Erlotinib's amorphous solid dispersion in Pullulan/Klucel matrix for oral chemotherapy

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ABSTRACT

Erlotinib (ERL) is a tyrosine kinase inhibitor (TKI) compound class of chemotherapeutic agent mainly applied for pancreatic cancer, non-small cell lung cancer (NSCLC). Due to its pH-dependency solubility in water, the drug presents a low solubility under neutral pH, which can result in a poor oral absorption. Therefore, this work aimed the development of amorphous ERL formulation based on polysaccharide to improve its solubility and inhibit the drug recrystallization, in oral administration. To do so, a blend of two polysaccharides, Pullulan (PUL) and Klucel (KLU), was applied as a polymeric matrix to obtain an amorphous solid dispersion (ASD) of ERL. The ASD formulations were prepared by hot-melt extrusion (HME), using two different mass ratios of drug:polymer (1:4 and 1:2.3). The amorphous properties of filaments produced by HME containing PUL were confirmed by XRD and MDSC technique. In-vitro dissolution tests performed to mimic the gastrointestinal passage could demonstrated a potential inhibition of ERL recrystallization after simulated gastric-to-intestinal transfer of cryo-milled ERL filaments and the interest of this kind of formulation of ERL for oral cancer treatment.

Keywords: Erlotinib, Pullulan, Klucel, Hot-Melt Extrusion, Amorphous solid dispersions

1 INTRODUCTION

The increasing incidence of cancer worldwide results in the search for new active pharmaceutical ingredients (API), or the improvement of chemotherapeutic agents' efficacy that are already available in the market. Erlotinib (ERL) is a tyrosine kinase receptor inhibitor medication mainly applied in non-small cell lung cancer (NSCLC) and pancreatic cancer, which has been recently approved as the brand Tacerva® by Food and Drug Administration as a standard chemotherapy for oral administration[1]. Even though, ERL presents poor bioavailability which is due to low aqueous solubility, instability in the gastrointestinal tract and extensive first pass metabolism[1,2]. Therefore, new formulations of ERL using biopolymers has been evaluated to improve its low solubility and bioavailability, since they present an excellent biocompatibility and biodegradability, besides, the processability in different types of pharmaceutical formulations[2,3].

Different methods of drug administration and formulation types have been applied to improve the drug bioabsorption by modifying the bioavailability of actives[4]. Amorphous Solid Dispersion (ASD) is a widely formulation strategy for improving oral bioavailability of drugs with poor aqueous solubility. In the ASD formulations, the drug is normally dispersed as an amorphous phase in an excipient carrier enhancing its solubility, wettability, rate dissolution and supersaturation concentration. The API supersaturation combined with the "parachute" effect (recrystallization retarding) is a potential way to improve oral bioavailability[5]. Hot melt extrusion is a technique to process pharmaceutical formulation, in a solvent-free way, which is commonly applied to obtain an ASD formulation. The process involves a mixture of polymer and active agent under high temperatures and pressure, resulting in a versatile material for the development of different administration forms, such as tablets and orodispersive films for oral use[6].

Polymers are integral excipients of ASDs, they are commonly applied as matrices for the development of API amorphous form, consequently modifying the drug bioavailability. Several types of polymers are investigated as potential for ASD, and polysaccharides obtained by fermentative processes stand out as promising in the development of active carriers[7]. Pullulan is a polysaccharide produced bythe fungus *Aureobasidium pullulans*, which presents a hydrophilic, biodegradable, nontoxic, and amorphous properties, with a structure composed of maltotriose units interconnected via α-(1→6) bonds. However, pure pullulan does not present the properties required for processes such as hot melt extrusion, or dispersion in aqueous solutions, being necessary its chemical modification or blend with another polymer to result in a better processability[8]. In the present work, Klucel (Hydroxypropyl cellulose), a common pharmaceutical excipient, was blend with Pullulan in the development of Erlotinib (ERL) ASD, using hot melt extrusion as formulation generation process. The impact of this microbial polysaccharide in the ERL-ASD formulation was also evaluated through in-vitro dissolution tests.

2 MATERIAL & METHODS

2.1. ASD Filaments production

The filaments were prepared to obtain amorphous solid dispersion with ERL and promote a future application as an orodispersible film (ODS). The preparation of ASD filaments was performed in a mini-extruder MiniLab 3 (Thermo scientific, HAAKE), equipped with a co-rotating twin-screw parallel and an integrated backflow channel to recirculate the melted samples. PUL maximum amount was settle 30%w/w in the blend since there is a limitation in the amount of this polysaccharide (high Tg)

that could be used in the hot melt extrusion. Two different mass proportions of PUL:KLU:ERL were mixture to prepare the ASD filaments, 30:50:20, 30:40:30 %w/w. A formulation without PUL (0:80:30 %w/w) was also prepared to be used as a reference. Each PUL:KLU:ERL mixture (5 g) were fed into the mini extruder at 160 °C, operating with a screw speed of 150 rpm and a recycle time of 3 min. The extrudates were pushed through out a die diameter of 1.5 mm, producing molten PUL:KLU:ERL filaments, which were characterized by thermal and crystallinity properties. For thermal analyses, a modulated differential scanning calorimeter (MDSC) (TA Instruments Q200, USA) was applied to evaluate the thermal transformation in each material. Using an aluminum pan and non-hermetically sealed and heated in a sinusoidal program from -50 to 250 °C at a rate of 2 °C/min with a modulation period of 40 s and amplitude 0.8 °C, under a nitrogen flow. The data were acquired using the Thermal Advantage software and analyzed by Universal Analysis software (TA Instruments). The crystallinity property was analyzed by an X-ray diffraction (XDR) technique in a PAN-analytical Empyrean ACMS 101 (Malvern, UK) diffractometer operating at room temperature, using a copper (Cu) X-ray tube with Kα radiation. The current applied was 40mA, and the voltage was 40kV. The experiments were conducted with a scan range from 10 to 90° (2θ), a step size of 0.02° (2θ), and a counting time of 50 s.

2.2. Erlotinib dissolution test

The methodology used was previously described by Mugnier et al. (2023). The PUL:KLU:ERL filaments were firstly cryo-milled using a MiniLab 3 in a 6775 Freezer/Mill (SPEX SamplePre, LLC), to prepare a powder, which is a physical form better suited to conventional pharmaceutical forms such as capsules and tablets. The filaments were first pre-cooled in 4 minutes, followed by 2 cycles of 1 minute and 30 seconds of milled, with a second cool time of 2 minutes between both milling cycles.

All the PUL:KLU:ERL powders and pure ERL were weight in a proper amount (samples containing 9 mg ERL in a gelatine capsule) and the dissolution experiments were performed. A six-station dissolution rate test type II apparatus (ERWEKA DT 126 Light-DH1520, Germany) was used at 37 ± 0.5 °C with paddle speed at 75 rpm. To evaluate the dissolution profile in an oral administration way, two pH stages was used to mimic the gastrointestinal passage. The dissolution test started with 230 g of dissolution medium of 0.1 M of HCl at pH 1.2 was used to simulate a stomach delivery of ERL during 2h. After, 70 g of 0.4 M sodium phosphate buffer solution was added to dissolution vessel, adjusting the pH to 6.8, and keeping it for 4h. All experiment was conducted in triplicate, and the samples were taken at both pH in a preestablished time interval. They were then centrifuged, and the supernatant analyzed in a UHPLC Agilent system Infinity II 1290 apparatus with a Kromaplus® C18 column using a mixture of acetonitrile, 10 mM pH4 Ammonium Acetate Buffer and Methanol in the ratio 50:30:20 v/v, respectively, as mobile phase and a flow rate was set at 1.00 ml/min. 15 µL of sample was injected and a UV detector at a wavelength of 254 nm was used to quantify.

3 RESULTS & DISCUSSION

The ASD filaments were prepared with two different amounts of ERL (20 and 30 %w/w) and 30%w/w PULL. One formulation was prepared with only Klucel and ERL to evaluate the influence of PULL in the mixture. The X-ray diffraction study (Figure 1) was conducted to evaluate the solid state of ERL, before and after processing on the hot melt extrusion. For pure ERL, the sharp peaks at 12.64, 18.16, 22.28 on 2θ confirmed its crystalline nature. Contrarily, the XRD pattern of all PUL:KLU:ERL filaments cryo-milled showed no ERL crystal peaks and confirmed the amorphous state of these processed formulations that can be considered ASD formulations.

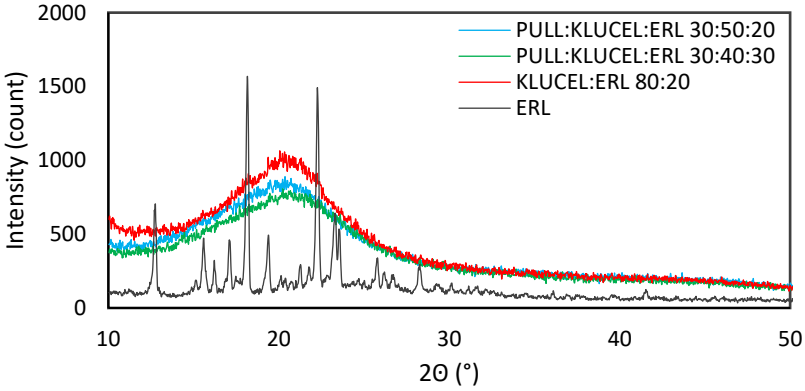

Figure 1 XDR pattern of pure ERL and ASD cryo-milled filaments with PUL, KLU, and ERL.

Concerning the dissolution behavior of these new ERL-ASD formulations in an aqueous environnement simulating the gastric-to-intestin transfer conditions, Figure 2 presents the obtained results. As can be observed in Figure 2a, compared to pure ERL dissolution, all ERL-ASD formulations presented a slower release under low pH, which can suggest a better control of ERL dissolution, when apply in oral administration. The increase of ERL content in the formulation (20 to 30%w/w) also led to ans increase ERL dissolution from the ASD-ERL formulation.

Figure 2b shows that, after adjusting the pH from acid to neutral condition, all ERL-ASD formulations presented higher concentration as pure ERL in the basic medium. It is important to observe that formulations containing PUL presented an

inhibition of ERL recrystallization, especially the formulation containing 30 %w/w of the API. The five minutes delay obtained represents a significant change in the bioavailable ERL under neutral pH. which could represent a great potential for future evaluation and pharmaceutical application.

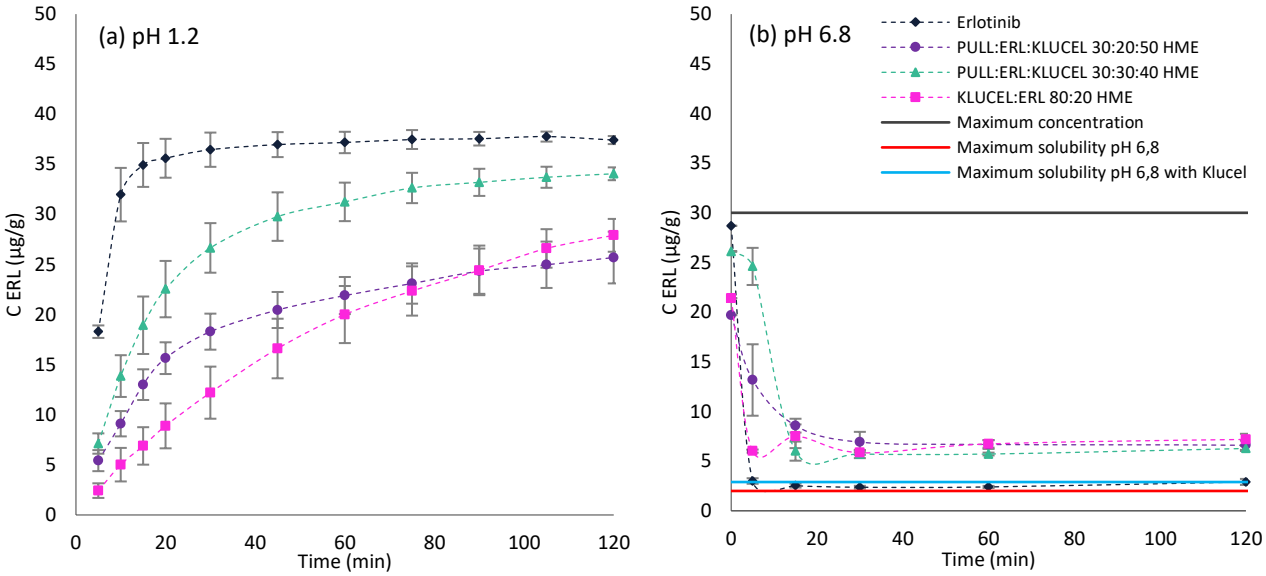

Figure 2 XDR pattern of pure ERL and ASD filaments with PUL, KLU, and ERL.

4 CONCLUSION

The poor solubility of ERL in aqueous medium presents a limitation of the drug in oral chemotherapy. Enhancing soluble fraction of ERL in aqueous medium could improve the bioavailability and bioadsoption of the chemotherapic in the body. The combination of pullulan and klucel as a polymeric matrix to produce ERL-ASD by HME process could represent an interesting approach to improve the pharmacokinetic behavior of ERL after oral administration.

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