Solid Crystalline Dispersions of Sildenafil Citrate in Ethyl Cellulose Produced by Hot-Melt Extrusion

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Abstract Summary

Solid crystalline dispersions of the model drug Sildenafil Citrate (SC) in the polymeric carrier ethyl cellulose (EC) were prepared using hot-melt extrusion (HME) technology. Thermogravimetric analysis and differential scanning calorimetry suggested that the API, excipients and physical mixtures were stable under the employed processing conditions. FT-IR chemical imaging and PXRD were used to determine the effects of multiple screw configurations, or arrangement of screw elements, on the distribution and physical state of the API in the dispersion.

Introduction

Hot-melt extrusion has gained considerable attention over the past several years due primarily to the technique’s ability to address a growing concern surrounding the poor solubility and bioavailability of many new chemical entities. Given some of the additional advantages inherent in HME processing (i.e. continuous processing, fewer processing steps, simple scalability, avoidance of toxic organic solvents, etc.), it becomes apparent that processing any suitable API by this technique is an attractive option regardless of which BCS class it belongs to. However, in the case of BCS class I and class III APIs it may be appropriate to preserve the initial crystalline structure as solubility enhancement is not necessary and common stability issues associated with the amorphous form, such as re-crystallization into an undesired polymorphic form, can be avoided.

While screw configuration is widely regarded as a critical processing parameter in HME processing as it plays a vital role in the physicochemical characteristics of the final extrudates, little practical information is available in the literature concerning the effects of screw configuration on pharmaceutical extrudates. Moreover, nearly all of that information is focused on the conversion of a crystalline API into its amorphous form. This research focused on the effect of screw configuration on the dispersion and distribution of the API as well as its post extrusion physical state.

Experimental Methods

\textit{Thermogravimetric Analysis (TGA):}

Thermogravimetric analysis (TGA, Pyris 1 TGA Perkin Elmer, MA, USA) was used to assess the thermal stability of the individual compounds and physical mixtures at the processing temperatures employed in the melt extrusion processing. The analysis was conducted on samples weighing 5-8mg over a temperature range of 25-185°C at a heating rate of 20°C/min.

\textit{Differential Scanning Calorimetry (DSC):}

The physical state of the drug, as well as processing stability, was analyzed in part using DSC (Diamond DSC, Perkin Elmer, MA, USA). 3-4mg samples were hermetically sealed in aluminum pans and heated of a temperature range of 25-185°C at a heating rate of 20°C/min and holding the samples at that temperature for 5 minutes in order to approximate residence time and thermal stresses applied during extrusion.

\textit{Hot-Melt Extrusion:}

The physical mixture was melt extruded into uniform rods using a fully intermeshing co-rotating twin-screw extruder (11 mm Process 11, Thermo Fisher Scientific) with a multiple screw designs at 100 rpm and over a temperature range of 140-160°C. The extrudates were stored in sealed glass containers under refrigeration until further analysis.

\textit{Chemical Imaging & FTIR Analysis:}

Infrared spectra were collected on an FTIR bench (Agilent Technologies Cary 660) fitted with a MIRacle ATR (Pike Technologies). The ATR utilized a diamond coated ZnSe internal reflection element. Chemical images were collected using an infrared microscope (Agilent Technologies Cary 620 IR) which was equipped with a focal plane array (FPA) detector. Images were collected with and without a germanium micro ATR.

\textit{PXRD:}

Powder X-Ray Diffraction (Bruker AXS D8) was utilized to support the findings of the FTIR chemical imaging. The apparatus used CuKα radiation at 35 mA and 40 kV, 2°/min, and diffraction angles (2θ) of 5-50°.

Results and Discussion

TGA thermograms indicated that the API, excipients and their physical mixtures were thermally stable under the conditions employed for melt extrusion processing. These findings were supported by DSC data wherein no unexpected thermal events were observed.

Conventional FT-IR analysis (Figure 1) allowed for differentiation between crystalline and amorphous phases of SC as they have different spectral signatures in the fingerprint region (4000-400cm\textsuperscript{-1}). These differences were utilized to produce IR chemical images (Figures 2 & 3), which were restricted to a region of 4000-850cm\textsuperscript{-1}.
Figure 2 represents an IR image of crystalline SC dispersed in the polymeric carrier at 5.5µm spatial resolution. Figure 3 is an IR image taken at 1.1µm spatial resolution. In Figure 3, it can be seen that maintaining the crystalline structure of SC has caused a slight inhomogeneity where pockets of crystallinity can be observed. However, this inhomogeneity was considered negligible as it did not appear in content uniformity testing. The application of chemical imaging for the examination of the extrudates was particularly advantageous in that simultaneous measurement of spatial distribution of the API as well as its physical state was readily achieved. Moreover, analyzing the extrudates without prior milling relieves any concerns regarding alterations that can occur during the milling process.

PXRD data supported the observations concerning the physical state of the API (i.e. amorphicity vs. crystallinity). However, there was a notable decrease in the intensity of the API’s most intense peaks in the extruded formulations wherein crystallinity had been maintained (data not shown). This was attributed to the dilution of the API in the carrier matrix.

**Conclusion**

HME is a flexible yet robust processing platform that is applicable to many pharmaceutical processing needs; however, a deeper understanding of the effects of the screw design is needed for pharmaceutical applications. Variations in the arrangement of the twin screw elements have a considerable impact on the final state of the API in the dispersion. In contrast to most HME experimentation, this research demonstrates the ability to maintain the crystallinity of a BCS class I API while still achieving excellent homogeneity. The ability to produce not only amorphous dispersions but to also produce crystalline dispersions lends this technology to a wider variety of applications than was initially intended.

**References**


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