Advanced Engineering Formulation Strategies for the Effective Delivery of Hydroxychloroquine.

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Introduction

Normally, coronaviruses cause mild illness, however there have been incidents where specific types can infect the lower airway, resulting in severe illnesses such as pneumonia or bronchitis. Two such previous examples include Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). In respect of SARS-CoV, the virus rapidly spread across 29 countries in 2003, infected more than 8000 people and resulted in almost 1000 deaths. In 2020, the world has witnessed a significant and rapid outbreak of a new coronavirus, COVID-19. To date (30th March 2020), there has been 723,700 confirmed cases across 196 countries and tragically 34,018 deaths. These numbers will continue to rise.

It is currently estimated that COVID-19 has a reproduction number (R0) of 2.5, meaning that every individual has the potential to infect 2.5 people. This is mainly due to people being infectious in the early stages of the disease when they are often asymptomatic. Consequently, this makes it difficult to identify and isolate infected people and moreover contacted individuals. It is estimated that pre-symptomatic individuals can account for up to 25% of transmission. As such, and in light of the lack of a current treatment or prevention strategy, there is undoubtedly a potential for a significant number of people to become infected and ultimately require hospitalisation, putting significant strain on global healthcare systems. Tragically, many hospitalised patients will require major medical intervention, ventilation and Intensive Care Unit (ICU) treatment. Due to the unprecedented burden on health services, it is inevitable that many patients will prematurely die due to a lack of resources. As a means of drastically reducing the death rate from COVID-19, most countries in Europe and around the world have introduced either containment and/or mitigation measures to slow down the spread of the virus. Detection, self-isolation, quarantine of contacts, physical distancing and whole country lockdown have been implemented to reduce the R0 of the virus to below 1, which may significantly reduce the spread of the virus.

According to the World Health Organization (WHO), the Centre for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA), there are currently no approved treatment or prevention medications for COVID-19. [1-3]. Furthermore, with the development of a vaccine being at least 12-18 months away, it is imperative that this immediate gap is bridged with studies that evaluate new and repurposed drugs in the immediate term, whilst vaccines are being developed in the longer-term.

In the absence of an established treatment regimen, there are numerous drug repurposing strategies that are emerging in a bid to treat COVID-19 [4]. For example, the China

International Exchange and Promotive Association for Medical and Health Care (CPAM) issued guidance on the use of lopinavir and ritonavir (also known under the brand name Kaletra and commonly used in the treatment of HIV) alongside nebulized alfa-interferon. Furthermore, there are also recommendations that chloroquine or hydroxychloroquine in combination with azithromycin may also be used particularly in older patients or patients with underlying conditions and serious symptoms [5, 6]. Despite the promise of drug repurposing, there are some concerns over the toxicity of chloroquine and hydroxychloroquine with some in vitro studies suggesting that the dose needed to be effective against COVID19 may be higher than that used in malaria. Moreover, there is literature to suggest that hydroxychloroquine may be preferentially used relative to chloroquine [7]. Indeed, the World Health Organisation (WHO) are currently running a clinical trial (SOLIDARITY), to evaluate the effectiveness of Hydroxychloroquine as a treatment for COVID19 while some countries have already included treatment with Hydroxychloroquine in their clinical guidance for patients with COVID19 [8 & 9].

Hydroxychloroquine is weakly basic drug used to treat malaria, lupus erythematosus and rheumatoid arthritis. Doses vary depending upon condition but normally are in the range 800mg – 200mg. It is also recommended to take hydroxychloroquine with food in order to reduce stomach irritation. Tablets contain 200mg of the hydroxychloroquine as the sulphate salt and are manufactured using standard compression processes. Moreover, hydroxychloroquine 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 good bioavailability with a mean fraction of 0.74 of dose absorbed [10].

In this proposal we address two fundamental issues that may be overcome through the use of melt extrusion technology to lower dose, minimize toxicity and continuously manufacture hydroxychloroquine granules.

1. Hydroxychloroquine is a poorly soluble weak base which presents significant delivery challenges. The sulphate salt of the drug is highly soluble in gastric fluid but may recrystallise in the higher pH environment of the small intestine, as the parent base is highly insoluble under these conditions. Furthermore, increased stomach pH in the post-prandial state may also present a solubility challenge. Ultimately in both cases, we would expect a drug solubility decrease to reflect in lower in vivo exposure and as such a solubility-enabling approach may overcome this GIT solubility variation. In particular, and as recently described in the literature by Zhang *et al*., salt forms of drugs can experience a significant decrease in solubility when transitioned to the higher pH of the small intestine [11]. The bioavailability of BCS II drugs can be increased through improving their solubility. Increasing the solubility of hydroxychloroquine would allow for the same efficacy using a lower dose, minimising toxicity. This approach may reduce toxicity and dosing issues associated in the treatment of COVID19. To overcome this issue and to offer optimised drug formulations we propose two such approaches that may be facilitated through melt extrusion technology

    a. Solid dispersion of drug in hydrophilic polymeric carriers
    b. Formulation of Cocrystals using hydroxychloroquine base

2. Hydroxychloroquine is manufactured using conventional tableting technology. This typically involves numerous steps and is often time consuming and difficult to scale. Just recently, pharmaceutical manufacturing companies have signalled their intention to increase production volume of hydroxychloroquine. A recent article details that Novartis, Teva, Mylan and Bayer will significantly increase production volume and donate millions of drug doses to those patients requiring this simple tablet formulation [12]. Traditional product and process development largely follows a sequential task structure and separates manufacture of APIs from that of the drug product. These processes can occur in different parts of the manufacturing plant, at different sites, and even in different countries. This arbitrary separation severely limits our ability to innovate. Continuous manufacturing processes on the other hand reduce the size of the manufacturing footprint, make scale up much more reliable or even unnecessary and speed up the development process. They also give opportunity for process innovation, the elimination of some intermediate unit operations, and are inherently developed and operate using Quality by Design (QbD) approaches. In this work we will utilise Rondol's state-of-the art vertical extruder [13] to continuously manufacture hydroxychloroquine granules in order to maximise production volume, optimise process efficiency, and grant access to what may be a vital medication during the COVID-19 pandemic.

Brief Project Synopsis

This project will focus on using hot melt extrusion (HME) to continuously manufacture solid dispersions and cocrystals of hydroxychloroquine. Traditionally, drug dispersions have been manufactured by melt, solvent or a combination of both methods. Due to the considerable number of disadvantages associated with these methods (e.g., use of organic solvents, long processing and drying times) they are less attractive to the industry. Hot-melt extrusion technology (HME) by comparison, is gaining increasing interest and is being more widely utilized in the pharmaceutical arena for the production of a diverse range of drug containing products including solid dispersions [14]. HME involves the precise feeding of the drug, a polymer and other manufacturing aids into the barrel of a twin-screw extruder. The materials are conveyed along by the twin-screw while being heated to temperatures just above or close to the melting point of the polymer. In some cases, the drug may also be melted. Once the polymer is softened or melted the drug is mixed into the polymer as a result of the shear forces provided by the screws. The homogenous extrudate is then forced through a die at the end of the extruder and shaped for the next processing step. Alternatively, HME can be set-up in such a way as to provide continuous granulation. In this work we will not only improve the dissolution performance of a weak base use a two-pronged approach but will additionally utilise continuous manufacturing of granules to concurrently offer drug enablement as an attractive proposition for the pharmaceutical industry. Not only does this offer the potential to improve manufacturing efficiency but it addresses one of the most significant challenges in formulation science, namely the limited aqueous solubility of emerging BCS class II drugs.

Aim

The overarching goal of the proposed collaboration is to immediately mobilise resources and fuse the capabilities of three significant international centres (School of Pharmacy, Pharmaceutical Engineering Group at Queen's University Belfast, School of Pharmacy, University of Birmingham and Rondol Industrie in Nancy), with input from key Multinational

Pharma (BASF and Sanofi), with the goal of establishing new drug formulations of hydroxychloroquine using hot melt extrusion technology. This initiative aims to provide immediate short-term solutions to aid the availability of potential COVID-19 drug products during the current global pandemic.

This proposal will use HME to improve the dissolution performance of hydroxychloroquine with the driver to increase bioavailability, improve efficacy and reducing toxicity. This proposal will also investigate the development of a combination product containing hydroxychloroquine and azithromycin.

Objectives

I. Determine the solubility of HCQ, HCQ sulphate and AZN in range of polymers suitable for HME.
II. Assess the ability of the different polymers to form solid dispersions or solid solutions of HCQ sulphate and AZN.
III. Assess the potential to form cocrystal products of HCQ and to manufacture using HME.
IV. Determine the HME processing parameters (feed rate, screw speed and temperature profile) for the HCQ sulphate and AZN polymer blends
V. Determine the HME processing parameters (feed rate, screw speed and temperature profile) for the HCQ cocrystal products
VI. Produce a series of test batches of different product types using HME
VII. Characterise the physical properties of extruded granules using pXRD and DSC to assess physical drug form.
VIII. Determine the dissolution profile of the granular product and compare to Plaquenil
IX. Assess the physical stability of extruded drug product using DSC and pXRD.
X. Manufacture a combination granular product containing both HCQ sulphate or HCQ cocrystal and AZN as a combination product.

Methodology

Pre-screening using Solubility Parameters

Calculation of solubility parameters will be performed using reference values of Van Krevelen and Hoftyzer's group contribution method for both drug and polymer candidates. Monomer units in place of polymeric compounds will be utilised. The δ_t, δ_d, δ_p and δ_h values obtained following application of this approach will be expressed as mean values and used to calculate the drug-excipient solubility parameter differences using the equations below.

$$\Delta\delta = \left|\delta_{t,1} - \delta_{t,2}\right|$$

$$\boldsymbol{\Delta\delta} = \sqrt{(\delta_{d,1} - \delta_{d,2})^2 + (\delta_{p,1} - \delta_{p,2})^2 + (\delta_{h,1} - \delta_{h,2})^2}$$

In both equations, the subscripts 1 and 2 refer to itz and the polymer, respectively.

Drug-polymer mixtures will be ranked based on the difference in solubility parameter of polymer and HCQ and AZN, with the least difference regarded as most miscible, conversely those with greatest difference will be deemed least miscible.

Determination of the solubility parameters of HCQ and AZN in a range of polymers.

Drug/polymer blends examining a range of ratios will be hand mixed with a pestle and mortar and analysed using DSC equipped with refrigerated cooling. 5.0-10.0 mg samples of physically mixed binary blends will be heated at a rate of 10°C/min. The temperature will be held at 30°C above the melting temperature or glass transition temperature of the polymer for 5 minutes and then increased to just above the melting temp of the drug. Samples will be cooled rapidly to RT and re-heated at 10°C/min (second heating cycle) to above the melting point of the drug. Data from DSC analyses will be used to determine the miscibility between candidate polymers and HCQ and AZN.

Where appropriate we will utilize Flory-Huggins modelling to identify the interaction parameter (χ). The value of Chi, which can be was estimated from melting point depression data, will be calculated as follows:

$$\frac{1}{T_m mix} - \frac{1}{T_m pure} = \frac{-R}{\Delta H_f}\left[\ln\Phi_{drug} + \left(1 - \frac{1}{m}\right)\Phi_{polymer} + \chi\Phi^2_{polymer}\right]$$

Where $T_m$mix is the melting temperature of the drug in the presence of the polymer, $T_m$pure is the melting temperature of the drug in the absence of the polymer, ΔH_f is the heat of fusion of the pure drug, and m is the ratio of the volume of the polymer to that of BL), Φ_{drug} and $\Phi_{polymer}$ are the volume fractions of the drug and the polymer, respectively.

Pre-extrusion Thermal Analysis (Volatile Degradants)

Thermogravimetric analysis will be used to examine the thermal stability of drugs and polymeric candidates. Experiments will be conducted using a Thermal Advantage Model Q500 TGA from TA Instruments (Leatherhead, UK). Samples will be heated at a rate of 10°C/min from 20 to 400°C and the mass remaining plotted as a function of temperature. Isothermal studies will also be conducted by heating materials at 20°C/min to extrusion temperature and holding for 10 minutes. In all experiments dry nitrogen will used as the purge gas for both the sample (flow rate = 40ml/min) and the furnace chamber (flow rate = 60ml/min).

Hot Melt extrusion of Solid Dispersions of HCQ

Selected polymeric candidates identified from pre-screening trials will be pre-mixed with HCQ and fed into a co-rotating 10mm twin-screw hot melt extruder (All in One, Rondol, Nancy, France) with full conveying screw configuration. Drug-polymer mixtures will be processed at suitably chosen temperatures for each respective polymeric carrier with a range of screw speeds. In further studies, combination products will be extruded containing AZN once successful HCQ formulations have been developed. Samples of extrudates will be ground with a mortar and pestle, passed through a 106µm sieve and stored in glass vials

over silica gel at 4°C. Extrudates will be analysed using a combination of DSC and pXRD to determine physical form of drug.

Hot Melt Granulation

Hot-melt granulation will be carried out on a twin-screw, co-rotating extruder (Rondol All in One, Nancy, France). The extruder will be operated with an open end. Mixtures will be prepared by hand mixing using a mortar and pestle for 5 minutes. Feeding rate should be controlled at 0.5 g/min into the feeding zone with the subsequent heating zones set at pre-defined extrusion temp. Temperatures in the extruder will be chosen to be above the Tm or Tg of the binding polymers to allow agglomeration of a solid excipient during extrusion.

Manufacture of Co-crystals of Hydroxychloroquine using Continuous Extrusion Processing

This aspect of the project will involve screening selected excipients as coformers followed by feasibility studies using HME. A range of molar ratios of drug and each respective candidate conformer will be subjected to liquid-assisted grinding (LAG) with addition of small amounts of appropriate organic solvent. The resulting material will be sized through a 180 µm sieve and stored in a vacuum desiccator prior to subsequent analyses using pXRD and DSC.

Feasibility to continuously manufacture HCQ cocrystals using HME will be conducted on the most promising candidate conformer. This step will involve novel approach to integrate synthesis of the HCQ cocrystal and formulation of such drug product intermediate (as granulate material) in a single step concurrent manner. Here the impact of specific operating parameters on the co-crystallisation process such as screw speed, temperature/time history and formulation composition will be investigated. Each manufacturing process will be benchmarked using standardised test methods (developed in-house). Design of experiment type testing will be employed to determine any critical operating parameters.

In-Vitro -Dissolution Testing

The drug release properties of extrudates will be assessed under non-sink conditions using dissolution testing. All dissolution tests will be conducted using a USP II paddle apparatus. The dissolution media will be maintained at 37 °C using Apparatus II set at 100 rpm and consisting of 750 ml of 0.1 N HCl for the first 2 h of analysis followed by pH 6.8 PBS (addition of 250 ml of 0.3 M sodium triphosphate buffer). Samples will be withdrawn every 30 min for the initial 2 h of dissolution then at 3 h, 4 h and every 2 h thereafter for 12 h. Sampled 3 ml aliquots will be analysed using either HPLC or UV spectroscopy accordingly.

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