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Continuous Manufacture of Hydroxychloroquine Sulfate Drug Products via Hot Melt Extrusion Technology to Meet Increased Demand During a Global Pandemic: From Bench to Pilot Scale

Suha M. Dadou^{1,2}, Valentyn Mohylyuk^{1,2}, Shu Li^{1,2}, David S. Jones¹, Pascal Boulet³, Lionel Aranda³, Sinan Karaboga⁴, Michel Souchet⁴, Stéphane Gégout⁴, Brian Murray⁵, Andrew Walker⁵, Christopher McConville⁶, Victoire de Margerie³, Gavin P. Andrews^{1,2}

¹ Pharmaceutical Engineering Group, School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, United Kingdom

² China Medical University - Queen's University Belfast joint College (CQC), No.77 Puhe Road, Shenyang North New Area, Shenyang, Liaoning Province, P.R. China

³ Institut Jean Lamour, UMR 7198 CNRS-Université de Lorraine, 2 Allée André Guinier, 54000 Nancy, France

⁴ Harmonic Pharma, Campus Artem, Nancy, France

⁵ Rondol Industrie, 2 Allée André Guinier, 54000 Nancy, France

⁶ School of Pharmacy, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, B15 2TT.

Abstract

During pandemics and global crises, drug shortages become critical as a result of increased demand, shortages in personnel and lockdown restrictions that disrupt the supply chain. The pharmaceutical industry is therefore moving towards continuous manufacturing instead of conventional technologies that involve numerous steps usually occurring at different sites. In order to validate large-scale commercial manufacturing, feasibility studies need to be performed first, using small-scale laboratory equipment. To that end, the scale-up of a continuous process and its effect on the quality of the end product were investigated in this work. Hydroxychloroquine Sulphate (HCQS) was used as the model drug, Soluplus® as a model polymeric carrier and Rondol machines as the extruders. Seven formulations were processed using a small scale horizontal extruder and a large-scale vertical extruder at various temperatures and speeds. On the horizontal extruder, low drug loading and high barrel temperatures were the main factors affecting the solid-state of HCQS. Similar trends were achieved upon scale-up using the vertical extruder. However, the extrusion process becomes less sensitive with less variability observed as a function of variation in content and drug dissolution. Furthermore increasing the screw speed of the vertical extruder had a greater impact on the loss of crystallinity compared to the horizontal extruder. Overall this paper demonstrates that scale up is feasible from an horizontal 10 mm L/D 20 to a Vertical All in One 10 mm L/D 40 which will allow for a significant saving of materials (especially APIs) during the formulation and process development stages. Furthermore, this study demonstrates that the vertical extruder provides a more robust manufacturing process compared with the horizontal extruder as neither the temperature profile of the barrel nor the screw speed significantly impacted the dissolution rate of the HCQS. This should be of great advantage to the pharmaceutical industry as production rate could be increased or decreased as needed, through an increase or decrease of the screw speed, with minimum and/or no impact on the

critical quality attributes of the final product and thus no need for additional bioequivalence studies.

Introduction

In December 2019, a novel strain of the family of coronavirus was discovered; COVID-19. Subsequently, COVID-19 was announced as a global pandemic by the World Health Organization (WHO) and the impact has been catastrophic. (World Health Organization, 2020). Strict measures were imposed by the majority of governments with the aim of controlling the spread of the virus and adjusting/preparing healthcare systems to cope with the challenges of this novel virus. These measures included national lockdowns, granting permission for work to essential services only and closure of national borders. Many sectors have been affected by the measures that were implemented causing economic disruption and recession. Due to the restrictions placed on international trading channels, the pharmaceutical industry and drug supply chain were of particularly high risk with significant potential to cause global drug shortages (Rowan and Laffey, 2020).

The United States Food and Drug Administration (FDA) defines drug shortages as ‘The period of time when the demand exceeds the supply of the drug’ (FDA, 2020). Different reasons can cause drug shortages including insufficient quantities of raw materials, drug discontinuation from the market, and issues related to legislation, manufacturing, or procurement (Badreldin and Atallah, 2020). During these unprecedented times, drug shortages may have a critical impact on patient care causing medication errors, compromised medical procedures, and the requirement to replace first-line therapies with alternative medications, which may not necessarily be as efficacious (Badreldin and Atallah, 2020). This necessitates the need to search for innovative and sustainable solutions that can tackle drug shortages during pandemics and other global crises. One such example is Hydroxychloroquine Sulphate (HCQS) which is used to treat lupus erythematosus, rheumatoid arthritis and for uncomplicated malaria. There were over 5.5 million

prescriptions of HCQS in 2017 in the US alone (ClinCal.com), with predictions that the global demand for HCQ could have increased 10-fold from 542.36 million USD in 2019 to 5,549.65 million USD by 2027 if it had of been used as a treatment for COVID19 (Globe News Wire). Furthermore, a study demonstrated that patients with rheumatic diseases across Africa, Southeast Asia, the Americas and Europe had trouble filling their prescriptions of antimalarial drugs, including HCQS, during the 2020 global coronavirus pandemic, when antimalarial drugs were touted as a possible COVID19 treatment. Patients who could not access their antimalarial drugs faced worse physical and mental health outcomes as a result (American College of Rheumatology). This demonstrates the need for a continuous, single unit manufacturing process that can allow for the flexible increase in the production of pharmaceutical dosage forms, at a single manufacturing site, during a global pandemic to ensure the supply of essential medicines is not disrupted.

HCQ base has a predicted partition coefficient (LogP) of between 2.89 and 3.87, with a water solubility of 0.0261 mg/mL, making it a Biopharmaceutical Classification System (BCS) II drug i.e. highly permeable, but poorly soluble. However, the sulphate salt form has excellent solubility with a bioavailability of 74% (USP Monograph for Plaquenil®). A reduction in the crystallinity of the HCQS could improve its bioavailability (Schittny et al., 2020), meaning that a lower dose of HCQ could potentially be required, which would also help to ensure the supply of HCQS during a global pandemic. Furthermore, continuous manufacturing at a single site and a reduction in the required dose of HCQS would make these treatments cheaper, which would be of particular benefit to low-middle income countries, especially those where malaria is prevalent.

Over the last twenty years, hot melt extrusion (HME) has received widespread interest as a continuous manufacturing technology from the pharmaceutical industry. In this process, a

single-unit is used to manufacture pharmaceutical products starting from raw materials through a continuous rotating process capable of implementing PAT for quality control purposes (Thiry et al., 2015). Various drug delivery systems can be produced using this technology including pellets, tablets, films, implants and nano-delivery systems (Patil et al., 2016; Thakkar et al., 2020). The main advantages of HME are that it is a cost-effective and solvent-free process that allows rapid production of drug product (Wilson et al., 2012) and offers ease of scale-up (Maniruzzaman and Nokhodchi, 2017). For the development of successful drug delivery products that must meet specific quality requirements, it is important to optimize both the formulation composition and the process parameters of the extruder since both have a major impact on the quality of manufactured extrudates. In particular, the impact of process parameters such as barrel temperature, screw design, screw speed and feeding rate have been widely investigated in the literature (Andrews et al., 2019a; Dadou et al., 2020b; Thiry et al., 2015). Varying parameters can influence the uniformity of mixing, the physical-state of incorporated drug and/or the drug release profile from the drug delivery system (Alqahtani et al., 2020; Tousif Ayyub et al., 2019).

Despite the potential of HME as an innovative technology and the advantages it offers, very few marketed drug-containing pharmaceutical products have been successfully manufactured (Zecevic et al., 2018). Ensuring identification of key process parameters that influence critical quality attributes of a pharmaceutical product are established during early stage development is essential for the successful scale-up to commercial production. Therefore, the manufacturing process and formulation needs to be robust enough to achieve a similar quality for the end product irrespective of whether small (developmental) or large-scale (industrial) equipment is used. Very few reports in the literature have investigated the scale-up of HME (Almeida et al., 2012; Maniruzzaman and Nokhodchi, 2017). In these reports, pilot scale production has been achieved by using an extruder with a larger barrel size and screw

diameter, or by performing HME for extended periods of time. The aim was to assess the feasibility and predict the quality of products upon the scale-up of HME for the purposes of commercial scale manufacturing.

Hot melt extrusion has been extensively used by our group for the production of amorphous solid dispersions (Andrews et al., 2019b, 2010; Kelleher et al., 2018). Additionally, we have identified and monitored the quality attributes of extrudates during processing and optimised to maximise the potential of HME as a continuous process by utilising the quality by design and process analytical technology frameworks (Andrews et al., 2019a; Dadou et al., 2020c). In this current work, we further our knowledge in the field of HME by scaling-up from a benchtop, horizontal twin screw extruder to a vertical twin screw extruder with the aim of ensuring a continuous supply of drug products during global pandemics. The innovative vertical twin screw extruder from Rondol Technology offers better mixing capability and temperature control along the zones of the barrel. In addition, it offers a low footprint of 0.5 m² comparing to 2.5 m² for horizontal extruders. This feature allows the extruder to accommodate downstream auxiliary units (a specialised cooling unit unique to the vertical extruder and a pelletiser) wherein extruded filaments can be cooled and pelletised immediately after exiting the extruder (de Margerie & Maier 2015).

The work reported herein investigates the manufacture and scale-up of HCQS- Soluplus (SOL) dosage forms using hot melt extrusion as an innovative continuous processing platform that could be utilised to meet any short-term increase in demand that may impact on the global supply of HCQS. The effect of formulation (drug loading) and process parameters (HME barrel temperature and screw speed) on the physical state of HCQS, content uniformity, and drug release profiles from extrudates produced using small-scale (*L/D* 20:1) and pilot-scale (*L/D* 40:1) extruders were investigated.

Materials and Methods

Materials

Hydroxychloroquine Sulphate (HCQS) was generous gift from Sanofi S.A. (Paris, France). Soluplus® (SOL, Polyvinyl Caprolactam-polyvinyl acetate-polyethylene glycol) was a generous gift obtained from BASF (Ludwigshafen, Germany). All Chemicals used for preparation of solubility and dissolution studies were of analytical grade and were used as received from VWR Chemicals (Leicestershire, UK) with no further treatment.

Solubility determination

A shake-flask method was used to determine the solubility of HCQS. Solubility studies of HCQS were performed in purified water, pH 1.2 HCl solution, pH 3.9 acetate buffer, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and pH 10.9 phosphate buffer (pH adjusted using 2M NaOH). Excess HCQS was added to 20 mL of each media and shaken for 48 h at a speed of 100 rpm at 37 °C. Samples (3 mL) were withdrawn from the supernatant and filtered using a 0.45 µm syringe filter. The quantity of HCQS was estimated using a UV–Vis spectrophotometer (Cary 50 Scan; Varian, USA) at a wavelength of 282 nm. All experiments were performed in triplicate.

Thermogravimetric Analysis (TGA)

A Thermal Advantage Q50 TGA (Thermal Analysis Instruments, Leatherhead, UK) was used to assess the thermal stability of raw materials. Milled samples (5 - 10mg) were heated from ambient temperature to 400 °C at a heating rate of 20 °C/min. Nitrogen was applied as the purge gas at a flow rate of 60 mL/min. Experiments were performed in triplicate and the data was analysed using TA instruments Universal analysis software. Onset of degradation was calculated as the temperature at which 5% weight loss of the material was detected.

Formulation and Hot Melt Extrusion

Pre-weighed powder formulation blends of Soluplus® (SOL) and HCQS were mixed using a stainless-steel V-shaped blender attached to a universal drive unit (AR401, Erweka, Germany) at a rotation speed of 25 rpm for 10 min. Three parameters, drug loading (w/w %), HME barrel temperature (T) and screw speed (SS), were varied –as outlined in Table 1– to investigate their effect on content uniformity, physical form and the subsequent release profile of HCQS from extrudates. The pre-mixed powder was subsequently fed into the hot-melt extruder (HME) using a twin-screw feeder (Rondol Industrie, France) set to a rate of 35 rpm. Extrudates were produced using a 10mm benchtop co-rotating twin-screw Microlab HME (*L/D* 20:1) or a 10mm co-rotating twin-screw ‘All in One’ Vertical (*L/D* 40:1) HME (Rondol Industrie, France). For lab-scale production, using the horizontal extruder, a 20 g batch was used, whereas a 100 g was prepared for the pilot-scale production using vertical extruder. All barrel zones were maintained at the set temperature (Table 1) with the exception of the feeding zone (100° C). Either a 2 or 3mm die was connected to the end of the barrel. Collected extrudates were allowed to cool at ambient temperature, pelletised and stored in glass vials for further analysis (content uniformity and dissolution). For thermal and solid-state analysis, samples were milled with a mortar and pestle, passed through a 500µm sieve and stored in glass vials.

Solid-State Characterisation

The solid-state of HCQS was examined to detect its crystalline nature in the physical mixtures (PM) and the milled extrudates using power compensation Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD). For DSC, a Q20 Thermal Advantage differential scanning calorimeter (Thermal Analysis Instruments, Leatherhead, UK) was used. All experiments were conducted with a sample mass of 5 - 10 mg crimped in

aluminium DSC pans. Nitrogen gas was used as the purge gas with a flow rate of 50 mL/min. Samples were heated from 0 to 260 °C at a heating rate of 20 °C/min. Scans were performed in triplicate.

For PXRD, a Mini-Flex II (Rigaku™, Japan) PXRD with a Cu K α radiation (30 kV) in the angular range (2 θ) varying from 5°- 40° was used. A step scan mode with a step width of 0.02° and a counting time of 2 seconds/step was used. PM and milled samples were then placed on a glass top loading sample holder with a 0.2 mm depression. Scans were performed at room temperature in triplicate.

Percentage crystallinity of the drug in the extruded samples and physical mixtures was calculated by integrating the melting endotherms of HCQS in DSC thermograms and using Equation 1:

$$\text{Percentage Crystallinity (\%)} = \frac{\Delta H_S}{\Delta H_D \times W} \times 100 \quad [1]$$

where ΔH_S is the melting enthalpy (J/g) of the sample (physical mixture or extrudates), ΔH_D is the melting enthalpy (J/g) of the pure drug, and W is the fraction (% w/w) of the drug in the sample.

Additionally, the percentage of drug crystallinity based on the enthalpy of the respective physical mixture (ΔH_{PM}) was calculated using Equation 2:

$$\text{Relative Percentage Crystallinity (\%)} = \frac{\Delta H_S}{\Delta H_{PM}} \times 100 \quad [2]$$

Drug content Uniformity

A defined mass of the pelletised extrudates from each formulation (depending on drug content) was dissolved in 100 mL of 0.1 M hydrochloric acid (HCl) solution, diluted when needed and analysed using a UV-Vis spectrophotometer (Cary 50 Scan; Varian, USA) at a

wavelength of 282 nm. A calibration curve of HCQS (in HCl solution) was pre-established in the concentration range of 20 – 200 µg/mL. All measurements were carried out in triplicate.

In-vitro Drug Dissolution Studies

SOL-based pelletised extrudates were sieved to collect a fraction of pellets with a particle size range between 1 and 2 mm. Drug release profiling from the pellets (around 667mg) was performed under sink conditions in 0.1 N HCl (pH 1.2, 750 mL) utilising USP Paddle Apparatus II (VK 7000; VanKel Industries Inc, USA) at 37°C and a paddle speed of 50 rpm for 2h. During the dissolution test, the absorbance of HCQS was measured (every 30s) at 282nm wavelength using in-situ fibre-optic UV-probes, equipped with 2mm pathlength tips and connected to the Rainbow® µDISS Profiler™ (Pion Inc., MA, USA). HCQS concentration was instantly measured in each vessel using a pre-determined calibration curve. Drug release was performed in triplicate.

Results and Discussion

Formulation Screen using a 10mm co-rotating twin-screw 'All in One' Vertical Extruder (L/D 40:1) from Rondol Industrie

Based on previous experience we selected a range of polymers (Kollidon 12PF, 17PF, 30, 90, VA64, Soluplus, Kolliphor P188, P338 and P407) for potential extrusion with HCQS. The melting temperature of HCQS is 240°C and our best chance of reducing its crystallinity will be to extrude at temperatures close to or above its melting temperature. The TGA analysis (Figure 1) of the polymers demonstrates that all polymers except for Soluplus and Kollidon VA64 had weight loss at 250°C and extruding at temperatures close to or above 250°C could result in their degradation influencing the integrity of the polymer. Therefore, we decided to move forward with Soluplus and Kollidon VA64.

Using our previous expertise and knowledge from working with pharmaceutical customers, our first extrusion trials were performed using the 10mm (L/D 40:1) 'All in One' Vertical extruder with a single mixing zone and the following temperature profiles, zone 1 at 40°, 2 at 80°, 3 at 100°, 4 at 140°, 5 at 150°C. 6 at 160°, 7 at 170°, 8 at 170°, die at 180° for Soluplus and zone 1 at 80°, 2 at 100°, 3 at 130°, 4 at 150°, 5 at 160°C. 6 at 170°, 7 at 180°, 8 at 185°, die at 200° for Kollidon VA64. The screw speed was set at 100 RPM for both polymers, while Soluplus had a feed rate of 10 g/h and VA64 had a feed rate of 30 g/h. The in feed roll of the pelletizer was set at 10 and 60 for Soluplus and VA64 respectively, while the cutter speed was set at 100 and 650 respectively. Both polymers produced acceptable pellets (data not shown) in relation to colour, size and shape. The acceptability of the pellets and the TGA data for both polymers would suggest that there was an opportunity to increase the temperature of the mixing zone, closer to the melting temperature of HCQS.

To save on HCQS we decided to further investigate Soluplus as a polymer for the extrusion of HCQS-loaded pellets. We investigated the influence of HCQS loading (20, 30 and 40%), mixing zone temperature (190, 220 and 240°C) and screw speed (100, 150, 200 and 300 RPM) on the crystallinity of HCQS in the extrudates using XRD analysis (Figure 2). The 30% w/w HCQ-loaded blend produced the most acceptable pellets in relation to colour, size and shape (Figure 3), while the XRD data demonstrated a 50% reduction in crystallinity for those 30% w/w HCQ-loaded pellets manufactured using an “ultra light” single mixing zone screw profile, temperature profile close to the melting temperature of HCQS T_g and a screw speed of 200 rpm. The fact that these process parameters are easy to scale up to commercial batch as well as the significant reduction in crystallinity of HCQS encouraged us to further investigate the use of HME to manufacture HCQS pellets with reduced crystallinity. For the next stage of study we decided to compare the use of the smaller 10mm (L/D 20:1) horizontal benchtop co-rotating twin-screw Microlab extruder with the 10mm (L/D 40:1) ‘All in One’ Vertical extruder.

Thermal and Solid-State Characterisation

TGA was performed to assess thermal stability of HCQS and SOL during the HME process and to determine the onset of degradation temperatures ($\geq 5\%$ weight loss). Thermograms obtained for HCQS and SOL using TGA are shown in Figure 4. Both materials showed good thermal stability with no significant weight loss at the temperature range (190-240 °C). The onset of degradation for HCQS and SOL was observed at approximately ~ 270 °C and 282 °C, respectively, which is in accordance with previously published results reported in the literature (Kelleher et al., 2018; Moraes et al., 2020). This indicates that both the drug and the polymer were stable at the processing temperatures used (190 – 240 °C).

DSC analysis was used to better understand the thermal properties of the drug, polymer, physical mixtures and extrudates, and to monitor the solid-state behaviour of HCQS following HME at different drug loading, screw speed and process temperature. HCQS showed an endothermic peak at 244.9 ± 0.7 °C indicating a melting (T_m) event which is in accordance with data reported in the literature (Kim et al., 2019). The second heating cycle of HCQS showed an absence of the T_m (Figure 4B). Rather, a T_g was detected around 127.1 ± 1.8 °C indicating the conversion of HCQS to its amorphous form when heated above its T_m followed by quench cooling; no recrystallization was observed during cooling (data not shown). For SOL, no endothermic event (melting) was detected, rather a glass transition (T_g) was observed around 77.8 ± 1.5 °C confirming its amorphous structure (Kelleher et al., 2018).

DSC was performed on physical mixtures containing 20, 30 and 50% w/w drug. These represented the drug content in all formulations F1-7. Thermograms obtained (Figure 5b) showed that the T_m associated with HCQS melting was still observed indicating that HCQS retained its crystallinity (or to some extent) during heating with no significant shifting from the original T_m value of pure drug. The magnitude of melting was proportional to drug load, $PM3 > PM2 > PM1$.

For extruded formulations F1-7, whenever a prefix H or V is added it indicates the type of the extruder that was used to produce the extrudates; **H**orizontal (lab-scale) or **V**ertical (pilot-scale), respectively. Post extrusion, the presence of crystalline drug fraction –which was depicted by the melting endotherm observed in the DSC thermograms- for all processed samples was confirmed using DSC (Figure 5). It was observed that the T_m of HCQS was shifted to a lower value in all formulations. This can be attributed to the effect of SOL inclusion which lowers the melting point during HME, a common feature when mixing miscible components that depresses the melting temperature (Andrews et al., 2019b; Tian et

al., 2013; Tousif Ayyub et al., 2019). The observed T_g of SOL in physical mixtures and extruded formulations as well as a T_m for HCQS indicates, again, that completely amorphous solid dispersions were not formed between SOL and HCQS following extrusion. The T_g detected at 122.8 ± 1.6 and 127.5 ± 2.3 °C in HF1 and HF5, respectively, which is attributed to amorphous HCQS (Figure 2B), suggests that HCQS exists in both crystalline and amorphous forms. Relatively, HF1 and HF5 displayed HCQS melt endotherms with the smallest enthalpy, suggesting that low drug load and high processing temperature, were the most likely formulation and process conditions to result in complete amorphisation of the HCQS. Upon scale-up using the vertical extruder, a similar observation was obtained with formulations VF1 and VF5 showing the lowest levels of HCQS crystallinity (Figure 3B). It is worth noting that the difference in the magnitude of the melting endotherm of HCQS across the range of extrudates manufactured using the vertical extruder was less pronounced when compared to extrudates batches produced using the horizontal extruder. This observation can be correlated to the size of the extruder. The dimensions of the screws used in the system are used to determine the size of an extruder and are represented as the length to diameter ratio (L/D) (Patil et al., 2016). The L/D is a very important parameter to consider during the development and optimisation of an HME process. Melting, amorphisation and/or thermal degradation of components being extruded occur due the energy in the barrel that results from mechanical and heat stress. Thus, varying the L/D will result in different shear conditions which will affect the energy and, hence, the properties of the extrudates. Usually, manufacturers prefer to maintain dimensional similarity between the lab-scale and pilot/large-scale extruders to provide similar shear conditions, throughput and residence time. This is achieved by keeping the L/D ratio constant (Zecevic et al., 2018).

In this work, we wanted to investigate the effect of changing the dimension of screws on the solid-state and release behaviour of HCQS in the extrudates. Therefore, the L/D was

increased 2-fold by moving from a horizontal lab machine (L/D 20:1) to a vertical extruder (L/D 40:1). This resulted in an increase in the barrel surface area available for mixing and in the residence time of the formulations within the barrel of vertical extruder (since screw speed and feed rate were similar for both extruders). This helps to explain the lower variability in the solid-state properties (percentage crystallinity) of HCQS in formulations manufactured using the vertical extruder with a L/D ratio of 40:1. Generally, the residence time of materials in the extruder is between 5 seconds to 10 min depending on the dimensions and design of the screws in addition to the process conditions (Jani and Patel, 2015; Crowley et al., 2007).

PXRD

PXRD was performed to examine the solid-state of raw materials and the physical form of HCQS in extrudates. PXRD profiles obtained for HCQS, SOL, PM and milled extrudates are shown in Figures 6-8. The diffraction pattern of HCQS confirms the crystalline nature of the drug with characteristic sharp peaks observed at 2θ angles in the range 18 to 30.5°. Conversely, SOL's diffraction pattern showed a wide halo indicating that the polymer is in an amorphous form. For physical mixtures of SOL-HCQS, the same characteristic peaks of HCQS were still observed with lower intensity due to dilution in SOL.

Results acquired from PXRD of the hot-melt extrudates support data obtained from DSC studies and confirm that HCQS exists in its crystalline form in all extrudates, except for HF1 and VF1, which did not show clear crystalline peaks. The PXRD patterns shown in Figure 6 suggests that the crystallinity content of HCQS in the extrudates increased with drug content which was expected since less fraction of the drug will be solubilised in the polymeric matrix when drug load increases. This observation was valid for formulations extruded using both horizontal and vertical extruders.

On the other hand, the intensity of the diffraction pattern decreased with an increase in the barrel temperature for extrudates processed with a horizontal extruder (Figure 7). The intensity of the PXRD diffractions was in the following order (HF4> HF2> HF5) which was inversely proportional to the temperature of the barrel (190, 220 and 240). However, increasing barrel temperature did not affect the intensity of the diffraction patterns of the extrudates processed with the vertical extruder which is in agreement with the previous observations obtained from DSC results.

When the effect of screw speed was investigated (Figure 8), no observable differences in the intensity of peaks for extrudates processed with the vertical extruder were observed (VF2, 6, 7), while for extrudates processed with the horizontal extruder, the intensity obtained for extrudates produced at low screw speed (HF6; 100rpm) was considerably higher than extrudates produced at higher screw speeds (HF2 and HF7).

Crystallinity Percentage

To support the results obtained from the qualitative analysis of HCQS solid-state and to quantify the crystallinity of HCQS post-extrusion, percentage crystallinity of HCQS in the extrudates was estimated from the DSC thermograms by integrating the enthalpy of melting endotherm of HCQS and correlate it to the enthalpy of melting for pure HCQS. The percentage crystallinity of HCQS in physical mixtures (PM) of formulations 1, 2 and 3 were as follows: 55.88 ± 7.06 , 90.16 ± 13.8 and 100.9 ± 3.56 %, respectively. For formulations produced using the horizontal lab-scale extruder, results shown in Table 2 confirm that the highest loss of drug crystallinity was associated with formulations F1 and F5 (lowest drug load and highest process temperature, respectively). This supports the results obtained previously from DSC and PXRD studies. Additionally, the highest levels of crystallinity were associated with the highest drug loading (F3) and lowest screw speed (F6). Upon the increase of drug load in the formulation, more polymer is needed to solubilise the drug during

extrusion and convert it to its amorphous form. This explains the increased percentage crystallinity of HCQS in extrudates as the drug load increases - F3 (50% w/w) relative to F1 (20% w/w). On the other hand, percentage crystallinity of HCQS was inversely proportional to barrel temperature ($F5 < F2 < F4$). As the range of temperatures used in this study (190-240 °C) were lower than the T_m of HCQS (244 °C), the presence of crystalline fraction of HCQS was evident in all formulations processed at different temperatures (F2, F4 and F5). However, approaching the T_m of HCQS (F5) resulted in the conversion of a higher fraction of HCQS to its amorphous form when compared to F2 (220 °C) and F4 (190 °C). When comparing the crystallinity of HCQS in the extrudates based on screw speed (F2, F6 and F7), no clear correlation was evident with the exception that the highest HCQS crystallinity was associated with the lowest screw speed (F6). This can be explained by the low values of torque and pressure during extrusion associated with low screw speed. Thus, less stress is exerted on the formulation and under these conditions the mechanical stress is not sufficient to drive the conversion of HCQS to its amorphous form. A similar trend regarding the relationship between HCQS percentage crystallinity, drug load and barrel temperature was observed with extrudates produced using the vertical extruder. However, increasing the screw speed of the vertical extruder had a greater impact on decreasing the percentage crystallinity of HCQS compared with the horizontal extruder. Considering the fact that process temperatures adopted in this study did not exceed the T_m of HCQS, in addition to the absence of a plasticiser component in the formulation that can facilitate extrusion, there was no formulation that displayed a complete loss of HCQS crystallinity resulting in the formation of a complete 100 percentage amorphous solid dispersion.

The previous results were obtained relative to the enthalpy (crystallinity) of the melting of pure drug. To estimate the solid-state properties of HCQS within formulations due to the

process itself (shear and temperature stress of HME), the relative percentage crystallinity of HCQS in the extrudates was subtracted from percentage crystallinity of HCQS calculated for the respective PM (PM1 for 20%, PM2 for 30%, and PM3 for 50% w/w drug load). Generally, the loss of crystallinity caused by the process was more profound in extrudates manufactured using the horizontal extruder when compared to vertical extruder. However, when higher a screw speed (F7) was used, the vertical extruder had greater impact on the loss of crystallinity.

Drug content uniformity

Drug content in the manufactured extrudates was measured to ensure the stability of HCQS during extrusion and the homogeneity of drug distribution in the extrudates. Results obtained from drug content measurements are presented in Table 3. Formulations extruded using the horizontal extruder showed good content uniformity with HCQS percentages ranging from ~ 90 to 106% within formulations with no significant difference in the mean values of HCQS content between the formulation was observed ($p= 0.07$). In general, extrudates produced using the vertical extruder showed drug content values lower than those obtained from the horizontal extruder, with HCQS content in the range of ~ 89 to 96%, which suggests that some process optimisation may need to be performed upon scale up from the horizontal extruder to the vertical extruder.

In-vitro Drug Release

Face cut pellets of extrudates were used to perform dissolution studies. The release of HCQS from all hot-melt extrudates met compendial requirements for immediate-release of HCQS from all formulations (more than 80 percentage release of initial HCQS dose was achieved within 30 min for all tested samples). Therefore, dissolution studies were carried out in HCl only with no need to transfer to pH 6.8 to replicate small intestinal media. Drug release

profiles (Figure 9A) showed that the percentage release of HCQS increased as the HCQS content in the formulations increased, and the percentage of SOL fraction in the formulation, decreased. For example, HF3 (50% w/w HCQS) demonstrated a faster release than HF1 and HF2 containing 20 and 30% w/w HCQS, respectively. This can be explained by the slower SOL dissolution (compared to HCQS) and the high swelling properties of the polymer. Polymer reduces the erosion of the extrudates and retards the release of HCQS, given that it acts as a swellable matrix. Thus, increasing the SOL concentration significantly retards the HCQS release rate. Furthermore, the microstructure of filaments obtained following extrusion might have an influence on the release of HCQS from extrudates. The presence of voids in the microstructure of hot melt extrudates may influence release, with an increase in the number of voids significantly increasing as drug loading increases (Alqahtani et al., 2020). As a consequence, the density per unit volume in pelletised extrudates of higher drug loading is lower resulting in a faster release rate of the drug from the extrudates. In another study, diclofenac sodium showed immediate release from hot melt extrudates when the drug load was 37.5% w/w and 25% w/w, whereas sustained release profiles were obtained when diclofenac load was 12.5% w/w in the extrudates (Bisharat et al., 2020).

Comparing the effect of HME processing temperature (at HCQS level of 30% w/w and 150rpm), the fastest drug release was obtained from the formulation containing the highest proportion of crystalline HCQS (HF4), which was prepared at lower temperature (190°C), Figure 7B. This might be due to the low proportion of HCQS that was converted to its amorphous form and solubilised in SOL relative to formulations HF2 and HF5 (~ 20% according to Table 2). This would allow free crystalline drug (that did not form amorphous solid dispersion with SOL) to dissolve rapidly in the dissolution media creating voids for the media to imbibe into the pellets. In addition to the known swelling behaviour of SOL in acidic solutions which results in sustaining the release of the amorphous content of

incorporated HCQS that formed solid dispersion with SOL upon extrusion (Andrews et al., 2019b; Hardung et al., 2010). Thus, formulations having more fraction of amorphous HCQS solubilised in SOL showed slower release (HF2 and HF5).

When changing screw speed (at HCQS level of 30% w/w and 220°C), the fastest drug release kinetics were associated with HF6 (prepared at low screw speed, 100rpm) that has HCQS in its crystalline form, Figure 7C. This behaviour was reported previously in the literature (Tousif Ayyub et al., 2019) and can be explained, again, by the swelling behaviour of SOL in acidic solutions which retards the release of drug that forms solid dispersions with SOL, while immiscible drug (or fraction of a drug) that remains in its crystalline form was released immediately. Additionally, a faster erosion and dissolution of the extrudates occur when coarse crystal domains are present due to a higher matrix porosity, within the microstructure of the polymeric matrix (Dadou et al., 2020a; Jeong et al., 2003).

Release profile of HCQS was similar ($p > 0.05$) from all formulations manufactured using horizontal extruder with the exception of HF3 (0.0001), HF4 (0.04) and HF6 (0.0).

Following scale-up of formulations using the vertical extruder, no significant differences in the release profile of HCQS from pelletised extrudates were observed. All formulations showed similar release profiles ($p > 0.05$) for HCQS with more than 80% of HCQS released during the first 30 min of the dissolution (Figure 9). The longer residence time of formulations in the barrel when using the vertical extruder might be the reason for the similarity of the drug release profiles obtained for HCQS for these extrudates. This can be explained, again, by the higher value of L/D for vertical extruder (40:1) when compared to the horizontal (20:1) allowing for a larger surface area available for mixing and longer time to stabilise the process. Thus, less variation in drug release between formulations extruded using the vertical extruder was achieved. This is evidence that the vertical extruder would

provide a more robust manufacturing process compared to the horizontal extruder. Dissolution rate is a critical quality attribute (CQA) of HME products with both barrel temperature and screw speed of the vertical extruder having limited impact on the dissolution rate of HCQS.

Conclusion

Realising the full potential of continuous manufacturing is of major importance to minimise shortages of pharmaceutical drug products during global pandemics. In this work, TGA was used to select polymers that were most suitable for the manufacture of HCQS products using HME. Soluplus was selected as the polymer and an extrusion trial performed using a vertical extruder to determine if HCQS-loaded pellets could be produced. The HCQS/Soluplus formulation produced aesthetically acceptable pellets with reduced HCQS crystallinity. HCQS drug products were subsequently produced initially using a 10mm benchtop hot melt extruder. Afterwards, a scale-up process was performed to assess the feasibility of extrapolating the results obtained from the benchtop lab-scale equipment (20:1) to a pilot-scale (40:1) vertical extruder when keeping process parameters and conditions constant.

The drug loadings and processing conditions utilised did not result in complete formation of amorphous solid dispersion of HCQS within the SOL matrix. The highest loss of drug crystallinity was associated with the highest processing temperature (HF5) and lowest drug loading (HF1). Rapid drug release was associated with formulations having a higher proportion of crystalline form of HCQS (e.g., HF3 and HF6). Upon scale-up to the 40:1 vertical extruder, the same trend of drug crystallinity was observed, with formulations VF5 and VF1 showing the least crystalline proportion of HCQS. However, the HME process becomes less sensitive with less differences observed as a function of variation in content and drug release studies. Furthermore, increasing the screw speed of the vertical extruder had a greater impact on the loss of crystallinity of HCQS when compared to the horizontal extruder. This might be due to the longer residence time of formulations inside the vertical extruder barrel (L/D 40:1) relative to the horizontal extruder (L/D 20:1) which allows for more mixing and less variation in the microstructure of the extrudates.

Overall, this paper demonstrates that with further understanding of the impact of the formulation and process parameters of the CQA of the end products, variables can be optimised/adjusted and the CQA of the end products maintained upon scale-up from a 10mm *L/D* 20:1 benchtop horizontal co-rotating twin-screw extruder to a 10mm *L/D* 40:1 co-rotating 'All in One' Vertical extruder. This allows for significant savings of material (i.e. excipients and API) during the formulation and process development stage as the 10mm *L/D* 20:1 horizontal extruder requires less material than the 10mm *L/D* 40:1 vertical extruder. Furthermore, this study demonstrates that upon scale-up, the 10mm *L/D* 40:1 vertical extruder provides a more robust manufacturing process as neither the temperature profile of the barrel or screw speed significantly impacted the dissolution rate of the HCQS compared to the 10mm *L/D* 20:1 horizontal extruder. This is of great advantage to the pharmaceutical industry as production rate can be increased or decreased as needed, through an increase or decrease of the screw speed, with minimum and/or no impact on the CQA of the final product and thus no need for additional bioequivalence clinical studies. Finally, the immediate release as well as the reduction in the crystallinity of the HCQS has the potential to improve its bioavailability, meaning that a lower dose could be administered, which would be of great cost saving benefit to those low-middle income countries where HCQS is highly used.

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Table 1. Composition and HME processing conditions of HCQS-SOL based formulations*

	F1	F2	F3	F4	F5	F6	F7
Drug (w/w %)	20	30	50	30	30	30	30
Polymer (w/w %)	80	70	50	70	70	70	70
T (°C)	220	220	220	190	240	220	220
SS (rpm)	150	150	150	150	150	100	200

* *T*, temperature; *SS*, screw speed; *F*, formulation

Table 2. Percentage crystallinity of HCQS in the extruded formulations as obtained from DSC.

Formulation	Crystallinity (%)^a		Relative Crystallinity (%)^b	
	Horizontal	Vertical	Horizontal	Vertical
F1	37.14 ± 0.18	47.07 ± 6.58	49.15 ± 0.24	
F2	63.36 ± 9.54	70.26 ± 8.99	67.92 ± 3.09	
F3	96.47 ± 3.81	-	93.67 ± 3.70	
F4	80.62 ± 2.90	77.09 ± 7.68	85.78 ± 10.2	
F5	45.86 ± 2.05	60.32 ± 1.84	48.45 ± 2.19	
F6	94.43 ± 6.26	104.1 ± 4.17	100.8 ± 6.69	
F7	83.34 ± 4.85	76.42 ± 6.67	88.96 ± 5.18	

^a Values represent the percentage of the drug remained crystalline in the formulation relative to the initial drug load (n=3).

^b Values represent the percentage of the drug remained crystalline in the formulation relative to the respective physical mixture (n=3).

Table 3. Content of HCQS in the extruded formulations as measured using UV spectroscopy

Formulation	Drug content (%)	
	Horizontal	Vertical
F1	90.12 ± 1.38	90.25 ± 3.68
F2	98.55 ± 6.50	91.83 ± 2.97
F3	95.06 ± 2.66	-
F4	106.1 ± 1.03	89.05 ± 0.46
F5	97.13 ± 7.86	90.09 ± 1.43
F6	104.9 ± 4.31	95.87 ± 1.86
F7	105.7 ± 1.72	92.03 ± 1.68

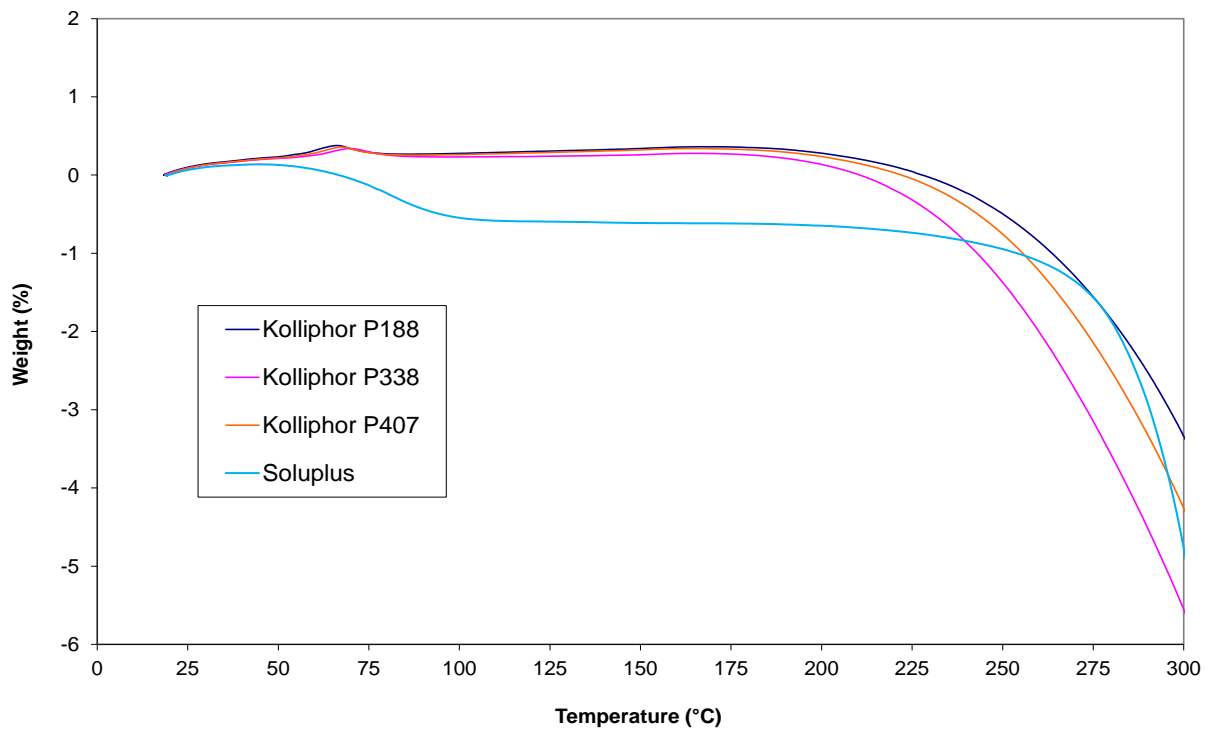
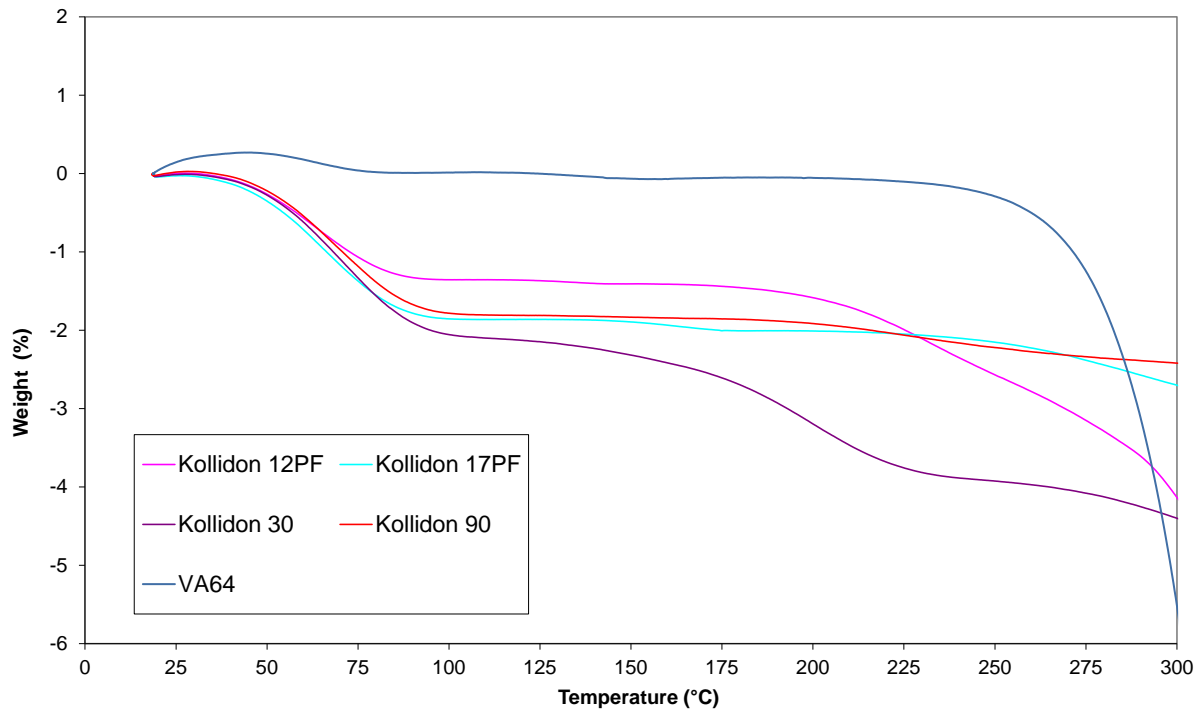


Figure 1. TGA-profiles of Kollidon 12PF, 17PF, 30, 90, VA64, Kolliphor P188, P338, P407 and Soluplus.

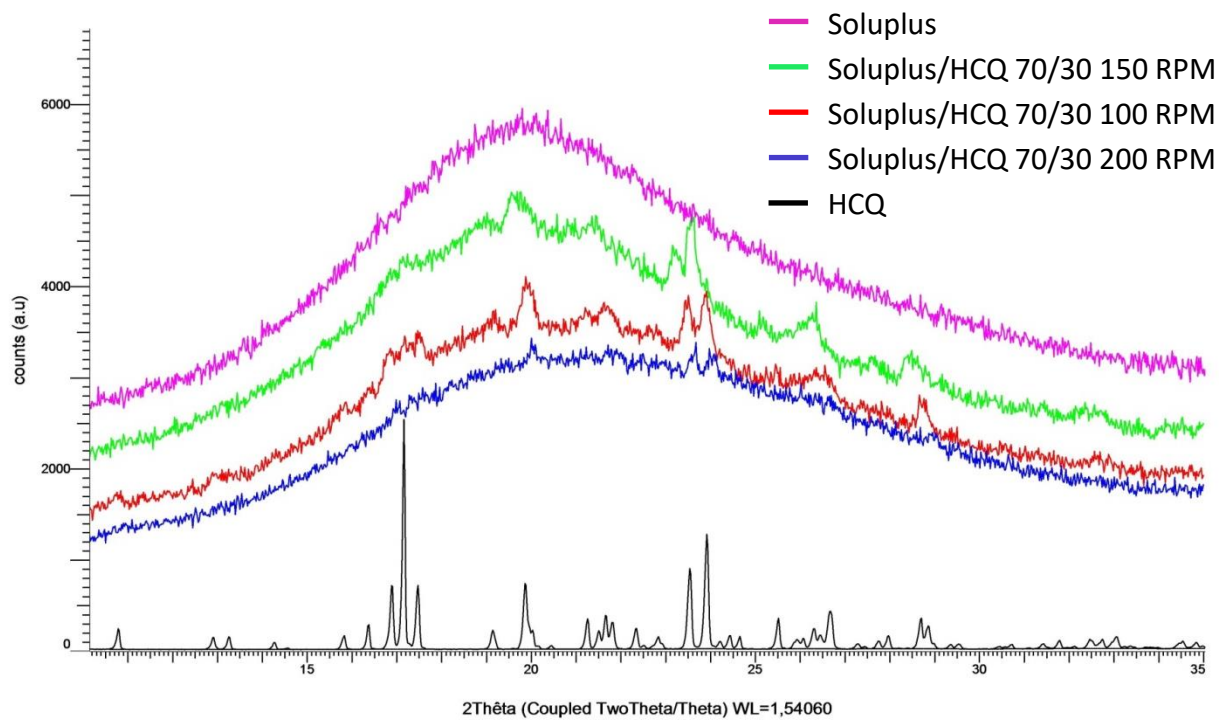


Figure 2. PXRD patterns for Soluplus, 70/30 Soluplus/HCQ and different screw speeds and HCQ.



Figure 3. Image of 30% w/w HCQ-loaded Soluplus pellets

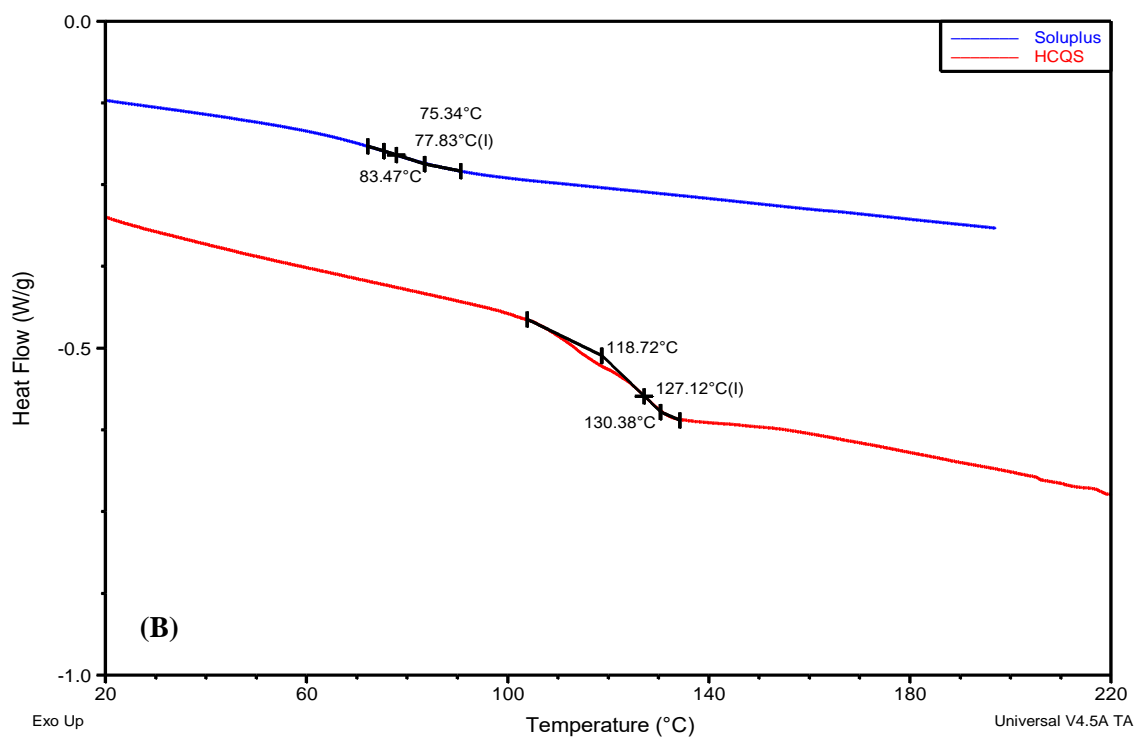
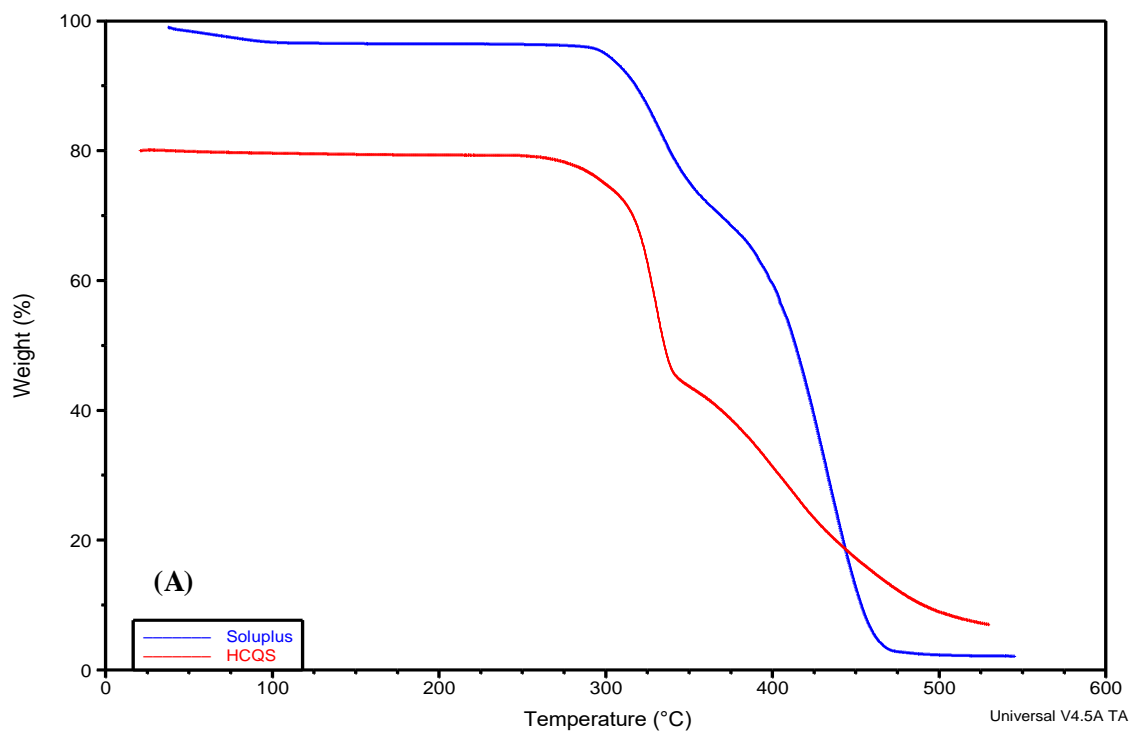


Figure 4. (A) TGA-profiles of HCQS and Soluplus. (B) DSC curves obtained for amorphous HCQS (second heating cycle) and Soluplus.



Figure 5. DSC-profiles of HCQS, mixtures of HCQS with SOL (PM1, physical mixture of F1; PM2, physical mixture of F2; PM3, physical mixture of F3) and processed formulations (F1-7) from (A) Horizontal lab and (B) Vertical extruders.

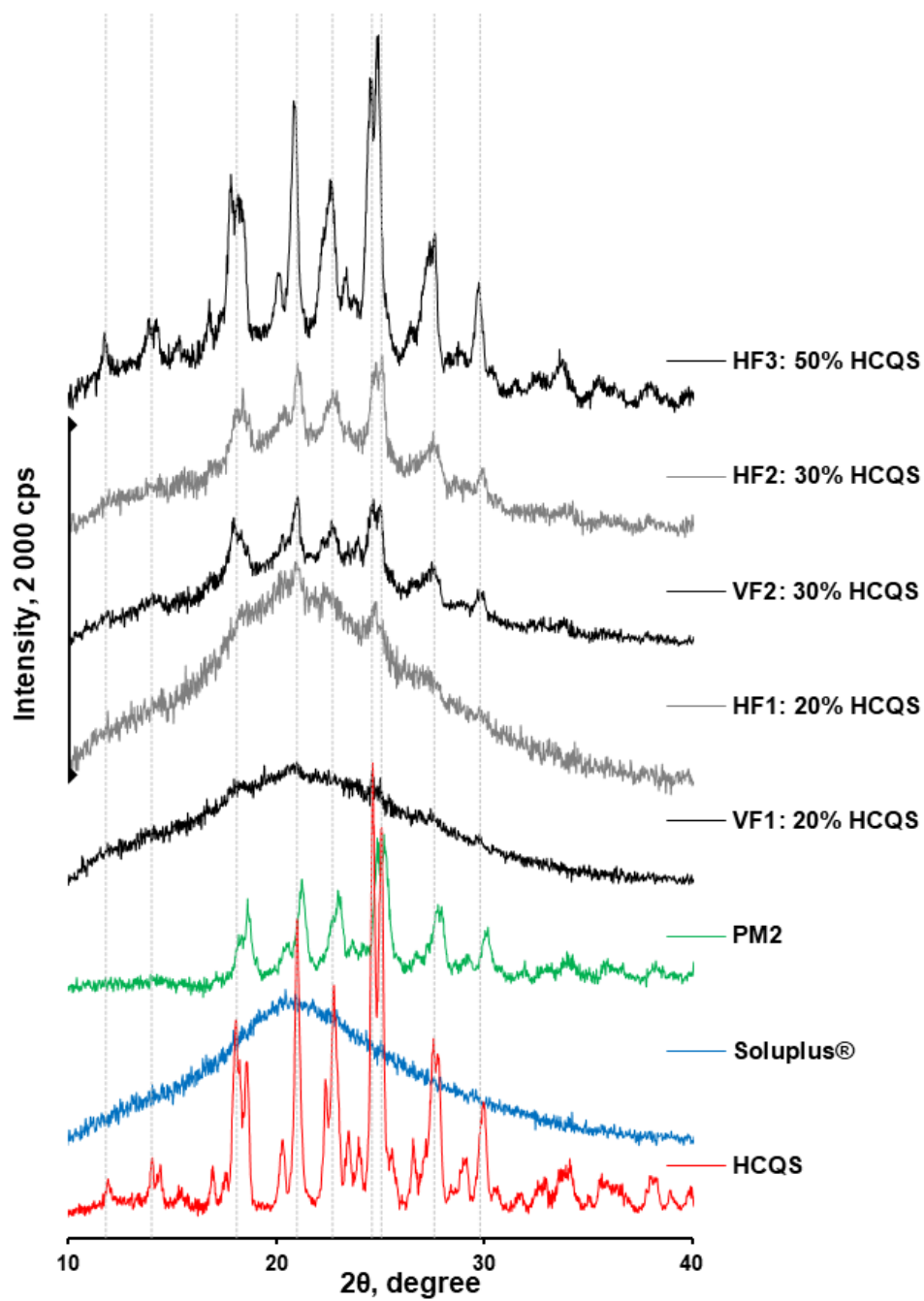


Figure 6. Effect of drug loading (at 220°C and at 150rpm) on the PXRD diffraction patterns.

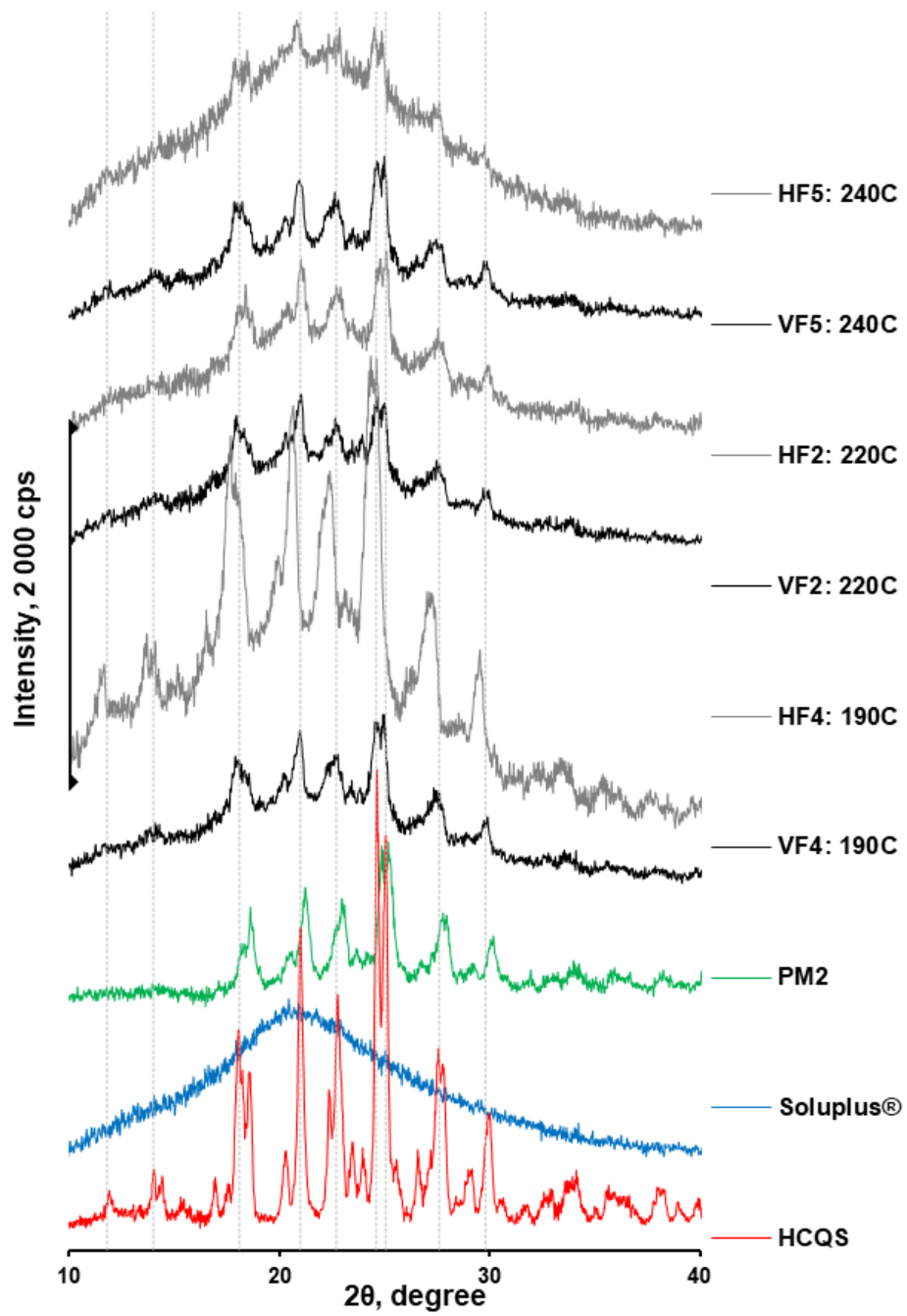


Figure 7. Effect of processing temperature (at 30% HCQS level and 150rpm) on the PXRD patterns.

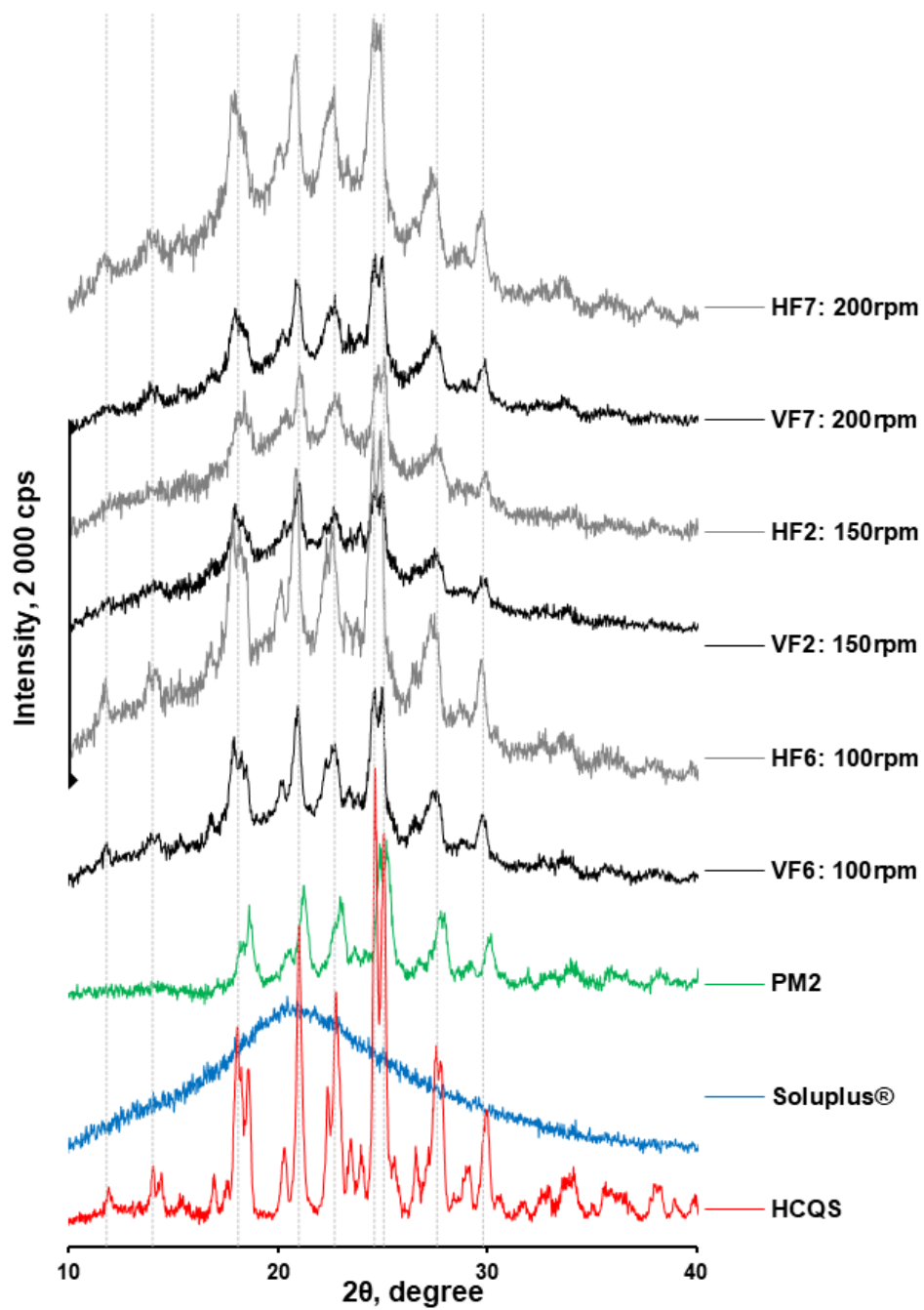


Figure 8. Effect of screw speed (at 30% HCQS level and at 220°C) on the PXRD patterns.

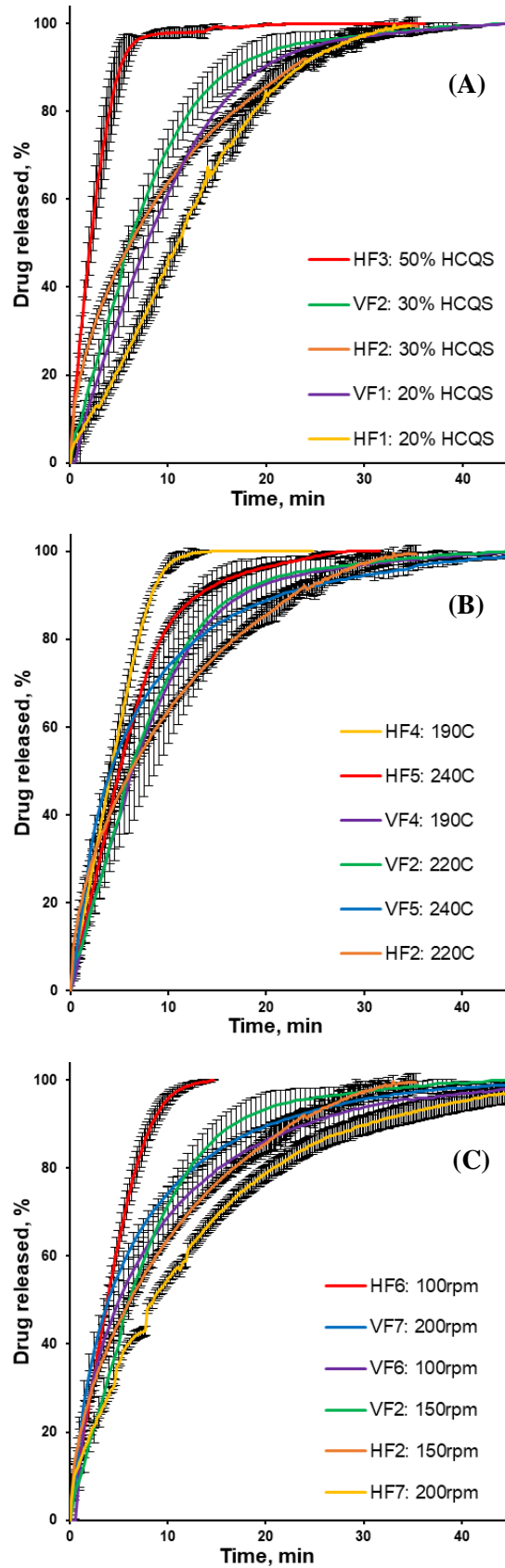


Figure 9. Effect of: (A) drug loading (at 220°C and at 150rpm), (B) processing temperature (at HCQS content of 30% w/w and 150rpm), and (C) screw speed (at HCQS content of 30% w/w and at 220°C) on drug release profile of HCQS from SOL based extrudates.

