soluble drugs (Nagy et al., 2012). The addition of PEG 6000 and the low glass transition temperature enhances the processability and eliminates the addition of a plasticiser. Soluplus® also improves the dissolution rates of poorly soluble drugs by forming a solid solution with the drug. Furthermore, the polymer is considered as a safe excipient and easy to handle with good flowability properties (Djuris et al., 2013; Nagy et al., 2012). Another polymer that is frequently used in the hot-melt extrusion (HME) process is Kollidon® VA 64 (polyvinylpyrrolidone-vinyl acetate copolymer). It has demonstrated the ability to enhance the dissolution rate of poorly soluble drugs (Ponnammal et al., 2018). Kollidon VA 64 works by solubilising poorly soluble drug and ultimately improve the dissolution rate. An enhancement in mechanical properties and the production of flexible extruded filaments has been reported for the use of Kollidon® VA64 (Solanki, Tahsin, Shah, & Serajuddin, 2018).

Glyburide (Gly) used as a model drug, is an example of a poorly soluble weak acid drug with an estimated pKa of 5.3 (Figure 1) (Löbenberg, Krämer, Shah, Amidon, & Dressman, 2000). The acidic properties of the drug and the value of pKa suggest that the drug will be favourably absorbed in the upper intestine. Wei et al. studied the solubility of Gly in biorelevant dissolution media. The study showed that the solubility of Gly in biorelevant media increased as pH increased, with FASSIF media at pH 7.4 having the highest solubility (Wei & Löbenberg,

2006). The objectives of this research was to prepare and characterise solid dispersion of Gly using Soluplus® and Kollidon® VA 64 at two different polymer levels. It was therefore the aim of the authors to characterise the surface of the filaments using a focus variation instrument and to determine the effect polymer type and polymer level on wettability. The authors also aim to investigate a correlation of the wettability of the solid dispersions (polymer level and type) to the performance of dissolution as to the best of our knowledge, there are no research articles that have studied this.

2. Materials and Methods

2.1. Materials

Poly (N-vinyl caprolactam)–poly (vinyl acetate)–poly (ethylene glycol) (57:30:13), under the trade name Soluplus® and vinylpyrrolidone-vinyl acetate copolymers branded as Kollidon® VA 64 were kind gifts from BASF (Germany). Gly was purchased from Kemprotec (Cumbria, U.K.). FASSIF (fasted simulated intestinal fluid) powder was purchased from Biorelevant Ltd (Surrey, United Kingdom). Monobasic potassium phosphate, sodium hydroxide, ammonium acetate, acetic acid and acetonitrile were all purchased from Sigma Aldrich, UK. All materials were of analytical grade and used as obtained.

2.2. Preparation of hot-melt extruded solid dispersions:

A 16 mm twin screw extruder (Pharmalab, Thermo Scientific, UK) was used to carry out the extrusion work. Gly and either Kollidon VA 64 or Soluplus® at two different ratios (1:1 and 1:2) were mixed using a T2F Turbula Blender System (Willy A Bachofen AG) for 10 min in order to ensure uniformity of powder mixing. Each powder mixture was then extruded using the hot-melt extruder. A maximum barrel temperature of 175 ^{o}C was used to ensure that the Gly was completely melted (melting point of Gly is 175 ^{o}C) (G. V. Betageri & Makarla, 1996).

The produced filaments were separated into two sub samples: the first samples were characterised as received from the HME process using an SEM and x-ray microtomography (XμT) to get an insight into the microstructure and its potential impact on dissolution. The second sample was further milled and sieved to 250 μm undersize (to ensure the same size fractions were used) for all the samples and characterised using DSC and XRPD to check the changes in the crystallinity of Gly. The latter samples were used in the dissolution testing and labelled as samples A-D (Sample A is 1:1 Gly: Sol, Sample B is 1:2 Gly: Sol, Sample C is 1:1 Gly: Kollidon VA 64 and Sample D is 1:2 Gly: Kollidon VA 64) and their corresponding physical mixtures labelled as samples PMA-PMD (Table 1).

2.2.2 Content uniformity of Gly in milled and sieved samples

50 mg of the milled and sieved samples A-D were dissolved each in acetonitrile and assayed to determine the Gly content using the HPLC method as explained in section 2.6.2. The results from the assay were further used to determine the amount of powder needed to fill the gelatine capsules to be ensure the same amount of Gly was present in each capsule.

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2.3. Solid State characterisation:

2.3.1. Scanning electron microscopy (SEM) and Image analysis using a focus variation instrument

A scanning electron microscope (Jeol JSM-6060CV SEM) operating at 10 kV was used to generate electron micrographs images. Filaments (Samples A-D) were cross-sectioned and mounted onto a metal stub using a double-sided adhesive tape. Samples were then sputter-coated with palladium for 60 s using a Quorum SC7620. Micrographs with different

magnifications were further taken to aid an understanding of the polymers and the ratios used impact on the filaments produced.

A focus variation instrument (Contour LS 3D Optical Profiler (Bruker)) was used to assess the surface topography of the filaments using 10 x objective and 2.9 μm lateral resolution. The obtained images were further analysed using the Surfstand™ software (Taylor Hobson, UK, and University of Huddersfield, UK) to obtain 2D and 3D profiles of the surfaces (Ward et al., 2017).

2.3.2. Differential scanning calorimetry (DSC)

Thermal studies for the milled samples and their corresponding physical mixture were investigated using the software obtained from Mettler-Toledo, Switzerland. 3-6 mg of milled and seived samples (Samples A-D) or its physical mixture (Samples PMA-PMD) was placed in a standard aluminium pan with a vented lid and sealed. The crimped pans were heated from 20 to 250 °C at a scanning rate of 10 °C/min using nitrogen gas as a purge gas in a DSC (Mettler-Toledo, Switzerland).

2.3.3. X-ray powder diffraction (XRPD)

Gly, the milled and sieved powder (Samples A-D) and their corresponding physical mixtures (Samples PMA-PMD) were scanned using Bragg–Brentano geometry, over a scattering (Bragg, 2θ) angle range from 5 to 100°, in 0.02° steps at 1.5° min−1 using a D2 Phaser diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) (Laity et al., 2015). The XRPD signals were further analysed using Microsoft Excel.

2.4. X-ray microtomography (XμT)

Filaments (as obtained from section 2.2) were imaged by XμT, (Nikon XT H 225, Nikon Corp. Tokyo, Japan), using a tungsten target, with 75 kV accelerating voltage and 250 μA gun current using a copper filter (thickness 0.125 mm). Filaments were mounted using a double-adhesive tape. A set of ……projections were collected, with …… frames per projection and …..ms exposure per frame, giving a total time of roughly 120 min for the complete XμT acquisition. The set of projection images was reconstructed using CT-Pro, then examined using VG Studio 2.1 software.

2.5. Dynamic contact angle measurement: (Daniel to add)

Initial studies in water before FASSIF. This was set up as in Figure 2

2.6. Dissolution analysis

2.6.1 Media preparation:

Biorelevant dissolution media was prepared by dissolving 2.24 g of FASSIF powder for each 1L of phosphate buffer (pH=7.4). The biorelevant dissolution media was further left under stirring conditions for 2 h. The phosphate buffer was prepared using monobasic potassium phosphate and sodium hydroxide according to the USP pharmacopoeia (Wei & Obenberg, 2006).

2.6.1. Dissolution of the Gly solid dispersions:

A USP I (basket method) dissolution apparatus was used for the dissolution testing. 900 mL of dissolution media was filled in a 1L dissolution vessel. The media was heated to 37 ± 0.5 °C. The physical mixtures (PMA-PMD) as well as the milled and sieved powder samples (samples A-D) containing an equivalent of 20 mg content of Gly (based on their content uniformity) were weighed and then used to fill a size 3 gelatine capsule before being transferred to the

basket. A rotation speed of 100 rpm was used. The dissolution study was conducted for 2 h. 10 mL of the dissolution media was withdrawn and filtered at the 1, 5, 10, 20, 30, 45, 60, 90 and 120 min time points for HPLC analysis of Gly content. A preheated biorelevant media was used to replace the 10 mL media taken out after each time point to ensure the constant 900 mL volume. All dissolution studies were conducted in triplicates.

2.6.2. HPLC analysis:

A Shimadzu HPLC system equipped with a C18 column (250 mm x 4.6 mm ID, 4µm, Phenomenex) was used for the Gly analysis. An Isocratic elusion type with a mobile phase of ammonium acetate and acetonitrile (45:55) was used at a flow rate of 1 mL/min. A UV-Vis detector was utilised, and the absorption peak for Gly was investigated at a maximum wavelength of 254 nm. The retention time for Gly was around 2.8 min (USP)

2.6.3. Dissolution parameters

Mean dissolution time (MDT) (Equation 1), defined as the mean time for the drug to dissolve under *in-vitro* dissolution conditions, is a model-independent method and is suitable for dosage forms that have different mechanisms of drug release (Nep et al., 2017; Kaialy et al., 2016; Al-Hamidi et al., 2013; 2014; Mu et al., 2003; Khan, 1975). The dissolution efficiency (DE) (Equation 2), which is the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of a rectangle described by 100% dissolution in the same time *t* (Khan, 1975; Asare-Addo et al., 2015) was also calculated.

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (1)$$

Where j is the sample number, n is the number of dissolution sample times, t_j is the time at midpoint between t_j and t_{j-1} and ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1}.

$$DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \qquad (2)$$

where, y is the drug percent dissolved at time t.

3. RESULTS AND DISCUSSION

3.1. Solid-state analysis:

The thermal analysis of Gly, the milled and sieved products (Samples A-D) and their corresponding physical mixtures (Samples PMA-PMD) are depicted in figure 3. DSC showed Gly to have a sharp melting point of 175 °C confirming its crystallinity. This was similar to the work published by Cirri et al. (Cirri, Maestrelli, Furlanetto, & Mura, 2004) who reported Gly to have a sharp melting point at around 175 ± 0.4 °C. The physical mixtures of Gly with both Soluplus® and Kollidon® VA 64 showed a similar peak at the melting point of Gly but with less intensity. It was also interesting to note that an increase in the polymer content brought about a general further reduction in the melting point of Gly. The physical mixture of Gly with Kollidon® VA 64 showed another peak at around 60 °C. This corresponds to the melting point of PEG4000 which added to the formulations as a plasticiser (reference the handbook of pharmaceutical excipients). The resultant extruded products of Gly: Soluplus® and Gly: Kollidon® VA 64 at the two drug loading levels used showed no obvious melting point peak for Gly thereby suggesting that Gly had been molecularly dispersed within the polymers used (Figure 3). XRPD confirmed Gly to be completely crystalline in the pure form (Figure 4). Upon inclusion with Soluplus® or Kollidon® VA 64, there was a significant reduction in the crystallinity of Gly. It was observed that an increase in the polymer content brought about a

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decrease in the crystallinity of Gly. The XRD data for the HME samples A-D proved interesting also (Figure 4). It showed sample A-D was not fully amorphous as suggested from the DSC data. Samples A and B however were observed to be more amorphous that C and D suggesting that with the process parameters used for the HME processing, Soluplus® had the greater ability in converting crystalline Gly to its amorphous form which may potentially have implications for dissolution testing.

3.2. SEM and focus variation analysis:

SEM images of both the drug, a cross-section of the HME filaments, the physical mixtures as well as the milled and sieved fractions of the HME filaments are shown in figure 5. Gly is crystalline in nature with irregularly shaped particles (Wei, Dalton, Di Maso, Kanfer, & Löbenberg, 2008). The microstructure of these filaments were different with different porosities observed (further analysed using XμT). Upon magnification, some of the crystalline drug could be seen on the surfaces of some extrudates (highlighted by yellow dashed circles) confirming the XRD analysis that Gly had not been fully molecularly dispersed into the polymers used (Figure 5). This was however less evident on the samples with increased polymer content (Samples B and D). The images produced from the focus variation instrument showed that Soluplus® (Sdr =XX) inferred a smoother surface on the formulation as compared to the Kollidon® VA 64 (Sdr =XX) (Figure 6). An increase in the polymer content also showed….(Figure 6). These may well give an insight as to how these materials wet and may an implication on the dissolution behaviour of these samples.

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3.4. X-ray microtomography:

The reconstructed diametral cross-sectional images obtained by XμT examination of filaments indicated differences in the microstructure of these filaments as confirmed by SEM (Figure 7). This method relays on the differences of density distribution absorbance of x-rays between

different materials (Stock, 1999, Baruchel et al., 2000). Sample A (1:1 Gly:Sol) showed a higher porosity compared to sample B (1:2 Gly:Sol) suggesting that an increase in the Soluplus® content brought about a decrease in the porosity (converted as a percentage) of the filaments produced (63.72 % and 57.41 %) respectively. This was true also for Samples C (1:1 Gly:PVP VA 64) and D (1:2 Gly:PVP VA 64). The porosity values for samples C and D were 19.47 % and 14.22 % respectively suggesting also that an increase in polymer content decreases the porosity of filaments produced. The porosity of all the samples were thus in the A > B > C > D order. These results suggest that the PVP VA 64 makes denser filaments which may well have dissolution consequences.

extrudate of 1:1 Gly:PVP VA 64 (Sample C) formulation and (D) HME extrudate of 1:2 Gly:PVP VA 64 (Sample D).

3.5 Contact angle measurement:

Contact angle measurements performed using deionised water initially showed Sample A (1:1 Gly:Sol) to have the highest contact angle (90.65 ± 7.06 °). This was followed closely by sample B (1:2 Gly:Sol) with a contact angle of 84.41 ± 2.60 °. Sample C had the lowest contact angle measurement (33.72 ± 1.24 °) followed by Sample D with an angle of 41.11 ± 2.33° (Figure 8). This suggested samples C and D to be significantly more hydrophilic than samples A and B. Contact angle measurements for the samples using FASSIF proved surprising and interesting. The contact angles for sample A (1:1 Gly:Sol) and B (1:2 Gly:Sol) could not be obtained as the droplet absorbed very quickly (within a few seconds). As such, the elapsed time for the droplet to be absorbed for these samples were taken into consideration. The mean time for sample A to be absorbed was 1.6648 ± 0.50294 s whereas the mean time for sample B to be absorbed was 0.16463 ± 0.05104 s. This indicates that sample B wets better than sample A.

This was in direct contrast to the results from deionised water suggesting that the presence of the various ions in the FASSIF media may have had a solubilising effect on the samples with an increase in polymer content having a greater effect. Samples C (1:1 Gly:PVP VA 64) and D (1:2 Gly:PVP VA 64) however had a lower absorption rate compared to samples A and B therefore the dynamic contact angle (Figure 9) was calculated. The figure suggests the initial contact angles for samples C and D to be similar however, it can be observed that sample D wets better than sample C over time. This was also similar to the trend observed for the samples A and B where and an increase in polymer content seemed to drive more media ingress. In summary, the order of wetting for samples was: B > A > D > C. This change in contact angle order in comparison with deionised water may have implications again for dissolution testing and as such consideration should be made with regards to making appropriate predictions for dissolution based on the media for contact angle testing.

3.4. Dissolution analysis:

Results of dissolution testing for capsules filled with the milled and sieved powders is presented in figure 10. The physical mixtures displayed dissolution profiles similar to that of the pure crystalline drug whereas the HME samples displayed dissolution profiles superior to that of the crystalline drug and the physical mixtures. It was also observed from the dissolution profiles that samples containing Soluplus® displayed higher dissolution rates in comparison with samples that contain Kollidon® VA 64. Furthermore, sample B which contained (1:2 Gly: Sol) showed a higher dissolution rate in comparison to sample A (1:1 Gly: Sol). This indicates that increasing the level of polymer content increased the dissolution of Gly. A similar trend was observed with sample C and D, with sample D (1:2 Gly: Kollidon® VA 64) showing a higher dissolution rate in comparison to sample C (1:1 Gly: Kollidon® VA 64). This was confirmed by the MDT, MDR and DE values which showed that sample A had MDT=55.40 min,

MDR=0.57 and DE=36.43 while sample B showed a MDT=29.70 min, MDR=1.03 and DE=60.53. Sample C showed a values of MDT=66.28 min, MDR=0.15 and DE=10.17. While sample D showed a values of MDT=65.30 min, MDR=0.22 and DE=14.44. It was interesting to note that the dissolution results married or correlated with the wetting results from the contact angle measurement using the FASSIF media.

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4. CONCLUSIONS

5. ACKNOWLEDGEMENTS

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