

Foam Hot Melt Extrusion of an Eudragit - Nifedipine Matrix Formulation using Supercritical CO₂

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ABSTRACT SUMMARY

Foam extrusion was investigated as a second generation of Hot Melt Extrusion (HME) technology to facilitate HME processing, improve the millability of the extrudate, and further increase the API release rate. In this investigation, the release rate of poorly soluble drug Nifedipine was improved by hydrophilic polymer Eudragit EPO using Foam HME.

INTRODUCTION

Hot Melt Extrusion (HME) is a widely used technology in the plastics industry and nearly half of the plastic products are manufactured using HME processing. Currently, pharmaceutical industry is investigating applications of HME technology in developing various drug delivery systems such as granules, pellets, tablets, implants, transdermal systems, and ophthalmic implants¹. The APIs can be mixed with various polymers at high temperatures to manufacture solid dispersions in different shapes². Further, various screw designs and temperature controlled barrel system can be utilized to tailor the processing conditions depending on the characteristics of the drugs and the polymers. Today, HME has become an attractive processing technique in improving the dissolution rate of poorly water soluble drugs to enhance their bioavailability after oral administration³. These crystalline hydrophobic drugs can be dispersed in hydrophilic polymers using HME to manufacture amorphous solid dispersions to improve their solubility and dissolution rate.

Although HME is an attractive process to manufacture pharmaceutical formulations, processing of high melting APIs and high glass transition polymers becomes difficult due to high melt viscosity. Hence, various plasticizers

such as triethyl citrate, tributyl citrate, dibutyl sebacate, and surfactants have been investigated to reduce the melt viscosity during HME process⁴. However, inclusion of these plasticizers not only adds extra weight to the formulation but also may increase the possibility of crystallization of amorphous APIs. Recently, carbon dioxide is being used as a plasticizer to reduce the glass transition of the polymers during HME without being present in the final formulation⁵. CO₂ acts as a molecular lubricant by increasing the free volume and reducing the chain entanglement after getting absorbed between the polymer chains⁶. Further, such CO₂ induced foam HME-product becomes more suitable for milling.

EXPERIMENTAL METHODS

In this investigation Nifedipine was selected as a poorly water soluble BCS class II API and Eudragit EPO was chosen as a hydrophilic polymer. The drug was mixed with the polymer to prepare physical mixtures with following ratios. EPO 70: API 10: Talc 20 (FOAM), EPO 89: API 10: Talc 1 (FOAM), and EPO 90: API 10 (NO FOAM).

These physical mixtures were extruded at 50 rpm. Supercritical CO₂ was injected into the extruder during extrusion. Temperature profiles along the screws were carefully set to assure optimal mixing and prevent thermal degradation. The polymer / API was fluxed at 150°C and the temperature was reduced to 90°C from the point of CO₂ injection to the exit of the machine. Appropriate screw configuration was selected to avoid the high pressure CO₂ from escaping the extruder through the feed port.

Differential scanning calorimetry (DSC) of milled HMEs was performed to confirm the transformation of crystalline API into its

amorphous form. The samples were sealed in aluminum pans and heated till 200°C.

Dissolution study was performed using USP apparatus II at 37.5°C, and 50 rpm in 0.1N HCl for 2 hours.

RESULTS AND DISCUSSION

Foamed HME product could be milled more easily compared to the un-foamed HME samples, and generated more uniform powders.

The melting endotherms of Nifedipine were not detected in the HME samples that confirmed formation of amorphous solid dispersions of Nifedipine in Eudragit EPO. Further, single glass transition temperatures were observed suggesting formation of molecular dispersions.

The dissolution rate and supersaturation of Nifedipine were significantly improved with the increase in polymer concentration as shown in Figure 1. Like un-foamed HME, Nifedipine was entirely released within 20 minutes from the foamed HME. Moreover, the dissolution rate of foamed HME was faster than the un-foamed HME, given the same excipient-drug ratio (blue and green curves). Two foamed samples are significantly different in terms of dissolution rate and the final degree of supersaturation in dissolution medium (blue and red curves), which is probably due to the different excipient-drug ratio or addition of talc.

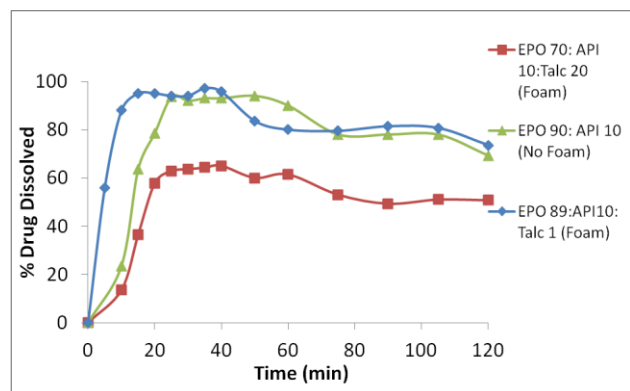


Figure 1. Effect of foam extrusion on dissolution profiles of Nifedipine HME product.

CONCLUSION

Supercritical carbon dioxide induced foaming was successfully used in improving the processing of HME technology. The foamed

HME molecular solid dispersions were found to be amorphous. Further, milling of foamed HME product was much easier compared to the un-foamed product. The release rate of Nifedipine could be tailored due to foaming. The study demonstrated the unique advantages of using CO₂ as a plasticizer for HME.

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ACKNOWLEDGMENTS

The authors wish to acknowledge the support of Charlie Martin and the American Leistritz Extruder Corporation, where the foaming trials were conducted.