International Journal of Pharmaceutics 461 (2014) 459–468

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Impact of surface area of silica particles on dissolution rate and oral bioavailability of poorly water soluble drugs: A case study with aceclofenac

Dinesh Kumar, S.V. Sailaja Chirravuri, Nalini R. Shastri *

National Institute of Pharmaceutical Education & Research (NIPER), Hyderabad, India

ARTICLE INFO

Article history:
Received 24 September 2013
Received in revised form
10 December 2013
Accepted 14 December 2013
Available online 22 December 2013

Keywords:
Aceclofenac
Mesoporous silica
MCM-41
Drug release mechanism
Non porous silica

ABSTRACT

This study aims to evaluate the impact of surface area of silica particles on *in vitro* release of poorly soluble drug aceclofenac and their *in vivo* performances. Mesoporous silicas of different surface area and porosity were synthesized and characterized. Aceclofenac loaded silicas were prepared by solvent evaporation technique and characterized for surface area, pore size, DSC, FTIR and p-XRD. The dissolution efficiency (DE) of the mesoporous and nonporous silica was ~2 times more than that of plain drug and marketed tablets in acidic discriminating media. A significant enhancement of 189% and 164% in oral bioavailability (AUC0-8) was observed for optimized aceclofenac loaded mesoporous formulation (MS11/72) and nonporous silica (NP), respectively, when compared to plain aceclofenac in male Wistar rats. However, no correlation could be established between the enhancements in their oral bioavailability and their corresponding surface area. The surface area of MS11/72 was 5 times more (~1011 m^2/g) when compared to NP (~200 m^2/g) and the enhancement in the oral bioavailability was only 1.15 times. This could be due to the limiting value of effective surface area of the drug available for *in vitro* dissolution beyond which, any further increase in surface area fails to improve the release rate or its bioavailability.

1. Introduction

Many active pharmaceutical ingredients show inadequate physicochemical (aqueous solubility, stability) and/or biopharmaceutical (dissolution rate, permeability) properties which significantly limit their oral bioavailability and hence oral delivery. Some of the various approaches employed to enhance the bioavailability of poorly soluble drugs include salt formation, micronization, co-solvency, hydrotropy, cyclodextrin complexation, micellar solubilization, pH modification, solid dispersions, nanosuspensions, spherical crystallization, etc. (Leuner and Dressman, 2000). In recent times, porous materials have been reported to be a step ahead for increasing oral bioavailability (Angelos et al., 2008; Wang, 2009). Porous materials are classified as per IUPAC as microporous (pore diameter < 2 nm), macroporous (pore diameter greater > 50 nm) and mesoporous (pore diameter 2–50 nm) (Rouquerol et al., 1994). According to IUPAC, a mesoporous material can be disordered or ordered in a mesostructure. Well-defined ordered mesoporous silicas may have hexagonal, cubic, lamellar or similar structures (Hoffmann et al., 2006; Rouquerol et al., 1994). Typical mesoporous materials include some kind of silica or alumina that has similarly-sized fine mesopores. The well defined large inner porosity and, consequently, the large surface area are the properties that make mesoporous silicate templates potentially useful drug carriers. Mesoporous silica is usually synthesized by reacting a self-assembling silica TEOS (tetraethyl ortho-silicate) or sodium silicate and a surfactant (usually quaternary ammonium salts) micelles that act as a structure directing agent. The cooperative action between the negatively charged silicate species and the positive charged quaternary ammonium micelles leads to an ordered structure of these materials. The surfactant is removed by calcination or extraction, leaving a porous silicate network. The pore size and surface area vary according to the conditions provided.

Enhancing the dissolution rate and subsequently the bioavailability by increasing the surface area is well documented (Hu et al., 2002; Mellaerts et al., 2007). In recent studies, many authors have reported the use of mesoporous silica particles for enhancing dissolution and oral bioavailability (Friedrich et al., 2006; Horcajada et al., 2004). This forms the basis our research. To the best of our knowledge, no work has been reported studying the impact of surface area on *in vitro* and *in vivo* drug release. Aceclofenac, a non-steroidal anti-inflammatory drug (Alvarez-Larena et al., 1992)

Abbreviations: NP, non porous; MS, mesoporous silica; PM, physical mixture; AUC, area under curve; DE, dissolution efficiency.

* Corresponding author at: Department of Pharmaceutics, NIPER, Balanagar, Hyderabad 500037, India. Tel.: +91 08125849395; fax: +91 040 23073751.
E-mail addresses: nalini@niperhyd.ac.in, svcphod@yahoo.co.in (N.R. Shastri).

0378-5173/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.12.017

was chosen as a model drug for this study. Aceclofenac is used to treat pain, inflammation, rheumatoid arthritis and osteoarthritis (Gonzalez et al., 1994). It exhibits elimination half life of 4 h, volume of distribution 25 L and ~50% oral bioavailability (Bort et al., 1996; Gonzalez et al., 1994). In the present study, porous silicas were synthesized and characterized, onto which aceclofenac was loaded by solvent evaporation and characterized for surface area, pore size, and dissolution pattern followed by comparative oral bioavailability study.

2. Materials and methods

2.1. Materials

Aceclofenac was generously gifted by Suraksha Pharma., Hyderabad, India. Ibuprofen was obtained as gratis sample from Meyer Lab, India. Sodium lauryl sulphate was procured from Finar, Pvt. Ltd., India. Aerosil® 200 IP was obtained from Degussa Pvt. Ltd., India. AR grades of sodium metasilicate nonahydrate, CTAB (cetyl trimethyl ammonium bromide), methanol, acetone, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid (35–38%) and sodium acetate anhydrous were purchased from Loba Chemie, India. MCM-41 (hexagonal) was procured from Sigma Aldrich, India. Heparin was procured (5000 IU/ml) from Bio E, India. Acetonitrile (HPLC grade) was purchased from Ranchem, India. In-house ultra-pure water from Millipore was used for all the experiments. All other reagents used were of analytical grades. Aceclofenac marketed tablets (Hifenac, Intas Pharmaceuticals Ltd., India) were procured from local pharmacy.

2.2. Synthesis of porous silica

Synthesis of mesoporous silicas were carried out according to reported methods (Ambrogi et al., 2008; Azaïs et al., 2006; Charnay et al., 2004b; Friedrich et al., 2006) using sodium metasilicate as silica precursor and CTAB in distilled water. Cationic surfactant CTAB was used as a structure directing agent to obtain mesoporous silica of hexagonal internal structure. A 26.82 g of sodium metasilicate nonahydrate was dissolved in 210 ml of deionized water and added to CTAB solution (3.64 g dissolved in 28.8 g of deionized water), under stirring. Various parameters like pH (4.8, 8, and 11) and synthesis time (6 h, 24 h and 72 h) were changed for optimizing processing conditions. The mixture was adjusted to required pH by adding 2 N HCl solution. A milky white precipitate was obtained. The stirring was continued for 1 h. Post stirring, the mixture was incubated at 100 °C for 6 h, 24 h or 72 h in a hot air oven. The resultant white solid material was recovered by filtration and washed with deionized water until the washings were neutral. The wet solid was dried at 55 °C in a hot air oven for 15 h and sifted through 100# sieve. High temperature calcination method was employed to ensure complete removal of CTAB. The mass was calcined in silica crucible at 600 °C for 6 h. Completeness of this reaction was monitored by weight loss during calcinations. Nearly 35–60% reduction in weight during calcinations confirmed the loss of CTAB. The mesoporous silica hence obtained was re-sieved through 100# sieve and stored in tightly closed glass containers. The batches were coded as 'pH/time of incubation'.

2.3. Aceclofenac loaded porous silica and physical mixture

Drug loading on all grades of silica were done by solvent evaporation (Van Speybroeck et al., 2010). Accurately weighed 500 mg of aceclofenac was dissolved in 20 ml of acetone. Accurately weighed 500 mg of silica carrier corresponding to (1:1) drug: carrier ratio by weight was dispersed in the drug solution under continuous stirring for half an hour to allow satisfactory loading of drug in pores. The solvent was allowed to evaporate at ambient conditions in a protected environment. The obtained product was dried at 50 °C for 2 h in a hot air oven. The dried, drug loaded carriers were pulverized and passed through a 100# sieve. Similar technique was employed for loading of drug onto non porous silica (Aerosil®) and MCM-41 (marketed mesoporous silica). Physical mixtures (PM) of different grades of synthesized mesoporous silicas, non porous silica (Aerosil®) with aceclofenac were prepared by trituration. Accurately weighed (500 mg) of aceclofenac and 500 mg of porous silicas were lightly triturated for 10 min in a mortar, sifted through 100# sieve and used immediately.

2.4. Densities

Silicas were evaluated for bulk and tap density (Santomaso et al., 2003). Bulk density was determined by pouring 2 g sample (M) into a 10 ml graduated cylinder in a fine stream and recording the bulk volume (V_b). The bulk density (D_b) was calculated using the formula $D_b = M/V_b$. The measuring cylinder containing a known mass (M) was tapped to get a constant volume (V_t). The tapped density (D_t) was calculated using: $D_t = M/V_t$

2.5. Surface area and pore size

Nitrogen adsorption–desorption isotherms of samples (0.01–0.02 g) were obtained using a gas sorption analyzer (Quantachrome Instruments Nova-1000) at 77.3 K. The surface area was determined according to the BET method (Fenelonov et al., 1999), and the pore size distribution from the desorption isotherm according to the BJH method (Storck et al., 1998).

2.6. Powder X-ray diffraction analysis (p-XRD)

p-XRD were obtained on D-5000 Semens X-ray diffractometer, using Ni-filtered Cu K_a radiation (wave length = 1.5406 A°), over a scanning 2θ range of 2°–50° at step time of 0.045 steps/0.5 s. Small angle p-XRD were recorded on a Rigaku Altima X-ray diffractometer (set at 40 kV and 40 mA) using Ni-filtered Cu K_a radiation (wave length = 1.5406 A°) radiation within the 2θ range from 0.7 to 5° at a rate of 2°/min in steps of 0.01°. The intensity and the inter planner distance (d) corresponding to the 2θ values were reported and compared. The values of the lattice parameter a_o corresponding to the distance between the centers of two close pores in MCM-41 was determined from the equation $a_o = (2/\sqrt{3})d_{100}$ (Chen et al., 1993).

2.7. Differential scanning calorimetry (DSC)

DSC analysis was performed using Mettler Toledo DSC821e, calibrated with indium. Accurately weighed 3–10 mg of sample was placed in a closed, pierced, flat bottom, aluminum sample pans. Thermograms were obtained at a constant rate 10 °C/min over the range 25–250 °C. A dry purge of nitrogen gas (20 ml/min) was used for all runs.

2.8. FTIR spectroscopy

Sample (about 5 mg) was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 min. The resultant disk was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and spectrum was recorded from 4000 cm^{-1} to 625 cm^{-1} in a scan time of 12 min.