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Short communication

Dissolution enhancement of the poorly soluble drug nifedipine by co-spray drying with microporous zeolite beta

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ABSTRACT

Dissolution enhancement of nifedipine (NIF), a BSC class II drug, was achieved after co-spray drying with zeolite beta (BEA) in two drug to carrier ratios (1: 1, 1: 2). Extraction studies revealed almost 100% encapsulation efficiency. Physisorption studies suggested successful drug incorporation within the carrier's pore network, as well as on its external surface area. A shift of ζ-potential towards less negative values following drug loading indicated possible drug deposition onto zeolite's surface. The physical state of loaded NIF was evaluated by means of FT-IR, DSC and XRD analyses, all corroborating towards drug's significant amorphization.

The *in vitro* dissolution rate of NIF from the co-spray dried formulations was substantially enhanced in simulated gastric (pH 1.2) and intestinal fluids (pH 6.8), compared to crystalline drug.

Results demonstrated the potential of zeolitic particles for the dissolution enhancement of sparingly soluble drugs, which in turn may increase their oral bioavailability.

1. Introduction

Zeolites constitute a diverse material with multi-purpose utilization ranging from industrial [1] and environmental [2,3] applications to biomedical [4,5] and medical [6] functionalities. These biocompatible aluminosilicate crystalline solids consist of a three-dimensional framework of AlO_4 and SiO_4 tetrahedrals, which generate a uniform network of channels and cages, yielding large surface areas and high porosity [7]. Their intrinsic structural and physicochemical properties are amenable to customization, regarding size and dimensionality of their porous network, surface properties and hydrophobicity [8]. In the recent years, an increased number of studies have introduced zeolitic particles in the field of drug delivery for oral [9–15], as well as topical administration [16–18]. Amongst the hundreds of natural and synthetic zeolites, beta zeolite firstly reported in 1967 by Mobile Oil [19] possesses high thermal and physical stability, high acidity, vast internal surface areas and extended pore networks [20]. Fairly few are, however, the references claiming BEA zeolite as a drug delivery system [9,21–24]. The cytocompatibility of BEA zeolitic particles has been previously evaluated and results demonstrated that the aluminosilicate material did not affect the viability of human epithelial colorectal adenocarcinoma cell lines (Caco-2) [9].

Herein we report the evaluation of a commercial zeolite of the framework type beta, as host-system for a BSC class-II drug, NIF. Nifedipine, a calcium channel antagonist mainly used in the treatment of hypertension and angina [25] exhibits poor absorption related to its low aqueous solubility. Spray drying is a key technology that simplifies solubility concerns, producing stable solid dispersion formulations [26,27]. On account of NIF's marginal water solubility (0.0177 mg/mL), spray drying was employed to enable drug incorporation in the siliceous carrier, utilizing the synergy of both the solubilization capacity of spray drying and the immense endogenous pore network and external surface area offered by the zeolitic carrier for drug hostage. The co-spray dried formulations of two different drug to zeolite ratios (1: 1 and 1: 2) were found to significantly enhance drug's dissolution rate in both simulated gastric (pH 1.2) and intestinal (pH 6.8) media.

Although there are several reports employing spray drying for the co-formulation of mesoporous materials and poorly soluble

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drugs [28–31], to the best of our knowledge this is the first study enrolling the spray drying method for the co-formulation of zeolitic particles and a poorly soluble drug for oral drug delivery.

2. Materials and methods

2.1. Materials

Commercial zeolite beta (CP814E: SiO_2/Al_2O_3 Mole Ratio: 25) was purchased from Zeolyst International (Philadelphia, US). Nifedipine, ethanol and sodium dodecyl sulfate (SLS) were purchased from Sigma-Aldrich Chemie GmbH (Munich, Germany). All chemicals were of analytical grade and used as received. Distilled water was used in all experimental procedures. All procedures were performed in light-resistant vials and under dark conditions.

2.2. Spray drying procedure

NIF (250 or 500 mg) was dissolved in an ethanolic solution (ethanol: water 2: 1 v/v). BEA zeolite (500 mg), overnight dried at 250 °C, was dispersed in the same solution and left under magnetic stirring for 1 h. Dispersions were subjected to spray drying in a Büchi-Mini Spray Dryer B-191 (Büchi, Switzerland) with a standard nozzle (0.7 mm diameter). Inlet temperature was set at 100 °C, feed flow rate at 7 mL/min, the airflow at 600 L/h and the aspirating setting level at 100%, resulting in an outlet temperature in the range between 70° C to 80° C. Particles were collected, weighted and stored in a desiccator till further characterization. Yield of the spray-drying process was calculated according to equation (1) and ranged between 44.2% for the zeolite: drug 1: 1 ratio and 67.2% for the zeolite: drug 2: 1 ratio, respectively.

$$\text{yield}(\%) = \frac{\text{weight of solids collected in the chamber(mg)}}{\text{total weight of solids(mg)}} \times 100 \quad [1]$$

2.3. Drug content quantification

Two (2) mg of each spray dried formulation were dispersed in 60 mL of phosphate buffer solution (pH 7.4) and left under stirring overnight.

2.3.1. Extraction method

Dispersions were then centrifuged at 4500 rpm for 15 min and supernatants were quantified spectrophotometrically (UV mini-1240, SHIMADZU) at 338 nm. Calibration curve revealed linearity ($r^2 > 0.999$) over the concentration range (1–20 μg/mL) tested. Drug content and entrapment efficiency were calculated according to the following equations:

$$\text{drug content}(\%) = \frac{\text{weight of nifedipine in the particles}}{\text{weight of particles}} \times 100 \quad [2]$$

$$\text{entrapment efficiency}(\%) = \frac{\text{weight of nifedipine in the particles}}{\text{initial weight of nifedipine}} \times 100 \quad [3]$$

2.3.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was also employed to confirm the results of the aforementioned 'extraction' method. Analysis was carried out using a TGA Q500 (TA instruments Ltd.) with a heating rate of 10 °C/min from 40 °C to 800 °C in air atmosphere. Samples were equilibrated at 40 °C prior measurements, to enable removal of excess moisture content. The TGA profile of nifedipine showed an onset of mass loss at 165 °C, reaching a constant value after 580 °C. Nifedipine content in the zeolitic particles was calculated by measuring the mass loss between 140 °C–640 °C (BEA: NIF 1: 1) and 150 °C–660 °C (BEA: NIF 2: 1) following appropriate corrections regarding zeolite's beta weight loss over the same temperature range. Since the mass of the particles was known, the drug content was calculated according to equation (2).

2.4. Physicochemical characterization

2.4.1. Scanning electron microscopy (SEM)

Visualization of the zeolitic and drug particles was assessed by means of scanning electron microscopy analysis (field emission scanning electron microscope, LEO 1530VP). Specimens were mounted on metallic sample stands using conductive adhesive tape (PELCO Image Tabs) and gold sputtered under high vacuum (~5×10^{-2} mbar) using a BAL-TECSCD-004 sputtering unit. The working distance was 4 mm and the accelerating voltage was set at 15 kV.

2.4.2. BET studies

Physisorption studies (N_2 adsorption/desorption measurements) were performed using a Nova 2200E Surface Area and Pore Size Analyzer (Quantachrome Instruments, Boynton Beach, Florida) at −196 °C. All samples were degassed at 50 °C for 24 h prior to analysis. Specific surface areas were calculated at a relative pressure $P/P_0 = 0.02–0.04$ using the Brunauer-Emmett-Teller (BET) method. Pore size distributions were determined using the Saito-Foley (SF) method for cylindrical pore geometry. Total pore volumes were estimated from the amount of N_2 adsorbed at a relative pressure of 0.995.

2.4.3. ζ-potential studies

The surface charge (ζ-potential) of the empty and NIF loaded zeolitic particles was measured in distilled water (1 mg/mL) using a Zetasizer Nanoseries, Nano-ZS analyzer (Malvern, UK). All measurements were repeated in triplicate.

2.4.4. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was conducted on a DSC 204 F1 Phoenix (Netzsch) apparatus under a nitrogen flow of 70 mL/min, at a heating rate of 10 °C/min from 30 °C to 190 °C. Samples (5 mg) were placed in aluminum crucibles and sealed with perforated lids.

2.4.5. Fourier-transform infrared (FT-IR) spectroscopy

FTIR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer (Shimadzu Corporation, Kyoto, Japan) with a horizontal Golden-Gate MKII single reflection ATR system (Specac, Kent, UK) equipped with ZnSe lenses. Spectra were recorded in the range between 4000 and 600 cm^{-1} after 64 scans with a resolution of 4 cm^{-1}, using the software IRsolution Version 1.20 (Shimadzu, Kyoto, Japan).

2.4.6. X-ray diffraction studies

XRD measurements were performed on a Bruker D8-Advance diffractometer equipped with a LynxEye type detector. Data were collected at a scan speed of 0.35 s/step and a step size of 0.02° using