Pharmaceutical Technology

Miscibility Studies of Indomethacin and Eudragit® E PO by Thermal, Rheological, and Spectroscopic Analysis

HUIJU LIU,[1] XUEYAN ZHANG,[2] HERMAN SUWARDIE,[3] PENG WANG,[4] COSTAS G. GOGOS[1]

[1]Otto York Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, Newark, New Jersey 07102

[2]Material Characterization Laboratory, New Jersey Institute of Technology, Newark, New Jersey 07102

[3]Polymer Processing Institute, Newark, New Jersey 07102

[4]Department of Chemical Engineering, University of Rhode Island, Kingston, Rhode Island 02881

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ABSTRACT: The objective of this study is to understand the underlying mechanisms responsible for the superior stability of indomethacin (INM)–Eudragit® E PO (E PO) system by exploring the miscibility and intermolecular interactions through the combination of thermal, rheological, and spectroscopic analysis. The zero shear-rate viscosity drops monotonically with the increase of INM concentration at 145°C, suggesting that E PO and INM form a solution and the small molecular drug acts as a plasticizer. Flow activation energy was calculated from the viscosity data at different temperature. The glass transition temperature (T_g) of the mixture at different composition was determined using differential scanning calorimetry. The T_g and flow activation energy peak at the INM concentration around 60%–70%. Fourier transform infrared analysis provided direct evidence for the intermolecular ionic interactions, which may disrupt the dimer formation of amorphous INM. The study explained the superior stability of INM–E PO mixtures, and demonstrated that a combination of thermal, rheological, and spectroscopic technologies can help us to obtain a full picture of the drug–polymer interactions and to determine the formulation and processing conditions. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2204–2212, 2012

Keywords: solid dispersion; molecular interactions; ionic interactions; stability; glass transition; Eudragit® E PO; indomethacin; thermal analysis; rheology; spectroscopy

INTRODUCTION

Amorphous solid dispersion (ASD) has gradually been accepted by the pharmaceutical industry as an important strategy for rendering active pharmaceutical ingredients (APIs) with poor water solubility readily bioavailable. The biggest advantage of the ASD technology lies in the faster dissolution rate and enhanced solubility of amorphous drug compared with its crystalline counterparts.[1,2] Recent discoveries of families of large number of potent and promising, but essentially water-insoluble, APIs further motivate researchers to explore relatively new formulation technologies including the ASD.[3] In practice, spray drying[4] and hot-melt extrusion (HME)[5,6] are the two most popular methods for preparing ASDs. The former method is solvent based, whereas the latter method is solvent free.

One of the biggest technical hurdles for the ASD technology is that the drug may crystallize during storage and thus lose the advantages of being amorphous.[7] A common approach to overcome the physical instability of amorphous drugs is to mix them with pharmaceutical polymers of high glass transition temperatures (T_g). Hopefully, the product's T_g can satisfy the "T_0 or $T_g - 50$ K rule"[8,9] commonly accepted in pharmaceutical field. Herein T_0 stands for the temperature at which the relaxation time goes to infinity, that is, zero mobility. The idea is that amorphous drugs should exist as a "frozen liquid" if the storage temperature is below T_0 or $T_g - 50$ K rule. Because the $T_g - 50$ K rule often fails and T_0 is generally too low to be the practical storage tempera-

Additional Supporting Information may be found in the online version of this article. Supporting Information

Correspondence to: Costas G. Gogos (Telephone: +973-642-7365; Fax: +973-642-4594; E-mail: costas.g.gogos@njit.edu)

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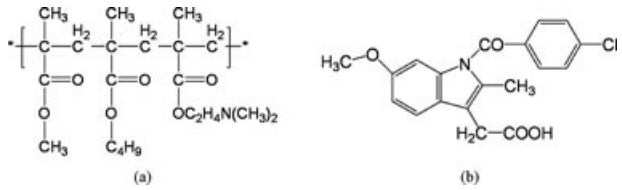

Figure 1. Chemical structures of (a) E PO and (b) INM.

ture, there has been an effort to address the instability issue from a different angle, namely, specific molecular interactions between APIs and excipients such as hydrogen bonding and ionic interactions.[9] For example, Yoo et al.[10] reported that all of the investigated systems having ionic interactions are physically stable after 50 days in the presence of moisture at 25°C even though the T_g of the mixture does not satisfy the "T_0 or T_g−50 K rule." However, it is not clear whether the conclusion can be applicable to other formulations given the limited study. In summary, although a lot of previous studies have been focusing on preparation and characterization of ASDs, how physical instability is affected by the miscibility or intermolecular interactions between APIs and excipients is still not fully explicit.[3]

The goal of this study is to understand the underlying mechanisms responsible for the superior stability of certain ASDs via a thorough characterization of the drug–polymer mixtures using thermal, rheological, and spectroscopic methods. To that end, indomethacin [INM, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] and Eudragit® E PO (E PO) were selected as the model drug and polymeric excipient, respectively. The chemical structures of E PO and INM are shown in Figure 1. E PO is a copolymer composed of neutral methyl and butyl methacrylate, and dimethylaminoethyl methacrylate repeating units. The copolymer is soluble up to pH 5 and it is capable of swelling and becomes permeable to water above pH 5 The excipient is widely used for masking unpleasant tastes and odors of drugs, and protecting drugs against moisture. INM is a nonsteroidal anti-inflammatory drug with a pK_a of 4.5, commonly used to reduce fever, pain, and swelling. It has a poor and pH-dependent water solubility (4.0–8.8 μg/mL in water).[11] The system of E PO and INM has been prepared by solvent method[12,13] and HME.[14–16]

It should be mentioned that Chokshi et al.[14,15] have investigated the solid dispersions containing INM and one of the three hydrophilic polymers, E PO, polyvinylpyrrolidone–vinyl acetate copolymer (PVP–VA), and polyvinylpyrrolidone K30 (PVP K30). They observed the antiplasticization effect of INM with E PO and superior physical stabilization of the amorphous INM with 30, 50, and 70 wt % E PO. Interestingly, the T_gs of these solid dispersions are in the range of 45°C–60°C. In other words, amorphous INM has good physical stability despite the T_g does not follow the "T_0 or T_g − 50 K rule." The authors postulated that the phenomena can be ascribed to the specific molecular interactions between INM and E PO. However, no direct evidence such as molecular spectroscopic spectra was provided in their work.[14,15] In a separate study, our experimental results clearly show that INM dissolves into E PO melt during the HME process. We further studied how the dissolution kinetics is affected by processing parameters.[16,17] Amorphous INM thus prepared shows significant improved dissolution rate and no recrystallization was observed after 1-year storage, consistent with the previous findings by Chokshi et al.[14,15]

MATERIALS AND METHODS

Materials

Eudragit® E PO (T_g = 48°C) was donated by Evonik Industries (Piscataway, New Jersey). INM (Melting point T_m = 162°C) was purchased from Spectrum Chemicals & Laboratory Products (Gardena, California). The INM is in γ-form. Both materials were in powder form.

Methods

Thermal Analysis

The T_g of the drug–polymer mixture samples was determined with a modulated temperature differential scanning calorimeter (MTDSC; DSC Q100, TA Instruments, Newcastle, DE). The physical mixture of INM and E PO particulates was obtained by using a rolling jar mill (JRM 2″ × 24″; Paul O. Abbe Inc., Bensenville, IL), at 250 rpm for 25 min. Physical mixture samples, about 4–8 mg, were accurately weighed, placed in an aluminum pan, and crimped with a lid. To prepare a homogeneous solid dispersion sample, each sample was first kept at 170°C for 10 min under nitrogen flow (40 cm^3/min) and then cooled to 0°C at 40°C/min. After that, a ±1.25°C of modulation amplitude with 60s of period was used for the MTDSC test. The underlying linear heating rate was 2°C/min from 0°C to 180°C. The differential scanning calorimetry (DSC) data were analyzed by using the Universal Analysis 2000 (TA Instruments, Newcastle, DE) software.

Rheological Experiments

Samples for rheological experiments were first blended using a jar rolling mill. Then, the physical mixtures were compressed into specimens with 2.54 cm in diameter and 1 mm in thickness using a compression molding machine at 170°C for 10 min. INM thus prepared was in amorphous state as evidenced by X-ray diffraction, polarized optical microscope, and Fourier transform infrared (FTIR).[17]