Process for Both Palatability and Dissolution Rate Improvement

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Abstract

This work aimed at obtaining an optimized itraconazole (ITZ) solid oral formulation in terms of palatability and dissolution rate by combining different polymers using hot melt extrusion (HME), according to a simplex centroid mixture design. For this, the polymers Plasdone® (poly(1-vinylpyrrolidone-co-vinyl acetate) [PVP/VA]), Kluce® ELF (2-hydroxypropyl ether cellulose [HPC]), and Soluplus® (SOL, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol) were processed using a laboratory HME equipment operating without recirculation at constant temperature. Samples were characterized by physicochemical assays, as well as dissolution rate and palatability using an e-tongue. All materials became homogeneous and dense after HME processing. Thermal and structural analyses demonstrated drug amorphization, whereas IR spectroscopy evidenced drug stability and drug-excipient interactions in HME systems. Extrudates presented a significant increase in dissolution rate compared to ITZ raw material, mainly with formulations containing PVP/VA and HPC. A pronounced improvement in taste masking was also identified for HME systems, especially in those containing higher amounts of SOL and HPC. Data showed polymers act synergistically favoring formulation functional properties. Predicted best formulation should contain ITZ 25.0%, SOL 33.2%, HPC 28.9%, and PVP/VA 12.9% (w/w). Optimized response considering dissolution rate and palatability reinforces the benefit of polymer combinations.

Introduction

Advantages of oral solid formulations are clear: high stability, dose accuracy, low production, and transportation costs, besides patient compliance. Still, unsatisfactory physicochemical properties may compromise drug bioavailability. It is estimated that 75% of drug candidates to give rise to new medicines are poorly water soluble. Such low solubility negatively affects pharmacokinetics, causing high rates of failure in clinical trials, which has considerably reduced the number of innovative medicines that reaches the market over the years. Other challenge for oral delivery is the unpleasant taste of drugs, which adversely in fluences patient compliance, especially when dealing with children and elderly. Most active pharmaceutical ingredients present bitter taste. Thus, considering the wide variety of bitter receptors on the tongue, camouflaging drugs unpleasant taste is not a trivial task.

Hot melt extrusion (HME) is a technological process for developing solid dispersions that has been capable of improving dissolution rates of many poorly water-soluble drugs. Remarkable advantages of this technique include avoidance of organic solvents, possibility of continuous manufacturing, easy processing scale-up, and enturdrate uniformity due to the high shear mixing capacity. Indeed, such a high mixing capacity provides a high drug-polymer interaction degree and, with the adequate formulation, bitter taste can be masked as polymers interact with tongue taste receptors masking the drug.

Despite all these advantages, a still limited number of HME pharmaceutical products are available on the market, around 15 products. A possible explanation is the complexity of experimental variables involved in the development of products by HME, which may compromise overall process robustness (mainly, the use of different temperatures throughout extrusion course and sample residence time into the system). Additionally, small fluctuations in
formulation composition can cause important changes in their properties. Evidently, all these factors raise quality issues, especially in large-scale production.9

Quality-by-design tools such as mixture designs are useful to rationalize the experimental work in order to establish the optimum formulation composition by determining a design space in which the components can fluctuate without impairing their functional characteristics, thus facilitating the scale-up process. Better yet, such approach also allows finding regions in the experimental space where the levels of formulation factors possibly provide the best performance.10

Therefore, this work evaluated a simplex centroid mixture design experiment as a tool for predicting the best polymer combination for HME of a bitter insoluble drug. The goal was to obtain the best formulation for HME with improved characteristics, specifically, palatability and dissolution rate, by simply selecting the better suited excipients, while maintaining the most simple process parameters: constant temperature and no recirculation. For this, itraconazole (ITZ) was selected as drug model, because it is a BCS II compound possessing a pronounced bitter taste and promising results when processed by HME.11-14

The hydrophilic polymers Plasdone® S-630, Klucel® ELF, and Soluplus® were chosen to improve drug dissolution through different solubilization mechanisms.

**Experimental**

**Material**

ITZ (lot 00569488, 99.5%) was provided by Roche (Basel, Switzerland). The polymers Plasdone S-630 (lot 0001810863, poly(1-vinylpyrrolidone-co-vinyl acetate) [PVP/VA], average molecular weight = 47 kDa) and Klucel ELF (lot 40915, 2-hydroxypropyl ether cellulose [HPC], average molecular weight = 40 kDa) were donated by Ashland Specialty Ingredients, whereas Soluplus ([SOL] lot 844143368EO, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol, average molecular weight = 118 kDa) was donated by BASF (Ludwigshafen, Germany). All other chemicals and solvents were of analytical grade.

**Drug Determination**

A spectrophotometric method using a UV-VIS Lambda XLS spectrophotometer (PerkinElmer) set at 255 nm was developed for ITZ determination in formulations and in dissolution rate experiments. Analytical method was validated. Selectivity against polymers was evaluated and no statistical interference with excipients was detected (Student t-test, p = 0.07). Linearity correlation coefficient (CC) was 0.9984 with slope different from zero and residues randomly distributed without tendency.

**Morphological Analysis**

Morphological characteristics of the individual compounds, physical mixtures, and extrudates were assessed with a stereo microscope (Laborana/SZ—SZT, China) and with a scanning electron microscope (JSM-7001F; Jeol, Akishima, Japan), in which the samples were previously metallized with gold.

**Table 1**

Summary of the Formulation Compositions and the Extrusion Parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition (% w/w)</th>
<th>Temperature (°C)</th>
<th>Rotation (rpm)</th>
<th>Design Representation</th>
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<td></td>
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<td>HPC</td>
<td>PVP/VA</td>
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