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Modified mesoporous silica nanoparticles for enhancing oral bioavailability and antihypertensive activity of poorly water soluble valsartan

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ABSTRACT

The aim was to improve the oral bioavailability and antihypertensive activity of poorly soluble drug valsartan (VAL) by modifying the design and delivery of mesoporous silica nanoparticles (MSNs). The synthesized MSNs were functionalized with aminopropyl groups (AP-MSN) through postsynthesis and coated with pH sensitive polymer Eudragit L100-55 (AP-MSN-L100-55) for pH dependant sustain release of anionic VAL. MSNs were characterized by Brauner-Emmett-Teller (BET) surface area analyzer, zeta sizer, Field Emission Scanning Electron Microscope (FESEM), Powder X-Ray Diffraction (PXRD) and Differential Scanning Calorimetry (DSC). Functionalized MSNs showed highest entrapment efficiency (59.77%) due to strong ionic interaction with VAL. *In vitro* dissolution of M-MSN [MSN-VAL and AP-MSN-VAL-L100-55 mixed equally] at physiological conditions demonstrated immediate release (MSN-VAL fraction) followed by sustained release (AP-MSN-VAL-L100-55 fraction) of 96% VAL in 960 min. The dramatic improvement in dissolution was attributed to the amorphization of crystalline VAL by MSNs as evidenced by DSC and PXRD studies. No noticeable cytotoxicity was observed for MSN, AP-MSN and AP-MSN-L100-55 in MTT assay. Pharmacokinetic study of M-MSN confirmed 1.82 fold increases in bioavailability compared to commercial Diovan tablet in fasted male rabbits. Blood pressure monitoring in rats showed that the morning dosing of Diovan tablet efficiently controlled BP for just over 360 min whereas the effect of M-MSN lasted for >840 min.

1. Introduction

Valsartan is a promising angiotensin II receptor blocker which is indicated for the first line treatment of hypertension (Markham and Goa, 1997). Valsartan (class II drug) is rapidly absorbed from GI tract after oral administration but suffers from the drawbacks of poor oral bioavailability of about 23% primarily due to its lack of solubility in the acid milieu of the GI tract. Valsartan is an acid in nature and therefore, has good solubility at pH > 5 (Flesch et al., 1997). Valsartan has other problems also leading to its poor oral bioavailability. Valsartan has an absorption window and is mainly absorbed from the upper parts of GIT where its solubility is low and shows fast pass metabolism. Various technologies were developed previously to address poor bioavailability issue of valsartan like β cyclodextrin complexes (Cappello et al., 2006), microcapsules (Li et al., 2010), solid dispersion (Yan et al., 2012) *etc.* However the potential of nanotechnology in improving bioavailability of valsartan has not been studied in detail till date.

Nanotechnology has benefitted a number of biomedical areas including drug delivery (Ramsden, 2005; Sahoo and Labhasetwar, 2003). Among nanoparticles different MSNs and their therapeutic applications have been studied extensively for the last few years. Some unique features of MSNs have made it an excellent candidate in the field of drug delivery. Mesoporous materials improve the solubility of the guest molecules by converting unstable crystalline to stable amorphous state without altering their lattice energy (Slowing et al., 2007; Wang, 2009). These materials creates larger surface for better adsorption of therapeutic cargo and protect the loaded drug from external attack by steric hindrance (Slowing et al., 2008; Rosenholma and Lindén, 2008). Moreover, tunable pore size and surface functionalization has made it a promising carrier for controlled release of therapeutic cargo (Kapoor et al., 2009; Lia et al., 2006). Free MSN consisting of negatively charged silanol groups (Lvov et al., 1997; Wani et al., 2012; Zhang et al., 2012) allows prompt release of entrapped drug due to the weak ionic interaction with negatively charged drug like valsartan (Tosco et al., 2008). In the past the focus of MSNs has been mainly on the development of slow release formulations, and fewer reports have been published on the application of the MSNs involving the dissolution enhancement of poorly water-soluble drugs (Wang, 2009; Salonen et al., 2005). Till date no study was documented on MSN for oral delivery of valsartan. Moreover the antihypertensive effect of commercial oral valsartan formulations lasts only 4–6 h. So a true once a day formulation

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with higher bioavailability is urgently required. This goal may be achieved by delivering it in pulses at different time intervals using mesoporous support. In addition the treatment side effects may be minimized by matching the drug release profile with the circadian pattern of hypertension.

In view of the aforementioned, the current work aims to maximize the therapeutic potential of oral valsartan by modifying the design and delivery of MSNs. To the best of our knowledge, most reported polymer-MSN hybrids have been prepared by three methods- layer-by-layer technique (Wang et al., 2005), graft-to (Carniato et al., 2010), and graft–from technique (Liu et al., 2011). Defiance of their novelty these strategies still possess some pitfalls such as tedious step synthesis, very low surface graftings efficiency *etc.* (Fleming et al., 2001). It is still challenging for the researchers to explore a facile and efficient method for producing a hybrid that can controllably deliver entrapped guest molecules. Herein we have synthesized novel bean shaped MSN and functionalized with aminopropyl groups (AP-MSN) through postsynthesis. After drug loading into the mesoporous support AP-MSN were coated with Eudragit L 100-55 an anionic methacrylic acid-ethyl acrylate copolymer having dissolution pH threshold of 5.5. Different MSN samples were characterized with BET surface area analyzer, zeta sizer, FESEM, PXRD, DSC. MSN-VAL and AP-MSN-VAL-L100-55 were encapsulated in 1:1 ratio (M-MSN) to obtain a typical dissolution pattern in gastrointestinal pH, immediate release followed by a lag time and then a sustained release. Oral bioavailability of M-MSN and commercial Diovan tablets were compared in fasted male albino rabbits. A Level A IVIVC (*in vitro in vivo* correlation) model was developed. Blood pressure lowering potential of oral M-MSN and Diovan tablet was estimated in hypertensive rats employing tail cuff method.

2. Materials and methods

2.1. Material

Gift samples of valsartan (VAL) and losartan (internal standard) with the assay value of 99.8% and 99.7% respectively were received from Ranbaxy Laboratories Ltd., India. Pluronic® P123 was a gift sample from BASF (USA). Tetraethyl orthosilicate (TEOS) and 1, 3, 5 tri methyl benzene (TMB) and (3aminopropyl)triethosysilane (APES) were purchased from Sigma Aldrich, USA. Analytical grade chemicals like water, hydrochloric acid, ethanol, *etc.* were purchased from Merck Ltd., Mumbai, India.

2.2. Synthesis of MSN

In a typical preparation 2 g of Pluronic® P123 was dissolved in 52 g water and 20 ml hydrochloric acid (37%) with stirring at 35 °C. Then 4.28 g of TEOS was added into the solution with vigorous stirring at 35 °C for 24 h (Zhao, 1998). The mixture was aged at 100 °C overnight without stirring. Trimethylbenzene (TMB) was added during synthesis in a 1:1 ratio with the surfactant. The solid product was filtered and washed repeatedly with water and ethanol. The product was dried in an oven at 90 °C for 20 h. The polymeric template was removed from MSN through thermal treatment. Isothermal annealing of the silica sample was done at 550 °C for 6 h in a PID controlled Muffle furnace (Grieken et al., 2003).

2.3. Functionalization of MSN

A post synthesis procedure (Zhang et al., 2010) was adopted to functionalize the MSN with aminopropyl groups. 1 g MSN was placed in a three naked flask and dehydrated at 100 °C for 6 h under nitrogen atmosphere. 5 ml (3aminopropyl)triethosysilane (APES) was dissolved in 100 ml ethanol and added to the flask. The system was refluxed at 77 °C with overnight magnetic stirring under nitrogen atmosphere. The obtained product was filtered and washed with ethanol repeatedly. The product was dried in an oven at 90 °C for 24 h.

2.4. VAL loading and Eudragit L 100-55 coating

Two separate ethanolic solutions were prepared by dissolving 100 mg of each VAL in 10 ml ethanol. Then 50 mg of each MSNs and AP-MSNs were added to this solution under magnetic stirring for 4 h. Thus VAL loaded MSNs and AP-MSNs were produced in separate beakers. MSN-VALs were filtered and dried in a hot air oven overnight at 60 °C. 100 mg Eudragit L 100-55 was dissolved in 5 ml ethanol under stirring for 4 h. Then this coating solution was added dropwise to the drug loaded AP-MSNs suspension (VAL: MSN: Eudragit L 100-55 = 2:1:2) under magnetic stirring at 40 °C for 12 h. Finally Eudragit L 100-55 coated AP-MSNs (AP-MSN-VAL-L 100-55) were filtered using cellulose acetate membrane (0.22 μm). Filtered materials were dried in a hot air oven overnight at 60 °C. Dried materials were scrapped, collected and stored in desiccator.

2.5. Characterization

2.5.1. Nitrogen sorption isotherms at 77 K

MSNs of different batches were characterized by nitrogen gas desorption/adsorption isotherm using Surface area analyzer (Micromeritics Gemini VII-2390t, USA). It was measured at −196 °C. Samples were degassed at 150 °C for 4 h. Total surface was determined using Brauner-Emmett-Teller (BET) model in the relative pressure range between 0.05 and 0.3. The pore volume and pore size distribution were derived from the adsorption branches of the isotherms using Barrett-Joyner-Halenda (BJH) method. Total pore volume was estimated from the amount adsorbed at a relative pressure of 0.99. Micropore volume and micropore areas were measured from t-plot. t values were calculated as a function of relative pressure using Harkins and Jura equation.

2.5.2. Average particle size and zeta potential measurements

The average particle size, polydispersity index (PDI), and zeta potential of different MSNs samples were accessed by dynamic light scattering technique (DLS) using a Malvern Zeta Sizer (Nano ZS 90). A small quantity of MSN sample was dispersed in a large volume of milli-Q water to obtain suitable light scattering intensity and vortex mixed for 5 min to prevent particle clogging. The sample was analyzed at 25 °C for 1 min in triplicate

2.5.3. Differential Scanning Calorimetry (DSC)

The DSC curves were recorded for the sample powder (Drug alone, MSN, AP-MSN, MSN-VAL, AP-MSN-VAL, AP-MSN-VAL-L100-55) using Pyris Diamond TG/DTA (PerkinElmer, Singapore) instrument in the temperature range of 20–200 °C, under a dynamic atmosphere of nitrogen (150 ml/min) and at a heating rate of 10 °C/min, using platinum crucibles and weighed samples of 20 mg.

2.5.4. Powder X-Ray Diffraction (PXRD)

The x-ray powder diffraction pattern were recorded at room temperature in Philips Analytical Powder XRD using Ni-filtered, and CuKα radiation operated at voltage of 35 Kv and current of 25 mA. The scanning rate employed was 1° min^{-1} over 5° to 50° diffraction angle (2θ) range. Samples of pure VAL, MSN, AP-MSN, MSN-VAL, AP-MSN-VAL, AP-MSN-VAL-L100-55 were analyzed.

2.5.5. FESEM

The shape and surface morphology of the samples were determined using a field emission scanning electron microscope (FESEM, Hitachi S-4800). The samples were gold-plated prior to imaging.