Factors Affecting the Formation of Eutectic Solid Dispersions and Their Dissolution Behavior

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ABSTRACT: The objective of this work was to obtain a fundamental understanding of the factors, specifically the properties of poorly water-soluble drugs and water-soluble carriers, which influence predominantly, the formation of eutectic or monotectic crystalline solid dispersion and their dissolution behavior. A theoretical model was applied on five poorly water-soluble drugs (fenofibrate, flurbiprofen, griseofulvin, naproxen, and ibuprofen) having diverse physicochemical properties and water-soluble carrier (polyethylene glycol (PEG) 8000) for the evaluation of these factors. Of these, two drugs, fenofibrate and flurbiprofen, and PEG of different molecular weights (3350, 8000, and 20000), were chosen as model drugs and carriers for further investigation. Experimental phase diagrams were constructed and dissolution testing was performed to assess the performance of the systems. The theoretical model predicted the formation of eutectic or monotectic solid dispersions of fenofibrate, griseofulvin, ibuprofen, and naproxen with PEG, holding the contribution of specific intermolecular interactions between compound and carrier to zero. In the case of the flurbiprofen-PEG eutectic system, intermolecular interactions between drug and polymer needed to be taken into consideration to predict the experimental phase diagram. The results of the current work suggest that the thermodynamic function of melting point and heat of fusion (as a measure of crystal energy of drug) plays a significant role in the formation of a eutectic system. Lipophilicity of the compound (as represented by cLog P) was also demonstrated to have an effect. Specific interactions between drug and carrier play a significant role in influencing the eutectic composition. Molar volume of the drug did not seem to have an impact on eutectic formation. The polymer molecular weight appeared to have an impact on the eutectic composition for flurbiprofen, which exhibits specific interactions with PEG, whereas no such impact of polymer molecular weight on eutectic composition was observed for fenofibrate, which does not exhibit specific interactions with PEG. The impact of polymer molecular weight on dissolution of systems where specific drug-polymer interactions are exhibited was also observed. The current work provides valuable insight into factors affecting formation and dissolution of eutectic systems, which can facilitate the rational selection of suitable water-soluble carriers.
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Keywords: solid dispersions; eutectic; monotectic; phase diagrams; poorly water-soluble drug; water-soluble carrier; polyethylene glycol; partition coefficient; specificinteraction; hydrogen bonding

INTRODUCTION

Delivery of poorly water-soluble drugs using solid dispersions is currently a highly active area of pharmaceutical research. The high level of

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interest is a result of the abundance of poorly water soluble new chemical entities identified for development.[1–4]

Solid dispersion delivery systems can be described in two broad classes based upon the state of the drug substance within the system, amorphous or crystalline. Significant drug delivery research has been dedicated to amorphous systems. However, there is a paucity of literature covering solid dispersion delivery systems where the drug substance is maintained in the crystalline state. Although, the dissolution improvement may not be as significant as that seen with amorphous solid dispersion delivery systems, crystalline solid dispersion delivery systems are thermodynamically stable, which is a distinct advantage over amorphous dispersion systems.

Crystalline solid dispersions, in which both the drug and carrier (or polymer) exist in the crystalline state, can be categorized into eutectic and monotectic systems. Eutectic solid dispersions are defined as systems where the melting point of the eutectic is below the melting point of both the drug and carrier alone (Fig. 1). Monotectic solid dispersions are defined as systems where the melting point of the carrier is unchanged in the presence of the drug[5] (Fig. 2).

In comparison to monotectic solid dispersions, eutectic solid dispersions offer several advantages such as particle size reduction of both the drug and polymer to ultrafine crystals at and below eutectic composition, higher solubility of the drug in the carrier, and lower processing temperatures. These advantages of eutectic solid dispersions results in improved dissolution rate which is the motivation to understand these systems.[1,3,6–13,24,25]

The feasibility of developing eutectic solid dispersions with improved dissolution behavior is

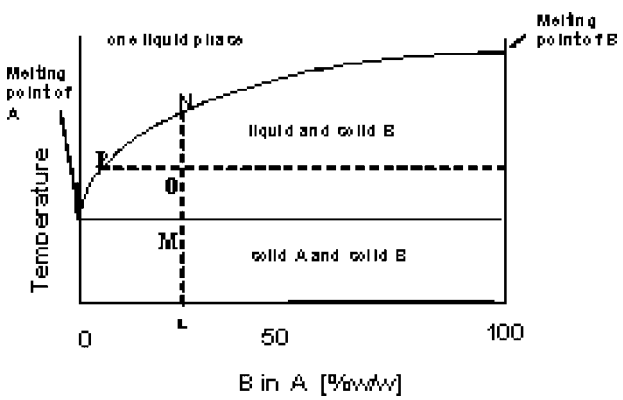

Figure 1. Phase diagram of a typical monotectic system.

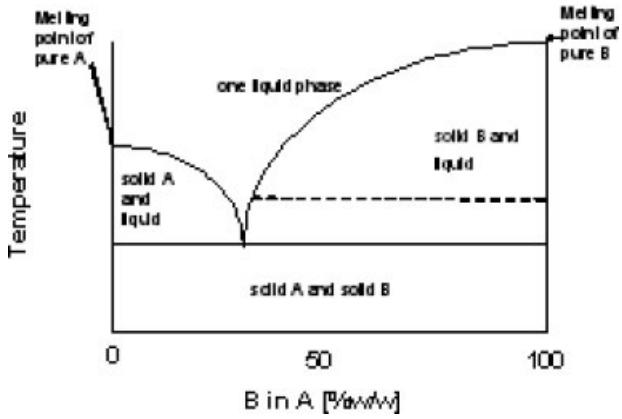

Figure 2. Phase diagram of a typical eutectic system.

dictated by the eutectic composition, dose required and the processing ease, as pointed by Law et al.[8] Determination of the eutectic composition requires construction of phase diagrams, which could be a time consuming and laborious process. Theoretical models have been developed to predict eutectic composition from knowledge of melting points, heats of fusion, molecular weight, molar volumes, and specific interactions between drug and carrier in the molten state.[7,14–18] Lacoulonche et al.[14] have derived a theoretical model based on thermodynamic principles assuming that the drug and polymer are not soluble in the solid state. Using the model, they predicted the eutectic phase diagram of flurbiprofen with PEG and showed that flurbiprofen forms specific interactions with the PEG carrier. Models such as these could be utilized to facilitate the experimental construction of phase diagrams. However, the robustness of these models to predict eutectic systems across compounds of different physicochemical properties is not established in the literature.

In this work the authors have attempted to assess the eutectic formation predictability and composition using the model developed by Lacoulonche et al.[14] Five diverse, poorly water-soluble drugs, fenofibrate, flurbiprofen, griseofulvin, ibuprofen, and naproxen (Figs. 3a–e, respectively) were studied in the current investigation. These compounds are known to form eutectic or monotectic systems with PEG polymers.[7,15,19,26] The knowledge gleaned should give an indication of the predominant factors which affect the eutectic composition and the predictability of the eutectic phase diagram. Additionally, some authors have suggested that the PEG molecular weight does not affect the eutectic phase diagram.[15,19] The influence of polymer molecular weight was further