Griseofulvin Taste Masking by Hot Melt Extrusion for Pediatric and Geriatric Reconstitutable Suspension

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INTRODUCTION

The taste masking of bitter APIs is a major challenge especially for pediatrics formulations. Various reported approaches include, fluidized-bed coating, supercritical fluids, complexing agents, Pro-drug approach, etc. However, there is an enormous need for more robust, cost effective and easy to scale-up taste masking technologies. Hot Melt Extrusion (HME) is a continuous, one step process that has been used for the development of solid dispersions of active substances for various applications.

HME has also been introduced for taste masking purposes of bitter APIs by involving the use of taste masking polymers that create solid dispersions to prevent bitter drugs from coming in contact with the patient's taste buds.

Therefore the main objective of this project was to investigate the potential of KLEPTOSE® Linecaps DE17 (a pea maltodextrin with a DE range of 15 – 20) in masking the bitter taste of antifungal drug, griseofulvin (GRI) by Hot Melt Extrusion (HME) and to formulate a reconstitutable suspension for pediatric/geriatric patients.

MATERIALS & METHODS

THERMOGRAVIMETRIC STUDIES: Thermogravimetric studies were performed on a Perkin Elmer Pyris 1 thermogravimetric analysis (TGA) equipped with Pyris software. Studies were performed on KLEPTOSE® Linecaps DE17, plasticizers and GRI to determine thermal stability during extrusion. Drug and polymers were heated from 30–200°C at 20°C/min.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES: The physical characterization of pure GRI, KLEPTOSE® Linecaps DE17 (KLD), plasticizers and extruded formulations was performed by DSC, using Perkin Elmer Diamond differential scanning calorimeter equipped with Pyris software (Shelton, CT, USA). Approximately 2–3 mg of the sample was hermetically sealed in a crimped aluminum pan and heated from 30°C to a temperature about 50°C higher than the melting point of the drug or the softening temperature of the polymers, at a heating rate of 20°C/min.

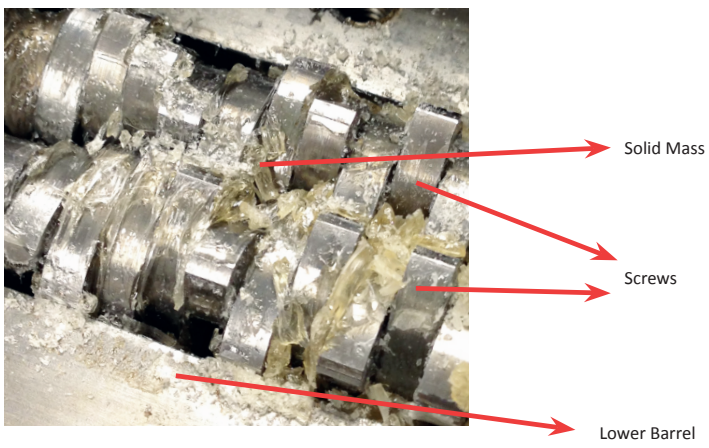
HOT MELT EXTRUSION: In order to increase KLD extrudability different polyols (Xylitol, Mannitol, Sorbitol, Erythritol and Maltitol) as plasticizers were evaluated at 10% and 20% w/w concentration. GRI at 10% -20% w/w drug loads were pre-mixed with KLD and plasticizer using a V-shell blender and further extruded using co-rotating twin screw extruder (16 mm Prism Euro Lab, ThermoFisher Scientific) at screw speeds of 50-150 rpm over a temperature range of 135-150 °C.

Milled extrudates were studied for in vitro dissolution release in simulated saliva fluid (pH 6.8) using USP Type-I apparatus at 37 ± 0.5 °C and 100 rpm. Samples (1 mL) were collected at predetermined time points (30, 60, 120, 180 and 300 sec) and were analyzed using a Waters HPLC-UV system (Waters Corp).

RESULTS & DISCUSSION

Thermogravimetric studies confirmed the stability of GRI, KLD and polyols at the employed extrusion temperatures. The DSC studies revealed a characteristic melting endotherm of GRI at 218-220°C in the physical mixtures as well as in all extrudates over the period of study, indicating the crystalline nature of the drug.

Figure 1. Hot Melt Extrusion of KLEPTOSE® LineCaps DE17 without plasticizer. Glassy solid mass formed at extrusion temperature.



Extrusion of plain KLEPTOSE® Linecaps DE17 was not possible due to formation of solid mass even at higher temperature (~165°C) (**Fig. 1**), which clogged the machine due to generation of high torque between the two screws located in between the upper and lower barrel.

The extrusion was performed without adding any water in the formulation. Therefore, the effect of plasticizers was evaluated to optimize the processing conditions during HME, to tailor the extrudates properties during hot melt extrusion or during post-die processing and to modify the release properties of the final dosage form.

Plasticizers are typically ingredients with low molecular weight, either in liquid or solid state. They add to the free volume of main constituent of the formulation i.e. polymeric carrier and thereby loosen the local liquid structure of the polymer.

It has been known that, plasticizers are known to decrease the glass transition temperature of amorphous polymers as a function of their concentration.

In principle this reduction in glass transition temperature during HME results in an improved processibility and reduction of thermal degradation of any of the constituents of the formulation.

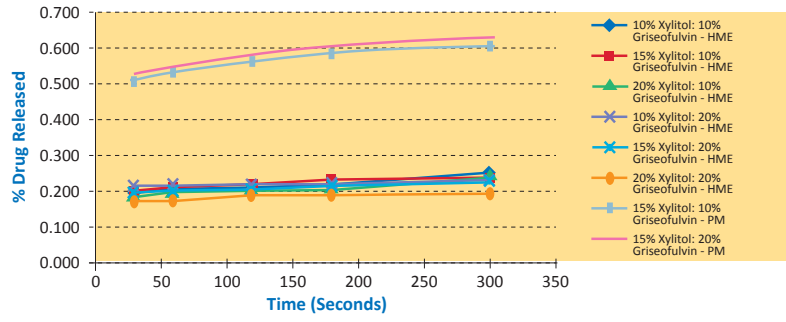
Among all the investigated plasticizers, xylitol showed improved processibility of KLD at all concentrations (**Table 1**).

Table 1. Torque generated during the HME of KLD with polyols as plasticizers.

Type of Polyol	Polyol Concentration (%)	Torque (%) (KLEPTOSE® Linecaps DE17)	Observation
Xylitol	10	25-30	Foamy Extrudates
	20	13-15	Transparent Extrudates
Maltitol	20	45-50	Opaque Extrudates
	30	35-38	Transparent Extrudates
Sorbitol	10	32-38	Foamy Extrudates
	20	15-20	Transparent Extrudates
Mannitol	10	45-40	Foamy Extrudates
	20	15-18	Transparent Extrudates
Erythritol	10	35-40	Foamy Extrudates
	20	20-25	Transparent Extrudates

Therefore, further studies were continued with xylitol as plasticizer. Dissolution profiles with xylitol as plasticizer at 10% and 20% w/w GRI load are shown in **Fig. 2**. The dissolution rates of GRI at both the drug loads and at three different concentrations of plasticizers (10%, 15% and 20% w/w) exhibited less than 0.5% release of the API in simulated saliva fluid (**Fig. 2**) (Lower the release, higher the taste masking effect), suggesting the potential use of KLEPTOSE® Linecaps DE17 in development of taste masked formulation by HME for a reconstitutable suspension. Dissolution rates of physical mixture (PM) - GRI at 10 % and 20% drug loads exhibited ~3 times more release than HME – GRI, suggestive of the potential use of KLD in development of taste masked formulation by HME for a reconstitutable suspension.

Figure 2. Dissolution profiles of HME formulations and PM containing 10% and 20% w/w drug loads with varying concentration of xylitol as plasticizer.



CONCLUSION

HME of GRI at varying drug load using KLEPTOSE® Linecaps DE17 as a matrix and Xylitol as a plasticizer demonstrated very good extrudability. Lower release of micronized GRI could suggest the potential use of KLEPTOSE® Linecaps DE17 in development of taste masked formulation by HME for a reconstitutable suspension.

REFERENCE

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