EFAVIRENZ - POLYMER HOT MELT EXTRUSION SYSTEMS FOR DISSOLUTION ENHANCEMENT: PHYSICO-MECHANICAL CHARACTERIZATION AND DRUG RELEASE STUDIES

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ABSTRACT SUMMARY

Efavirenz (EFV) is a non nucleoside reverse transcriptase inhibitor used for the treatment of human immunodeficiency virus (HIV) type 1 infection.1 This drug has been classified as a Biopharmaceutics Classification System (BCS) Class-II compound with good permeability but poor aqueous solubility with a dissolution rate dependent absorption. This drug has very low oral bioavailability (40-45%) and high inter (56%) and intra (22%) individual variability in its absorption.2 The very low aqueous solubility (~3-9 µg ml−1) hinders its administration, oral absorption and bioavailability.3 By improving dissolution, it is possible to enhance its oral bioavailability and reduce side effects. This study summarizes the physico-mechanical properties and drug release studies of EFV-polymer systems prepared by hot melt extrusion.

INTRODUCTION

Hot melt extrusion (HME) is a promising method to enhance the dissolution of poorly soluble drugs. The improvement in dissolution by HME can be attributed to the improved wetting of the drug, deagglomeration and micellization of the drug with hydrophilic polymers.

Amorphous drug substances are physically unstable due to their high energy state and tend to recrystallize upon storage. In order to stabilize these systems various polymer carriers have been used because they readily generate amorphous forms and may be able to retain the amorphous nature of the drug upon storage. The long polymeric chains can sterically hinder the association between drug molecules and thereby inhibit the recrystallization of drug. In addition, the interaction between the drug and polymer provides an increased energy barrier for nucleation and consequently enhances the physical stability.

EFV has a very low intrinsic dissolution rate of 0.037 mg min−1 cm−2, which suggests dissolution rate-limited absorption problems for this drug. The primary objective of this study was to characterize amorphous EFV - polymer systems prepared by HME in order to enhance the dissolution of the drug.

EXPERIMENTAL METHODS

Amorphous systems of efavirenz with Eudragit EPO (a low glass transition polymer) or Plasdone S-630 (a high glass transition polymer) were prepared by using HME. The binary physical mixtures of these systems were characterized for their thermal and rheological properties as a function of drug concentration to understand their miscibility and processibility by HME. Thermal analysis was performed by measuring Tg of these binary systems using a Differential Scanning Calorimetry (DSC). The rheological properties of the polymers and binary mixtures were studied using a rotational rheometer. The measured and calculated parameters were zero shear viscosity (η0) and activation energy (Ea).

Composites of drug and polymer in a 1:1 ratio were prepared by using a Haake Minilab twin screw extruder with counter rotating screws at 50 rpm. The formulations were analyzed for drug content and saturation solubility and further characterized by DSC, X-ray Diffractometry (XRD), Fourier-Transform Infrared Spectroscopy (FT-IR) analyses. The dissolution studies of the formulations were performed using USP II apparatus in 0.01N HCl with 0.2% sodium lauryl sulfate (SLS) in water dissolution medium. The stability studies were conducted to determine the effect of aging on the physical and chemical stability of the drug in various formulations. The extrudes were stored in screw capped glass vials at room temperature (~23°C) and ~30-40% relative humidity. The samples collected at 3, 6 and 9 month intervals were characterized by DSC, XRD, FT-IR, drug content and dissolution studies.

RESULTS AND DISCUSSION

The calculated solubility parameter (δ) for EFV is 24.55 MPA1/2 and for Eudragit EPO and Plasdone S-630 are 20.55 and 22.94 MPA1/2, respectively. Both polymers and drug have similar values for solubility parameters and hence are likely
to be miscible with the drug in the HME formulations. Thermal and rheological studies revealed that the drug is miscible with both polymers and a decrease in melt viscosity was observed as the drug concentration increased.

The polymers and binary mixtures display a Newtonian plateau that transitions to shear thinning behavior as described by the Cross model. The binary mixture of EFV: Plasdone S-630 at 4:1 ratio displayed Newtonian behavior thus, was not represented by the Cross model. The zero shear viscosity continuously decreases with drug loading, signifying the solubilization and plasticizing effect of the drug on the polymer. The inverse relationship between $E_a$ and the drug concentration also suggests the plasticization effect of EFV on both polymers.

Transparent extrudates were produced with both polymers at 50 wt% drug loading. The drug content determined by HPLC in the extrudates was at 96% to 103%. XRD and DSC studies confirmed the existence of amorphous state of EFV in the extrudates during storage. FTIR studies revealed an interaction between the EFV and Plasdone S-630 which reduced the molecular mobility and prevented crystallization upon storage. EFV and Eudragit EPO systems lack specific interactions, but are less susceptible to crystallization due to the antiplasticization effect of the polymer.

Both DSC and XRD results on aged samples confirmed that there was no recrystallization of the amorphous drug in the HME formulations suggesting good physical stability. The dissolution profiles of aged samples relative to fresh HME formulations further proved that the amorphous state of the drug was maintained in the aged formulations.

CONCLUSION

Dissolution rate enhancement of EFV was obtained by preparing amorphous glassy solutions with Eudragit EPO and Plasdone S-630 polymers by HME. The crystalline EFV was converted to the amorphous state during the extrusion process. Enhanced physical stability of the Plasdone S-630 HME formulation is attributed to drug-polymer interactions and for Eudragit EPO systems, the antiplasticization effect of the polymer.

REFERENCES


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