# Amorphous Stabilization and Dissolution Enhancement of Amorphous Ternary Solid Dispersions: Combination of Polymers Showing Drug–Polymer Interaction for Synergistic Effects

**DEV PRASAD,[1] HARSH CHAUHAN,[2] EMAN ATEF[1]**

[1]School of Pharmacy, MCPHS University-Boston, Boston, Massachusetts 02115
[2]School of Pharmacy and Health Professions, Creighton University, Omaha, Nebraska 68178

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**ABSTRACT:** The purpose of this study was to understand the combined effect of two polymers showing drug–polymer interactions on amorphous stabilization and dissolution enhancement of indomethacin (IND) in amorphous ternary solid dispersions. The mechanism responsible for the enhanced stability and dissolution of IND in amorphous ternary systems was studied by exploring the miscibility and intermolecular interactions between IND and polymers through thermal and spectroscopic analysis. Eudragit E100 and PVP K90 at low concentrations (2.5%–40%, w/w) were used to prepare amorphous binary and ternary solid dispersions by solvent evaporation. Stability results showed that amorphous ternary solid dispersions have better stability compared with amorphous binary solid dispersions. The dissolution of IND from the ternary dispersion was substantially higher than the binary dispersions as well as amorphous drug. Melting point depression of physical mixtures reveals that the drug was miscible in both the polymers; however, greater miscibility was observed in ternary physical mixtures. The IR analysis confirmed intermolecular interactions between IND and individual polymers. These interactions were found to be intact in ternary systems. These results suggest that the combination of two polymers showing drug–polymer interaction offers synergistic enhancement in amorphous stability and dissolution in ternary solid dispersions. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3511–3523, 2014

**Keywords:** poorly water-soluble drugs; solid dispersion; solubility; supersaturation; amorphous; Interaction; Crystallization Inhibition; Indomethacin; Polymer

## INTRODUCTION

Enhancing the oral bioavailability of poorly water-soluble compounds is an important challenge during formulation development.[1,2] Various methods, such as micronization,[3] salt formation,[4] use of surfactants, lipid formulations,[5] formation of prodrugs, and development of amorphous solid dispersion[6,7] have increasingly been utilized to enhance the solubility and dissolution rate of drugs. The amorphous formulations have recently gained attention and offers solubility advantages to a large number of poorly soluble drugs. Being a high-energy form, the solubility and dissolution rate of the amorphous form are higher than the stable crystalline form.[8,9] However, the higher free energy of the amorphous form gives rise to physical instability and crystallization tendency. Thus, the solubility and dissolution advantage is offset by the possibility of crystallization during dosage form processing or storage.[1,10–12] In an attempt to improve the physical stability of these amorphous forms and delay crystallization, different polymers have been used to prepare amorphous binary solid dispersions. Polymers, usually used at high concentrations, stabilize the amorphous form of the drug by increasing the glass transition temperature ($T_g$) of the system, thus reducing the molecular mobility of the amorphous drug in binary systems. Another important mechanism of stabilization is the crystallization inhibition of amorphous drugs due to drug–polymer intermolecular interaction in amorphous binary solid dispersion.[13,14]

The selection of appropriate polymers and their quantities are crucial for the success of solid dispersion formulations. Currently, the empirical screening of various polymers at different concentrations is common practice for binary solid dispersions formulations.[15,16] Further, high polymer concentrations are often utilized to guarantee the stability of the amorphous drug in these binary dispersions. This can lead to an increased mass load in successive formulation processes, which may result in multiple challenges, including failure of tablet disintegration, sticking to punches, final size of the dosage form, and so on. Moreover, organic solvents used in the solid dispersion preparation are proportional to the polymer–drug ratio. The increased use of such solvents is neither environmentally safe nor economically sound. High concentrations of polymers in formulations can also add significant toxicity to the formulations.[17–20] Thus, there is an obvious need to develop amorphous solid dispersions with higher stability using minimum polymer concentration.

Recently, amorphous ternary systems had been successfully used for dissolution enhancement and stabilizing the amorphous form of drugs. However, in most of these studies, high concentrations of polymers were used to achieve the desired results.[21,22] In many cases, polymers were combined with surfactants to achieve higher dissolution rates. A challenge for these amorphous ternary dispersions has been the characterization of these complex systems. Still, amorphous ternary solid dispersions can give formulation scientists a window for

*Correspondence to*: Eman Atef (Telephone: +617-732-2982; Fax: +617-732-2228; E-mail: eman.atef@mcphs.edu)

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significantly decreasing the concentration of polymers and reducing the toxicity associated with polymers.

As discussed earlier, drug–polymer interactions can play an important role in amorphous stabilization in binary solid dispersions. There are many examples in the literature proving the role of specific interactions in stabilizing solid dispersions, for example, Taylor and Zografi[13] showed the presence of intermolecular hydrogen bonding interactions in solid dispersions of indomethacin (IND) and PVP. Polymers interacting with drugs have shown a stabilization effect even with no significant change in the molecular mobility of these systems. In the study, no change in the $T_g$ of the system was observed, confirming limited anti-plasticizing effects (specially at low polymer concentrations).[13] Further, the role of hydrogen bonding has been confirmed by many researchers in stabilizing the amorphous phase through disruption of drug–drug interactions and the formation of drug–polymer interactions.[12,23–26] Therefore, combining two polymers having interaction with drugs for solid dispersions development can be utilized as an approach to achieve the above goals.

Based on the above concepts, we decided to investigate the effect of combining two polymers showing drug–polymer interaction for solubility enhancement and stabilization of the solid dispersion. The study emphasizes the effectiveness of two polymers at low concentrations in amorphous ternary solid dispersions. We studied the combined stabilization effect of polymers showing drug–polymer interaction on amorphous stabilization of IND (figure 1), with the goal of investigating this effect and probing the mechanism behind the solid-state stabilization. Eudragit E100 and PVP K90 (figure 1) were chosen as polymers based on their interaction IND. Chauhan et al.[27] from our research group had screened different polymers in solution and have reported Eudragit E100 and PVP K90 to be very efficient in precipitation inhibition because of molecular interactions. Both the polymers have shown interaction with IND individually and have been successfully used in solubility and stability enhancement of poorly soluble drugs as reported by many studies.[13,28,29] Finally, both the polymers are listed in United States Food and Drug Administration inactive ingredient list and it would be judicious to understand their behavior in solid dispersion development. This will add to the existing knowledge of polymers in solid dispersions and will help in future product development.

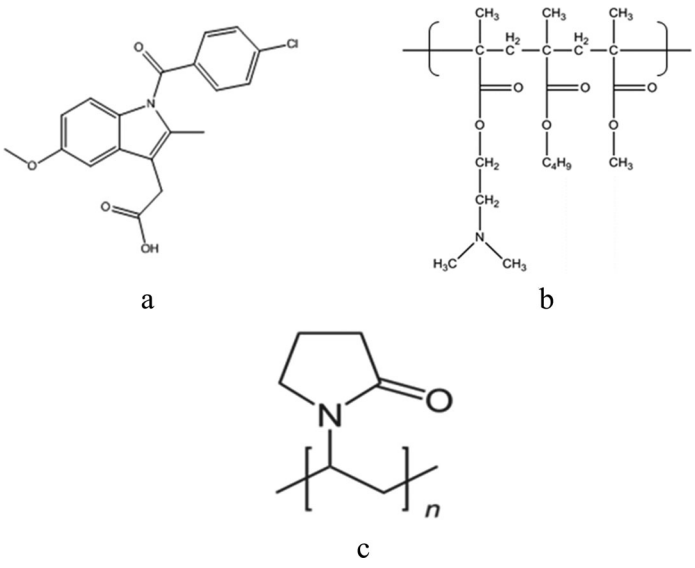


**Figure 1.** Structure of (a) indomethacin (IND), (b) Eudragit E100, and (c) PVP K90.

## MATERIALS AND METHODS

### Materials

Indomethacin was purchased from Sigma–Aldrich, St. Louis, Missouri. Eudragit E100 was a gift from Degussa (Parsippany, New Jersey). PVP K90 was purchased from Sigma. HPLC-grade organic solvents (acetonitrile, methanol) were purchased from J.T. Baker, Phillipsburg, New Jersey. Hydrochloric acid, 10 N, ACS grade (lot #SN0543), potassium phosphate monobasic, crystals, lot #VQ 0785, and sodium hydroxide, lot #QX0299 were purchased from Spectrum Chemical Mfg. Corporation, New Brunswick, New Jersey.

### Methods

#### *Solubility Determination*

A test of the solubility of IND in 0.1 N hydrochloric acid was carried out. An excess amount of IND (50 mg) was added to the 20 mL vial containing 10 mL of media. The vials were shaken for 24 h at 25°C. After centrifugation and filtration through 0.22 μm filters, the samples were analyzed using HPLC.

#### HPLC *Assay*

An HPLC method was used to quantify IND (Hewlett Packard 1100 series HPLC system, HP ChemStation software, A Hypersil ODS C18, 150 × 5.4 $mm^2$ column). The mobile phase consisted of acetonitrile and 0.1 M glacial acetic acid (60:40, v/v), at 0.8 mL/min, using UV detection at $\lambda = 228$ nm.[30]

#### *Preparation of Solid Dispersions*

The solid dispersions were prepared by the solvent evaporation method. The required amounts of drug and polymer or polymers were dissolved in methanol, which was then evaporated using a rotary evaporator at 60°C. The solid dispersions were sieved through 350 μm mesh, dried under vacuum for 12 h, and then stored in desiccators over phosphorous pentoxide. The solid dispersions were characterized by modulated differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), IR, and Raman spectroscopy.

#### *Preparation of Physical Mixtures*

#### *Drug–Polymer Physical Mixtures*

The binary and ternary physical mixtures were prepared by geometric mixing of the drug and polymer or polymers using a spatula at the required drug–polymer ratio. The obtained physical mixtures were sieved, dried, stored, and characterized using the same conditions and techniques as the solid dispersions.

#### *Polymer Physical Mixtures and Coevaporates*

To probe any possible polymer–polymer interaction, the polymer physical mixture and solid dispersion were prepared and characterized following the same methods as drug–polymer