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Research paper

Two-phase amorphous-amorphous solid drug dispersion with enhanced stability, solubility and bioavailability resulting from ultrasonic dispersion of an immiscible system

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ABSTRACT

Amorphization of active pharmaceutical ingredients (APIs) and the preparation of solid dispersions are strategies that can be synergized to improve the solubility of oral drugs. Immiscibility between an API and a carrier in the molten state that could be perceived as a problem in the preparation of solid dispersions, may actually introduce an advantage. In the present work, a two-phase amorphous-amorphous solid dispersion (AASD) was prepared by ultrasonicating a molten immiscible mixture of indomethacin (IND) and glucose (GLU) prior quenching. By introducing this novel ultrasound assisted method, the immiscible API particles were uniformly dispersed as microscopic glassy clusters of the drug in the solid amorphous GLU matrix; particle sizes of IND in the AASD range from 600 nm to 1.4 μm. As a result of the amorphization and particle size reduction of IND, its aqueous solubility increased to reach almost 40 ppm (8 times more soluble compared to indomethacin in its crystalline state). In addition, the oral bioavailability and its resistance against crystallization were also enhanced; AASD samples have remained amorphous for more than two years of storage.

1. Introduction

Two of the most promising strategies to solve the problem of low solubility of drugs are: (1) the conversion of the active pharmaceutical ingredient from its crystalline form to its amorphous state and (2) the preparation of formulations as solid dispersions. In the first strategy, the enhancement of solubility is due to the fact that the amorphous state lacks of long range three-dimensional order leading to a metastable phase with a higher chemical potential compared to the more stable crystalline form. This higher chemical potential is the driving force for a higher dissolution rate and saturation concentration when dissolved in water [1,2]. For the case of solid dispersions, a decrease in the particle size of the API (which is distributed or spread across in a solid state carrier) and the increment in the porosity of the two component system favor a water solubility enhancement [3]. Synergizing these two strategies, by forming amorphous solid dispersions where the API, the carrier or the two components of the dispersion are in the amorphous state, can lead to an optimized dissolution process.

Amorphous solid dispersions can exist as glassy solutions or glassy suspensions (also called fully glass solutions and amorphous solid suspensions). A glass solution is a homogeneous single-phase, in which an amorphous solute is completely dissolved in an amorphous solid or glassy solvent. Here the two components (drug and carrier) are mixed at a molecular level. The term amorphous solid suspension refers to precipitated particles, which are suspended in a solid glassy solvent; in other words, it refers to an immiscible two-phase system where API and carrier are physically separated [4,5]. If the immiscible API is in amorphous state; we can refer to this system as a two phase amorphous-amorphous solid dispersion (**AASD**).

The mechanism associated with solubility enhancement of amorphous solid dispersions (prepared with an amorphous carrier), has been explained by Chiou et al. [6]. According to these

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authors, if a water-insoluble drug forms a glass solution or glass suspension with a water-soluble glass-forming carrier, the dissolved or suspended drug is rapidly released into the aqueous medium because the glassy carrier quickly dissolves upon exposure to the aqueous medium. Most solid dispersions reported in the literature are prepared with polymers, since these type of carriers stabilize the binary system in the amorphous state and avoid crystallization of the API [7–9]. Besides polymers, small molecular weight molecules like sugars can be used as carriers; despite the advantages that saccharides can offer such as low toxicity, high solubility and low price, compared with polymers and other molecules, just a few works have studied sugars as amorphous carriers in solid dispersions. Table 1 summarizes these previous studies of solid dispersions with sugars; as it can be seen, in most cases the API ends up in its crystalline form [10–20]. Even though these dispersions with sugars as carriers have demonstrated to enhance solubility of drugs when compared to dissolution of pure API in crystalline state, there is still an opportunity to maximize solubility enhancement by achieving the stability of the API in the amorphous state dispersed in an amorphous sugar carrier.

In order to obtain an effective amorphous solid dispersion, in general it is believed that the drug and the carrier have to be miscible in the molten state [21]; in other words, immiscible drug-excipient formulations are normally discarded because the product suffers phase separation. Since it is assumed that this phase separation may induce recrystallization, results presented here prove otherwise.

In the present work, the immiscibility in the molten state between a drug and an excipient was taken as an advantage to control and reduce the particle size of a drug dispersed in a solid glassy sugar carrier. This was achieved by applying an ultrasound assisted dispersion method during melting (prior to the amorphization achieved by quenching). In this study, a two phase amorphous-amorphous solid dispersion (AASD) of indomethacin (IND) – glucose (GLU) was prepared and fully characterized.

Indomethacin, a BCS class II (low solubility, high permeability), non-steroidal anti-inflammatory drug was chosen as a model API because the aqueous solubility of this drug (in the amorphous and crystalline state; as well as binary systems with sugars as carriers) has been previously studied [2,15,22–24]. Therefore, there are sufficient data to compare the advantages of enhanced solubility and bioavailability of the novel formulation presented in this work.

To the best of our knowledge there are no other studies reported in which immiscibility between an API and sugar carrier in the molten state has taken as an advantage to reduce particle size and to uniformly disperse a drug in an immiscible solid glassy matrix; resulting in a formulation with enhanced solubility, bioavailability and high stability in the amorphous state.

2. Experimental

2.1. Materials

γ-Indomethacin (IND, USP 99.5%, and TLC grade, MW: 357.79 g/mol), anhydrous Glucose (GLU, 99.5%, MW: 180.16 g/mol) and Losartan Potassium (Internal Standard IS, 99.5%, MW: 461 g/mol) were purchased from Sigma-Aldrich (St. Louis, MO, USA). HPLC grade methanol (MeOH) and acetonitrile (ACN) were purchased from Tedia (Fairfield, OH, USA) and J.T. Baker (Columbus, OH, USA), respectively. Amorphous samples of pure components were prepared by melt quenching method.

2.2. Crystalline physical mixture and binary amorphous sample preparation

Physical mixtures (PM) of crystalline IND – GLU with different molar compositions were gently mixed in a mortar for five minutes, and then analyzed. Preliminary amorphous binary systems were prepared in situ by melt-quenching mixtures of IND-GLU in DTA and DSC cells (see Section 2.3).

2.3. Thermal characterization

Thermal analysis was performed using two complementary calorimetry techniques: differential thermal analysis (DTA) and differential scanning calorimetry (DSC). For both techniques, the heating and cooling method applied during thermal analysis to identify phase transitions of crystalline samples of pure active ingredients was as follows: samples were heated at a rate of 10 °C/min from 30 °C until samples were molten (170 °C). After identification of the endothermic signal corresponding to melting temperature, molten samples were quenched inside the instrument from 170 °C to −5 °C at a cooling rate of −70 °C/min. The purpose of this cooling step was to produce amorphous samples in situ by the method of melt-quenching. Once amorphous samples were

Table 1
Previous reports of solid dispersions (SDs) using sugars as carriers in which crystalline (C) and amorphous (A) phase characterization has been reported.

API	Method of preparation	Sugar as carrier	Phase of components of SDs		Ref
			Carrier	API	
Ethenzamide	Melt quenching	Maltose	A	C	[10]
		Galactose	A	C	
		Sucrose	A	C	
		Mannitol	C	C	
Griseofulvin	Roller mill	Maltose	A	C	[11]
		Lactose	A	C	
Carbamazepine	Melt quenching	Lactose	A	C	[12]
Ethenzamide		Lactose	A	C	
Clotrimazole	Melt quenching	Mannitol	C	C	[13]
		Fructose	C	C	
		Dextrose	C	C	
		Maltose	C	C	
Diazepam	Freeze drying	Trehalose	C	A	[14]
Indomethacin	Solvent evaporation	Isomaltose	A	C	[15]
Indomethacin	Melt quenching	Xylitol	A	C	[16]
Triamterene	Spray drying	Mannitol	C	C	[17]
Diazepam	Spray drying	Trehalose	A	C	[18]
Nifedipine	Melt quenching	Mannitol	C	C	[19]
Etoricoxib	Freeze drying	Lactose	A	A	[20]