Journal of Pharmaceutical Sciences xxx (2017) 1-11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Hot Melt Extrudates Formulated Using Design Space: One Simple Process for Both Palatability and Dissolution Rate Improvement

Lorena F.B. Malaquias [1], Heidi L. Schulte [1], Juliano A. Chaker [2], Kapish Karan [3], Thomas Durig [3], Ricardo N. Marreto [4], Tais Gratieri [1], Guilherme M. Gelfuso [1], Marcilio Cunha-Filho [1, *]

[1] Laboratory of Food, Drug and Cosmetics (LTMAC), School of Health Sciences, University of Brasília, 70910-900 Brasília, Federal District, Brazil
[2] Faculty of Ceilândia, University of Brasília (UnB), 72220-900 Ceilândia, Federal District, Brazil
[3] Ashland Pharma and Nutrition, 500 Hercules Road, Wilmington, Delaware 19808
[4] School of Pharmacy, Federal University of Goiás, 74 605-170 Goiânia, Goiás, Brazil

ARTICLE INFO

Article history:
Received 24 July 2017
Revised 12 August 2017
Accepted 17 August 2017

Keywords:
dissolution rate
e-tongue
hot melt extrusion
hydrophilic polymers
itraconazole
palatability

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]), Klucel® 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.[1] 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.[2] 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.[3] Other challenge for oral delivery is the unpleasant taste of drugs, which adversely influences patient compliance, especially when dealing with children and elderly.[4] 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.[5]

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.[6,7] Remarkable advantages of this technique include avoidance of organic solvents, possibility of continuous manufacturing, easy processing scale-up, and entrudate 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.[5]

Despite all these advantages, a still limited number of HME pharmaceutical products are available on the market, around 15 products.[8] 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

* *Correspondence to:* Marcilio Cunha-Filho (Telephone/Fax: +55-61-31071990).
E-mail address: marciliofarm@hotmail.com (M. Cunha-Filho).

http://dx.doi.org/10.1016/j.xphs.2017.08.014
0022-3549/

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.

HME Extrudates

Extrudates were prepared by HME combining ITZ with 3 polymers (PVP/VA, HPC, and SOL) following a simplex centroid mixture design without constraints (in detail in section *Design of Experiment*). For this, ITZ concentration was fixed at 25% w/w in each sample (Table 1). Physical mixtures of each formulation were prepared using a mortar and were then extruded using constant temperature without sample recirculation in a Pharma Mini HME (ThermoScientific). Extrusion parameters, temperature and rotation speed, were set with the purpose of obtaining an adequate extrusion flow and translucent extrudates without darkening (Table 1). Extrudates were milled in a knife mill and the fractions were separated using sieves with different mesh. After separation, a powder fraction having a size ranging from 180 to 125 μm, which was the fraction with the best yield, was selected for further tests.

Characterization Assays

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 stereoscope (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

Formulation	Composition (% w/w)			Temperature (°C)	Rotation (rpm)	Design Representation
	SOL	HPC	PVP/VA			
FA	75	0	0	170	50	
FB	0	75	0	170	50	
FC	0	0	75	170	100	
FD	37.5	37.5	0	170	50	
FE	0	37.5	37.5	170	50	
FF	37.5	0	37.5	170	50	
FG	25	25	25	170	50