Miscibility/Stability Considerations in Binary Solid Dispersion Systems Composed of Functional Excipients towards the Design of Multi-Component Amorphous Systems

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ABSTRACT: The correlations between amorphous miscibility/physical stability of binary solid dispersions (a highly crystalline additive—an amorphous polymer) and the physicochemical properties of the components were investigated. Crystalline functional excipients including surfactants, organic acids, and organic bases were prepared in binary solid dispersions in amorphous polymers by solvent evaporation method. Amorphous miscibility and physical stability of the systems were characterized using polarized light microscope, differential scanning calorimeter, and powder X-ray diffraction. Physicochemical parameters (solubility parameter (δ), hydrogen bond energy, Log P, pK_a value as an indicator of acid-base ionic interaction, and T_g of the dispersion as a surrogate of system's mobility) were selected as thermodynamic and kinetic factors to examine their influences on the systems' amorphous miscibility and physical stability. All systems possessing acid-base ionic interaction formed amorphous state. In the absence of the ionic interaction, solubility parameter and partition coefficient were shown to have major roles on amorphous formation. Upon storage condition at 25°C/60% RH for 50 days, systems having ionic interaction and high T_g remained in the amorphous state. This binary system study provides an insight and a basis for formation of the amorphous state of multi-component solid dispersions utilizing their physicochemical properties. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:4711–4723, 2009

Keywords: amorphous; solid dispersion; physical stability; physicochemical; properties; excipients

INTRODUCTION

The improvement of solubility for poorly water-soluble drugs, such as BCS II and BCS IV drug compounds, is a major issue in pharmaceutical research as poorly water-soluble synthetic drug candidates have been increasing for decades. Diverse methodologies have been employed for the enhancement of the solubility and dissolution of poorly water-soluble drugs, but comprise drawbacks in practical usage.[1–4]

Multi-component amorphous solid dispersions conceptually are considered drug delivery system options for these compounds. These systems embrace three major concepts for improving the solubility of poorly water-soluble drugs. A multi-component system, incorporating functional excipient besides drug and amorphous polymer matrix, modifies the microenvironment at the dissolution front resulting in the enhance-

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ment of drug solubility. By transition into amorphous state from crystalline form of a drug, the high energy amorphous form lowers the energy barrier of drug dissolution. The solid dispersion[5] of drug in amorphous polymer at molecular level provides extended surface area of a drug that increases dissolution of the drug,[6] while resolving wettability issues occurring in conventional particle size reduction. The amorphous system formation and its physical stability can be enhanced by the dispersion process into amorphous polymer matrix and by the selection of appropriate matrix components.[7] Uniform and efficient incorporation of functional excipients can also be achieved. Therefore, multi-component amorphous solid dispersion systems composed of drug, functional excipient, and amorphous polymer matrix are considered to be a propitious system for the enhancement of the dissolution of poorly water-soluble drugs.

However, in designing such systems, several issues such as homogeneous amorphous formation from inclusion of highly crystalline additives and the physical stability of the multi-component amorphous system should be considered. Damian et al.[8] observed the decrease of dissolution of ternary solid dispersion system (composed of polymer, drug, and an additive) as an amorphized additive recrystallized as a function of time. Wang et al.[9] observed phase separation of drug and amorphous polymers by adding crystalline additive in the binary amorphous solid dispersion system. These examples emphasize the importance of maintaining a physically stable amorphous system including functional additives.

There is a paucity of literature on the use of multi-component amorphous systems. In addition, few studies have focused on binary amorphous solid dispersion systems composed of functional excipient and amorphous polymers. It would seem that a rational starting point for the design of a multi-component amorphous system where the drug substance is one of the amorphous state components would be binary mixtures of polymer and functional excipients. Thus in the current work, binary amorphous solid dispersion systems of highly crystalline functional additives and amorphous polymers were investigated. Two surfactants which have different ionic characteristics (ionic and nonionic), and four pH modifiers (two basifiers and two acidifiers), were used, as these additives are commonly utilized to modulate dissolution of poorly water-soluble compounds. As amorphous matrices, nonionic and ionic (acidic and basic) water-soluble polymers were chosen. The selection of these components was based on the anticipation that a difference of their characteristics may distinguish the critical factors affecting amorphous miscibility and physical stability of solid dispersion systems more clearly (such as the selection of counterionic additives and polymers).

Practically, a stable amorphous dispersion system could be achieved by a careful design of the system balancing the thermodynamic driving force of crystallization and a kinetic factor that lowers molecular mobility to delay the crystallization process. Therefore, in order to provide a fundamental basis for the design and development of a stable amorphous solid dispersion system, the investigation of thermodynamic and kinetic factors of the system is considered to be essential for resolving the issue of amorphous system formation and the physical stability of solid dispersions. Several physicochemical properties describing molecular interactions (solubility parameter, partition coefficient, hydrogen bonding, and acid-base ionic interaction) and one physical factor (glass transition temperature as a surrogate of molecular mobility of a system) were observed as thermodynamic and a kinetic factor, respectively. Solubility parameters and partition coefficients are used as estimates of molecular similarities between components, so that a solid dispersion which has similar characteristics of the components indicated by these parameters are expected to have good miscibility in the amorphous state and thus physical stability. Hydrogen bonding and acid-base ionic interaction are specific interactions between components in a system. The stronger interactions between the constituents reflected by these parameters would suggest a higher tendency of forming stable, homogeneous amorphous systems. If there is high intermolecular interaction between two components large enough to overcome the barrier of crystal lattice energy of a crystalline component, a system satisfying this condition should form a physically stable homogeneous amorphous system.

In the literature, relation of such parameters to the stability of amorphous solid dispersion has been reported. Greenhalgh et al.[10] correlated solubility parameter and miscibility between ibuprofen and various excipients. Weuts et al.[11] observed the benefit of salt formation between a basic drug and acidic polymer to the physical stability of amorphous solid dispersion. Karavas