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Development and characterization of nifedipine-amino methacrylate copolymer solid dispersion powders with various adsorbents

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ABSTRACT

Solid dispersions of nifedipine (NDP), a poorly water-soluble drug, and amino methacrylate copolymer (AMCP) with aid of adsorbent, that is, fumed silica, talcum, calcium carbonate, titanium dioxide, and mesoporous silica from rice husks (SRH), were prepared by solvent method. The physicochemical properties of solid dispersions, compared to their physical mixtures, were determined using powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC). The surface morphology of the prepared solid dispersions was examined by scanning electron microscopy (SEM). The dissolution of NDP from solid dispersions was compared to NDP powders. The effect of adsorbent type on NDP dissolution was also examined. The dissolution of NDP increased with the ratio of NDP:AMCP:adsorbent of 1:4:1 when compared to the other formulations. As indicated from PXRD patterns, DSC thermograms and SEM images, NDP was molecularly dispersed within polymer carrier or in an amorphous form, which confirmed the better dissolution of solid dispersions. Solid dispersions containing SRH provided the highest NDP dissolution, due to a porous nature of SRH, allowing dissolved drug to fill in the pores and consequently dissolve in the medium. The results suggested that solid dispersions containing adsorbents (SRH in particular) demonstrated improved dissolution of poorly water-soluble drug when compared to NDP powder.

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1. Introduction

The oral drug administration is the most preferred route of drug delivery due to convenience, patient adherence and rational production investment of oral solid dosage forms. After oral ingestion, the drug must be liberated and then solubilized in gastrointestinal (GI) fluid before it can be absorbed and has a systemic effect. Poor solubility of drug in GI medium generally leads to low dissolution rate and insufficient bioavailability [1,2]. The selection of suitable formulation is of great significance in the development of successful product for oral administration of poorly water-soluble drugs. Several formulation approaches can be used to improve the bioavailability of poorly water-soluble drugs. The most common method of increasing dissolution rate is to reduce the size of solid drug particles, which leads to an increased surface area available for dissolution [3]. The dissolution rate can also be increased by inducing salt formation or prodrug synthesis, which the new chemical entity has better solubility profiles but the same pharmaceutical activity after absorption in systemic [4,5]. Another common method of improving bioavailability for the poorly soluble drugs is to prepare an amorphous formulation allowing faster drug dissolution in comparison to its corresponding crystalline form. Solid dispersion is known as one of the effective methods for preparing amorphous solids and can be used for enhancing dissolution rate of poorly water-soluble drugs [6]. The mechanism of dissolution enhancement of solid dispersions can be explained by the transformation of a stable crystalline drug into a less stable amorphous state, a reduction in drug particle size and an increase in wettability and solubility of drug surrounded by hydrophilic carriers, such as polyethylene glycol, hydroxypropylcellulose and polyvinylpyrrolidone [1,2,7].

Amino methacrylate copolymer (AMCP) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It can be dissolved in gastric fluid up to pH 5.0 and swelled above pH 5.0. Previously, AMCP was used as a carrier for solid dispersions, for example, chlordiazepoxide-AMCP solid dispersions [8]. It was observed that all AMCP-based solid dispersion formulations produce higher dissolution rate than the physical mixtures and the pure chlordiazepoxide. Li et al. [9] prepared solid dispersions of curcumin using AMCP as a matrix carrier by simple solution mixing method. They found that the solubility of curcumin was increased by forming curcumin-AMCP solid dispersions. Nevertheless, the prepared solid dispersions of AMCP tend to be sticky or tacky, resulting from the intermolecular interaction of eutectic composition between drug and polymer [10]. This leads to a decrease in the yield of solid dispersions and results in inconvenience handling in the subsequent manufacturing process.

Recently, adsorbents (e.g., fumed silica (FS), magnesium aluminum silicate, etc.) have been extensively applied as carriers in fabrication of solid dispersions to improve dissolution of poorly water-soluble drugs [11]. In general, adsorbents are used when there is a need to add a liquid or semisolid ingredient in the formulation; adsorbents are capable of sorbing the liquid component onto the dry powder. Most commonly used adsorbents in pharmaceuticals are anhydrous calcium phosphate, kaolin, magnesium carbonate, magnesium silicate, magnesium oxide, starch and silicon dioxide. By using the adsorbents, the melt of solid dispersion could be adsorbed in the pores and/or rough surface of absorbents, thus improving powder flowability and compressibility for further manufacturing processes [7,12–14].

In our preliminary study, the solid dispersions composed of nifedipine (NDP), AMCP and FS were developed (at ratios of NDP:AMCP:FS = 1:0.5–4:0–1) [15]. With no FS, gelatinous mass of solid dispersions was obtained. The free-flowing powder was achieved when inert FS was added. The results from dissolution test revealed poor and slow dissolution of pure NDP. On the other hand, solid dispersions with low amount of AMCP (i.e., the ratios of 1:0.05:1, 1:1:1 and 1:2:1) showed an improved drug dissolution. Nevertheless, the dissolution profiles of these solid dispersions resulted in slow release with drug dissolution about 20–30% after 2 h. The enhanced drug dissolution was observed when high amount of AMCP (at a ratio of NDP to AMCP of 1:4) was used, regardless of the addition of adsorbent [15]. However, the influence of the type of adsorbents on drug dissolution has not been investigated in details. Therefore, in this research, the powder form of solid dispersions was developed using various types of adsorbents. Solid state characterization, i.e., powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM), was performed. The influence of NDP:AMCP:adsorbent on drug dissolution was also evaluated.

2. Materials and methods

2.1. *Materials*

NDP was purchased from Xilin Pharmaceutical Raw Material Co., Ltd. (Jiangsu, China). AMCP (Eudragit® E) and FS (Aerosil® 200) were received from Evonik Industries (Hanau, Germany). Mesoporous silica from rice husks (referred to as SRH) was prepared by depolymerization at high temperature, as described in previous report [16]. Simulated gastric fluid USP without pepsin (SGF) was prepared by dissolving 2 g of sodium chloride and 7 mL of hydrochloric acid with distilled water to make a total volume of 1000 mL of solution. All other chemicals used in this study were of pharmaceutical grade and used as received without further purification.

2.2. *Preparation of NDP-AMCP solid dispersions with adsorbents*

Solid dispersions of NDP and AMCP with various adsorbents were prepared by solvent method. NDP (1 g) and various amounts of AMCP were dissolved in sufficient amount of methylene chloride to obtain a clear solution, and various amounts of different adsorbents were then added to obtain uniform suspensions. After mixing, the solvent was removed at ambient temperature (25 °C). The solid dispersion obtained was dried at 40 °C in a vacuum oven for 24 h. In this study, the adsorbents investigated were FS, SRH, titanium dioxide (TiO_2), calcium carbonate ($CaCO_3$), and talcum. The NDP, AMCP and adsorbent ratios were 1:0.5:1, 1:1:1, 1:2:1, 1:4:1 and