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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

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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 batch manufacturing involving numerous steps, that normally occur at different sites. In order to validate the use of large-scale industrial processes, feasibility studies need to be performed using small-scale laboratory equipment. To that end, the scale-up of a continuous process and its effect on the critical quality attributes (CQAs) 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 both horizontal and vertical twin screw extruders used to undertake this hot melt extrusion (HME) study. Seven formulations were processed using a small-scale horizontal extruder and a pilot-scale vertical extruder at various drug loadings, temperature profiles and screw speeds. When utilising a horizontal extruder, formulations with the highest drug load and processed at the lowest screw speed and temperature had the highest crystallinity with higher drug release rates. Upon scale-up to a vertical extruder, the crystallinity of the HCQS was significantly reduced, with less variation in both crystallinity and release profile across the different extrudates. This study demonstrates improved robustness with the pilot-scale vertical extruder compared to lab-scale horizontal extruder. The reduced variation with the vertical extruder will allow for short increases in production rate, with minimum impact on the CQAs of the final product enabling high-performance continuous manufacturing with minimum waste of raw materials. Finally, this research provides valuable information for the pharmaceutical industry in accessing continuous technologies for the manufacture of pharmaceutical products, allowing for efficient utilisation of resources upon scale-up and mass production during global pandemics and drug shortages.

1. Introduction

In December 2019, a novel strain of the family of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered. SARS-CoV-2 was responsible for coronavirus disease 2019 (COVID-19), which was subsequently 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

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