International Journal of Pharmaceutics 478 (2015) 773–778

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Aerosil as a novel co-crystal co-former for improving the dissolution rate of hydrochlorothiazide

Sanaa A. El-Gizawy, Mohamed A. Osman, Mona F. Arafa, Gamal M. El Maghraby *

Department of Pharmaceutical Technology, College of Pharmacy, University of Tanta, Tanta, Egypt

ARTICLE INFO

Article history:
Received 8 November 2014
Received in revised form 15 December 2014
Accepted 16 December 2014
Available online 18 December 2014

Chemical compounds studied in this article:
Hydrochlorothiazide (PubChem CID: 3639)
Acetone (PubChem: CID 180)

Keywords:
Hydrochlorothiazide crystals
Liquid assisted grinding
Dissolution efficiency
Colloidal silicon dioxide

ABSTRACT

Co-crystallization of drugs with benign co-formers is promising for enhancing dissolution rate of poorly soluble drugs. The selection of safe and pharmacologically inert co-formers is a critical step in this process. Accordingly, the objective of this work was to investigate aerosil 200 as a potential co-former for the preparation of hydrochlorothiazide co-crystal. Co-crystal formation involved acetone assisted co-grinding after mixing hydrochlorothiazide with increasing molar ratios of aerosil (1:1, 1:2 and 1:4). The prepared formulations were subjected to Fourier transform infrared spectroscopy, differential thermal analysis, and powder X-ray diffraction studies. These investigations provided evidence for co-crystal formation between the drug and aerosil. Complete co-crystallization was even achieved at the lowest tested concentration of aerosil suggesting that the stoichiometric ratio of co-crystal formation is 1:1 molar ratio. The dissolution studies revealed faster dissolution rate of the drug from co-crystals compared to the pure unprocessed drug or that which was subjected to wet grinding in absence of aerosil. Increasing the molar ratio of aerosil increased the amount dissolved in the first 5 min. This may be attributed to adsorption of the formed co-crystal on the surface of excess aerosil. In conclusion, aerosil can be considered as co-crystal co-former with potential future application.

1. Introduction

The dissolution rate of drugs is a determining factor for drug bioavailability after oral administration. This factor provides a challenge for development and formulation of effective drug. Currently more than 40% of drugs in the development pipelines and about 60% of the drugs coming from synthesis are poorly soluble and hence have a poor oral bioavailability (Merisko, 2002). Alternative strategies have been adopted to improve dissolution rate, solubility and subsequently the bioavailability of these drugs. These include formulation of solid dispersions with hydrophilic polymers (Sareen et al., 2012), microemulsification (He et al., 2010), solubilisations using co-solvents (Amin et al., 2004), inclusion complex formation with cyclodextrines (Kurkov and Loftsson, 2013) and salt formation etc.

Co-crystallization is an emerging powerful technique which can modify the physical properties of the drugs such as dissolution rate and stability while maintaining the pharmacological effect of the drug candidate. Co-crystal can be defined as "a stoichiometric multi-component system connected by non-covalent interactions where all the components present are solid under ambient conditions" (Aakeröy and Salmon, 2005; Bhogala and Nangia, 2008; Jones et al., 2006). A pharmaceutical co-crystal composed of an active pharmaceutical ingredient and a suitable benign molecule called a co-former. The safety and pharmacological inertness of co-former are essential for its selection. Accordingly, researchers are concentrating on employing the commonly used pharmaceutical excipients as potential co-former. Researchers went even farther to attempt co-crystallization of two drugs which are approved for treatment of the same pathological condition (Cheney et al., 2011). This later strategy is being adopted with caution with the former being extensively researched in recent years. Developing of a new benign co-former can be considered as an addition to the field as it can create chances for more drug to be formulated using the co-crystal technique. Accordingly, the objective of this work was to investigate the efficacy of Colloidal silicon dioxide (aerosil 200) as a potential co-former. Aerosil 200 is widely used in pharmaceutical industry for improving flow properties (Ibrahim et al., 2011). It is biologically inert material and recognized as safe by FDA. It has the ability to form hydrogen

* Corresponding author. Tel.: +20 403336007; fax: +20 403335466.
E-mail addresses: selgizawy@hotmail.com (S.A. El-Gizawy), mosman4444@yahoo.com (M.A. Osman), drmona_arafa@yahoo.com (M.F. Arafa), gmmelmag@yahoo.com (G.M. El Maghraby).

http://dx.doi.org/10.1016/j.ijpharm.2014.12.037
0378-5173/

bond with other compounds with its silanol group (Ambike et al., 2005). These specifications attracted our attention to select aerosil as a potential benign co-former. To achieve this goal, hydrochlorothiazide was used as a poorly water soluble model drug.

Hydrochlorothiazide is a potent diuretic which inhibits the kidney's ability to retain water. It is widely used in the management of hypertension in combination with cardiovascular drugs. Hydrochlorothiazide is considered as a class IV drug according to the BCS. It has low and variable oral bioavailability which is attributed to poor solubility, slow dissolution and poor membrane permeability (Patel et al., 1984). The dissolution rate of this drug was previously enhanced by co-crystallization with other co-formers (Almarsson et al., 2007; Sanphui and Rajput, 2014). This will provide a chance for comparing the dissolution enhancing efficacy of the developed aerosil-hydrochlorothiazide co-crystals with that reported for other co-former.

2. Materials and methods

2.1. Materials

Hydrochlorothiazide and aerosil 200 were gift from Sigma for Pharmaceutical Industries, Egypt. Hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide, acetone (pharmaceutical grade) were obtained from El Nasr Pharmaceutical Chemicals Company. Acetonitrile (HPLC grade) was obtained from BDH, England.

2.2. Preparation of co-crystals

Co-crystals were prepared by liquid-assisted grinding method (also referred to as wet co-grinding) (Shan et al., 2002).

Hydrochlorothiazide and aerosil were mixed in different molar ratios (1:1, 1:2 and 1:4) before wet grinding in presence of acetone using a mortar and pestle. The amount of acetone added was just enough to dissolve the mixture. This deposited crystals immediately and grinding continued until evaporation of the solvent and formation of free flowing powder. This was left to dry for an overnight at ambient temperature and stored in tight containers. The pure drug was similarly treated with acetone and the resulting powder was used as a positive control along with the unprocessed drug. The composition of the prepared formulations is presented as both molar and weight ratios in Table 1.

2.3. FTIR spectroscopy

This employed FT-IR spectrophotometer (Bruker Tensor 27, Germany) which was used in potassium bromide diffuse reflectance mode for collecting the IR spectra of the samples. The system is equipped with a DLaTGS detector. Samples were mixed with potassium bromide (spectroscopic grade) and were compressed into disks using hydraulic press before scanning from 4000 to 400 cm^{-1}. Data analysis was performed using Opus IR, FT IR spectroscopy Software.

Table 1
The compositions of the tested formulations presented as both molar and weight ratios.

Formulation	Hydrochlorothiazide	Aerosil
Wet ground drug	1	0
HA (1:1)	1 (1)	1 (0.201)
HA (1:2)	1 (1)	2 (0.403)
HA (1:4)	1 (1)	4 (0.806)

Values between brackets represent the weight ratios. H = hydrochlorothiazide and A = Aerosil.

2.4. Differential thermal analysis (DTA)

Thermal analysis of the sample**s** was performed on differential thermal analyzer (DTA) (PerkinElmer STA 6000 module, USA). Samples equivalent to 2–4 mg of the drug loaded into the pans before being crimped. The thermal behavior of each sample was investigated at a heating rate of 10 °C/min, covering the temperature range of 30–360 °C. This was performed under a continuous flow of dry nitrogen (20 ml/min). The instrument was equipped with a refrigerated cooling system. The data were collected and analyzed using Pyris software.

2.5. Powder X-ray diffraction (PXRD)

The X-ray diffraction pattern of the pure drug, co-former and co-crystals were collected on GNR APD 2000 pro-X-ray diffractometer with Cu Kα radiation (1.54056 Å) (Italy). The diffractometer was equipped with a primary Gobel mirror and a super-speed VÅNTEC-1 detector (a position sensitive detector). The X-ray data was collected at ambient temperature, using 2theta scan axis with continuous scan mode at scanning step size of 0.03° and scan range of 3–65°.

2.6. Chromatography

Drug analysis employed high pressure liquid chromatography (Agilent technologies 1260 infinity, DE, Germany). The system was equipped with a variable wavelength UV detector (VWD 1260) and an automatic sampling system (TCC 1260). The whole system was under computer control. Separation was achieved on a reversed phase column 150 mm × 4.6 mm (i.d.) BDS Hypersil C18 with an average particle size of 5 μm (Thermo scientific, USA).

A mixture of 0.04 M of potassium dihydrogen phosphate buffer (adjusted to pH 3 with ortho-phosphoric acid) and acetonitrile (70:30) was used as the mobile phase. The mobile phase was pumped at a rate of 0.8 ml/min with the effluent being monitored at 210 nm. The samples were suitably diluted (if required) with filtered distilled water before loading into the HPLC vials and injecting 30 μl into the HPLC. Data analysis was performed using Agilent OpenLAB ChemStation software.

The method was validated for linearity, selectivity, precision and lower limit of quantification (LOQ).

2.7. Dissolution studies

The dissolution studies utilized the USP paddle method. Drug dissolution was monitored in the acidic environment (0.1 N HCl, pH 1.2). The dissolution medium (1000 ml) was maintained at 37 ± 0.1 °C and the paddle speed was adjusted to 50 rpm. Dry samples equivalent to 50 mg of hydrochlorothiazide was added to a dissolution vessel after equilibration of the system. At appropriate time intervals (5, 10, 20, 30, 45 and 60 min), samples (5 ml) were collected and the dissolution medium was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The collected samples were immediately filtered through a 0.45 μm Millipore filter and analyzed by the HPLC method after neutralization with 0.1 N sodium hydroxide solution. Each dissolution test was performed in triplicate. The cumulative amount dissolved was plotted as a function of time to produce the dissolution profile. The amount of drug dissolved in the first 5 min (Q_5) was calculated and used as a parameter for comparison. The dissolution efficiency (DE) was calculated from the area under the dissolution profile at time *t*. This was determined using the nonlinear trapezoidal rule and was expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. In addition, the similarity factor test was applied to investigate the similarity between different