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Application of SBA-15 mesoporous material as the carrier for drug formulation systems. Papaverine hydrochloride adsorption and release study

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ABSTRACT

SBA-15 mesoporous material was used as a matrix in three different drug formulations (powders, granules and tablets). Hydroxypropyl cellulose (HPC) and stearic acid (SA) were applied as modifiers of papaverine hydrochloride release from mesoporous carriers. The samples were characterized by thermogravimetry, differential scanning calorimetry (DSC), X-ray diffraction (XRD) and nitrogen sorptometry at −196 °C. High pressure applied during the drug formulation (granules, tablets) decreases both specific surface area and porosity of SBA-15. The changes in BET surface area were also observed after drug deposition. The Korsmeyer–Peppas model was applied to evaluate the kinetics of papaverine hydrochloride release from hydroxypropyl cellulose- and stearic acid-containing drug formulations. The extended drug release resulted from slow diffusion of the active substance from micro- and mesoporous channels blocked by hydrophobic stearic acid and organic polymer.

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1. Introduction

The recently observed enormous growth of chronic diseases such as asthma, hypertension and diabetes inspired scientific groups to develop new drug formulations with extended active substance release. The treatment of these diseases requires continuous doses of a drug during the daytime. Repeated drug administration of traditional drug formulation is very frequently troublesome, especially for the elder. Therefore the Drug Delivery System (DDS) providing the constant therapeutic drug concentration in blood serum might markedly improve therapy [1].

Mesoporous siliceous materials of e.g. MCM-41 or SBA type are a new class of matrices applied in DDSs. Initially, these materials served as supports in heterogeneous catalysis [2,3]. Later on, mesoporous materials demonstrated the potential of an excellent drug carrier [4]. Both MCM-41 and SBA-15 have been already tested in drug adsorption and drug delivery [5]. Mesoporous materials are characterized by large surface area (>1000 m^2/g), uniform pore size distribution and large pore volume (~1.0 cm^3/g). Moreover, high biocompatibility [6,7], low toxicity [8] and the presence of micropores (in SBA-15) [9] promote their application as carriers in drug formulations of prolonged release. The application of MCM-41 loaded with ibuprofen was described in 2001 for the first time [10]. Since then, numerous studies with other mesoporous siliceous materials (SBA, MSU type) as drug carriers were undertaken. Siliceous mesoporous systems were loaded with a wide range of active substances such as antibiotics [11,12], vitamins [13], antiinflammatory drugs [14–16], hypertension drugs [17,18], natural antimicrobial agents [19] and other biomolecules [20,21].

In order to improve the adsorption properties of mesoporous matrices and to obtain better kinetics of the drug release from the drug–carrier complex these materials should be appropriately functionalized. The presence of free silanol groups inside the SBA-15 mesoporous channels can significantly improve its adsorption properties during modification with alkoxysilanes [22–24]. Moreover, modification of mesoporous materials with suitable organic polymers influences the kinetics of the drug release [25,26]. Photo-sensible [27] and magnetic [28] drug delivery systems based on mesoporous materials have been described. It should be mentioned that the industrial production techniques based on spray-drying process have been also considered [29].

This paper describes the application of SBA-15 mesoporous material as the carrier for papaverine hydrochloride. Papaverine hydrochloride is known as a non-selective smooth muscle relaxant [30]. The activity of this drug is based on the inhibition of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) phosphodiesterases [31]. Moreover, this alcaloid can be also applied in vasospasmic diseases such as spasm associated with subarachnoid hemorrhage [30], erectile dysfunction [32] and spasms of alimentary channel [33]. The aim of this study was to formulate a drug (tablets, granules and coated powders) based on SBA-15, papaverine and excipients and to achieve the extended-release profiles of the active substance.

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2. Experimental

2.1. Synthesis of SBA-15

SBA-15 was synthesized according to the procedure described by Zhao et al. [34] applying triblock copolymer Pluronic P123 as a template and tetraethoxyorthosilicate (TEOS) as a source of silica. During the synthesis 48 g of block copolymer of Pluronic P-123 was dissolved in 360 cm^3 of water and 1440 cm^3 of 2 M HCl at 35 °C. After complete dissolution of co-polymer, 102 g of TEOS was added and the obtained mixture was stirred 20 h at 35 °C. Next, the suspension was transferred into tightly closed vessel and kept for 24 h at 110 °C without stirring. The obtained white solid was filtered and washed repeatedly with deionized water. The air-dry white powder was next calcinated at 500 °C for 6 h (heating rate 1 °C/min).

2.2. Adsorption of papaverine hydrochloride on SBA-15

10.0 g of pure, dehydrated powder of SBA-15 was introduced into 500 cm^3 of water solution of papaverine hydrochloride (15 mg/cm^3). The adsorption process was performed at 25 °C for 24 h. After adsorption the sample was filtered and dried at room temperature for 24 h and another 24 h at 100 °C. The amount of papaverine hydrochloride in dry carrier was estimated from elemental analysis. This sample was marked as SBA-15-Pap.

2.3. Drug formulation

2.3.1. Granulation of SBA-15 materials

The granules of pure SBA-15 and SBA-15-Pap samples were obtained in dry granulation process. The discs of 25 mm in diameter were formed from 10.0 g of appropriate powder using a hydraulic press. The compression pressure was 10–20 MPa. Next, the sample was crushed (Erweka apparatus) and fractionated by sieve analyzer (Fritsch). The fraction between 0.5 and 1.0 mm was collected. Samples were designated as SBA-15-GX and SBA-15-Pap-GX for granules of pure SBA-15 and granules of SBA-15 loaded with papaverine hydrochloride, respectively. The X value corresponds to the applied pressure (in MPa).

2.3.2. Coating process

2.5 g of SBA-15 loaded with papaverine hydrochloride was introduced into 100 cm^3 of 0.5 wt.% n-hexane solution of stearic acid (SA). The suspension was stirred at room temperature for 2 h. Next, the sample was filtered and the remaining n-hexane solvent was removed at 40 °C for 24 h in a vacuum. The obtained sample was designated as SBA-15-Pap-SA.

2.3.3. Tablet preparation

The tablets were prepared from an appropriate amount of mechanically mixed SBA-15-Pap and hydroxypropyl cellulose (HPC). The tablet weight was 0.7 g. The amount of HPC in tableting bulk was from 10 to 50 wt.%. Next, the mixture was compressed into 15 mm discs under pressure of 6 MPa. These samples were designated as SBA-15-Pap-TX%, where X represents the amount of the applied HPC (wt.%).

2.4. Release of papaverine hydrochloride from the drug formulation

The release of papaverine hydrochloride from powdered samples, granules and tablets was performed in Erweka DT 60 apparatus, according to US Pharmacopeia (paddle method) in 0.1 M HCl (500 cm^3) at 37 °C with stirring rate of 50 rotations per minute. After the indicated period of time (0.25–24 h) the solution of the drug (alternatively suspension) was centrifuged. The amount of released drug was calculated from the absorbance value measured spectrophotometrically at 250 nm (0.1 M HCl).

2.5. Characterization of the sample

Both thermogravimetric analysis and differential scanning calorimetry were performed in the air with Setsys-TG-DSC apparatus from Setaram. The XRD measurements of powdered samples were performed using an AXS D8 Advance diffractometer from Bruker ($CuK\alpha = 1.5406$ Å — Bruker). The amount of drug in the carrier and the amount of stearic acid in the formulated samples were based on calculation of C and N contents established in elemental analysis (Vario EL III Elemental Analyser). The amount of released drug was determined from absorbance values at 250 nm using Cary 100 UV–vis spectrophotometer. Adsorption and desorption isotherms of nitrogen at −196 °C were measured using an ASAP 2010 sorptometer (Micromeritics). Before nitrogen adsorption–desorption measurements all samples were degassed at 120 °C for more than 12 h.

3. Results and discussion

3.1. Characteristics of SBA-15 and SBA-15-Pap samples

Thermogravimetric analysis of SBA-15 loaded with papaverine hydrochloride (SBA-15-Pap) shows that adsorption of the drug within the hexagonal channels of mesoporous material does not influence its thermal stability (Fig. 1). Comparison of the DSC curves (see insert in Fig. 1) of pure papaverine hydrochloride and that of SBA-15 loaded with the drug, indicates the absence of an endothermic peak at ~230 °C in the case of the drug–carrier complex. Differential scanning calorimetry confirms an amorphous character of adsorbed papaverine hydrochloride. Endothermic peak on DSC curve (a) corresponds to the melting point of papaverine hydrochloride (220 °C). An amorphous character of the adsorbate is due to its molecular dispersion at the surface of mesoporous SBA-15 structure. Similar results were obtained by Mellaerts et al. [35] while adsorption of itraconazole on SBA-15. Amorphous character of adsorbed papaverine hydrochloride was also confirmed in wide angle X-ray diffraction measurements [17].

Synthesized SBA-15 material had BET surface area of 776 m^2/g, pore volume of 0.89 cm^3/g and microporosity of 0.0863 cm^3/g. These parameters are in agreement with those presented in the literature [36]. Large BET surface area of hexagonal channels in SBA-15, the presence of micropores and free silanol groups [5] at the surface of mesoporous matrix promote the drug adsorption. The results of elemental analysis of the SBA-15-Pap sample indicated that the amount

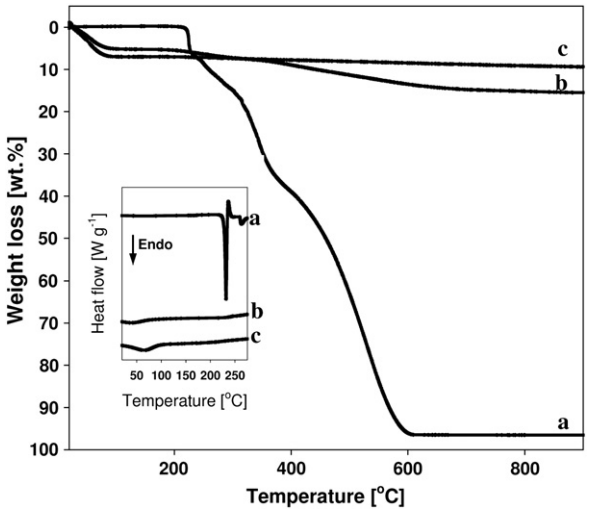

Fig. 1. Thermogravimetric analysis of the sample: (a) papaverine hydrochloride, (b) SBA-15 loaded with papaverine hydrochloride, (c) SBA-15. Insert: curves of differential scanning calorimetry analysis of these samples.

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