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Polymer–silica composite as a carrier of an active pharmaceutical ingredient

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ABSTRACT

The present article describes the synthesis of a novel type of a composite which has potential application in controlled drug release. The system comprises of the porous polymer matrix with embedded active agent and the silica gel. The silica is introduced into the polymer beads with encapsulated drug by swelling in tetraethoxysilane as the silica precursor. After the condensation of the silica source, the silica membrane is formed inside the core of pores. Scanning electron microscopy (SEM) combined with energy dispersive X-ray spectroscopy (EDX) allow for the assumption that the examined polymer–drug–silica composite is rich in silica, homogeneously dispersed within the polymer matrix. What is more, the introduction of the siliceous membrane significantly changes the porosity, which affects drug diffusion. The purpose of this study was to investigate the drug release process from the pure polymer and polymer–silica composite with regard to their structural parameters. The drug desorption was examined in a NaCl solution and in a simulated body fluid (SBF) at different temperatures.

1. Introduction

In recent years, tremendous progress has been made in the areas of controlled drug delivery systems. Undoubtedly, sustained release of drugs at a therapeutic level over a long period of time constitutes a serious advantage. Consequently, the dosing frequency can be considerably reduced without the loss of the effectiveness of the therapeutic activity. The benefits of the controlled delivery systems include the protection of the drug against in vivo degradation, its prolonged therapeutic level and the reduction of side effects. Therefore, it is understandable that the development of innovative biomaterials has attracted growing interest in different fields, in biomedicine and pharmaceutics, in particular. Among a wide range of materials, silica gel is considered to be especially valuable for many applications due to its highly porous internal structure and a variety of morphological forms.

The ordered mesoporous silicas are an excellent example of materials that have received a lot of interest due to their specific characteristics: uniform structure, large pore volume and surface area, as well as the tuneable pore size with narrow distribution [1–3]. All of the abovementioned attractive features make silicas suitable for novel controlled delivery systems and make it possible to achieve a high loading capacity of drugs [4–8]. Furthermore, the easy surface functionalisation of the silica is an important advantage in controlling the drug-surface affinity [9–11].

Multi-component silica/organic composites are another large group of porous materials which have attracted a great deal of attention because of their potential application in the developed drug delivery systems [12,13]. It has been demonstrated that the sustained release of drugs out of polymer-based carrier systems can be achieved by controlling a simple diffusion process [14]. Therefore, the interest in the introduction of a silica gel as a filler into a polymer matrix is growing as it allows for the formation of additional porosity. This process exerts a decisive influence on the diffusion of the introduced active pharmaceutical ingredient [15,16].

Undoubtedly, the stage in which the drug is loaded into a host material is of fundamental importance in the development of new drug delivery systems. This process has to be appropriately adjusted to the character and synthesis conditions of the carrier as well as to the nature of the active pharmaceutical ingredient and can be achieved in different ways. One of them involves the immersion of the porous siliceous carriers into a continuously stirred solution in which the desired drug is dissolved [4,17,18]. Subsequently, after a certain amount of time, the solvent is removed

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by evaporation and, in consequence, certain amount of the drug crystallises on the outer surface of the silica material. It is commonly known that the dissolution rate of such externally loaded substances differs significantly from the dissolution rate of those located in the pores. Thus, in most cases, additional rinsing – a process difficult to control – may be required. Moreover, it is known that with the increase in the drug concentration, the active agent solubility may limit the carrier loading capacity due to the phase separation.

Another way of drug loading is the incipient wetness impregnation, a technique used commonly in the synthesis of heterogeneous catalysts. Typically, the desired drug solution is added to the dry siliceous matrix until the mixture achieves the appropriate viscosity. Therefore, a controlled amount of the drug is dispersed within the solid and there is no excess drug on the outer part of the carrier particle [5,19].

A different approach has been proposed by Madieh et al., who studied the possible mechanisms behind the enhanced dissolution rate in physical mixtures of crystalline drugs and porous adsorbents as carriers [20]. An interesting solvent-free method of a poorly water-soluble drug loading has been proposed by Hanawa et al. [21] and Kinoshita et al. [22]. The process known as melt-adsorption comprises of melting drug crystals and their simultaneous adsorption on a porous calcium silicate in the amorphous state. A very similar procedure consists in the addition of an active substance during sol–gel process. [23].

The present article describes a polymer–silica composite which can serve as a carrier in a sustained release drug delivery system. The composite was synthesised using the method which involved the swelling of preformed porous polymer particles with a desired pore structure in the active agent solution, and then in the tetraethoxysilane TEOS. This method is based on the previously presented synthesis of pure polymer–silica composites [24–27]. The composite was tested for the systems containing naproxen, a representative of the non-steroidal anti-inflammatory drugs (NSAIDs) which are one of the most frequently used medications in the world [28,29].

The profiles of naproxen release were demonstrated and the characteristics of the composite system were reported with the use of scanning electron microscopy (SEM) combined with energy dispersive X-ray spectroscopy (EDX) and porosimetry studies of the support material [25,27,30].

2. Experimental section

2.1. Synthesis of drug carrier

The Amberlite XAD7HP from ROHM & HAAS (now Dow Chemical Co.) was used as the polymer matrix of the desired porosity. Firstly, 1 g of Amberlite XAD7HP beads (P), rinsed with distilled water in accordance with the manufacturer's suggestion, was saturated with the 2.5 wt.% solution of naproxen (INN, (S)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, 98 wt.%, Sigma–Aldrich) in anhydrous ethanol (POCH, 99.8 wt.%). Its amount was adjusted so that the solution was fully adsorbed during the polymer swelling. The beads swollen in the naproxen solution were dried at 80 °C under vacuum for 8 h and labeled as the P–INN. The final concentration of naproxen was 2.3 wt.%. The polymer–naproxen–silica sample was prepared analogically to the one reported by Halasz et al. [25], i.e. by swelling 1 g of the P–INN material in 1.79 g of tetraethoxysilane (TEOS, Sigma–Aldrich, 98%) which served as the silica source. Next, the beads swollen in TEOS were transferred into 100 ml of the 0.2 M aqueous solution of hydrochloric acid (POCH, 36 wt.%) and kept there for gelling and aging at room temperature for 8 h. The solid spheres were filtered, rinsed with ion-free water to reach neutral pH and dried at 80 °C under vacuum for 12 h. Particle aggregation was not observed. The dry composite sample was kept afterwards in ambient conditions and tested as the P–INN–SiO_2.

The amount of the silica remained after combustion of the organics (polymer and naproxen at 600 °C for 8 h) indicates that the final sample (P–INN–SiO_2) contains about 17 wt.% of the silica gel.

2.2. In vitro naproxen release study

The release profiles of naproxen were determined by soaking 0.2 g of the drug-loaded sample in 70 ml of 0.9% NaCl or 70 ml of simulated body fluid SBF [31]. The experiments were performed under stirring at 270 rpm at room temperature and at 36 ± 0.1 °C in a thermostated bath. 5.0 ml of the release medium was sampled from the studied system at the predetermined time intervals. The volume of the solution taken for the analysis was immediately replaced with 5.0 ml of fresh release fluid for each experimental point. This procedure was applied to stimulate desorption of the active agent and to avoid the equilibration of the solid/solution system. The continuous thinning of the liquid mixture was necessary to reach the complete release of the drug from the sample. The amount of the released naproxen was determined by using a Varian Cary 100 Bio UV/Vis spectrophotometer tuned to the maximum absorption peak related to the free form of the drug in 0.9% NaCl solution (λ_{max} = 315 nm). The final concentrations of naproxen were corrected with respect to the dilution procedure.

2.3. Methods of characterization

The standard characterization of the samples was performed through the measurements of nitrogen adsorption–desorption isotherms at 77 K, using a volumetric adsorption analyzer ASAP 2405 (Micromeritics, Norcros, GA). The Brunauer–Emmett–Teller (BET) method was used to evaluate the specific surface areas, S_{BET}, whereas the total pore volume, V_p, was estimated from a single point adsorption at the relative pressure of 0.985 [32]. The Barrett–Joyner–Halenda (BJH) procedure was used to determine the pore size distribution (PSD) from the desorption branch of the isotherm [33].

The internal structure of the studied samples was analyzed using scanning electron microscope (FEI Quanta 3D FEG microscope) equipped with EDX spectrometer, working at 5, 10 and 30 kV.

3. Results and discussion

The most representative SEM micrographs of the pure Amberlite XAD7HP, composites P–INN and P–INN–SiO_2 are shown in Fig. 1. It is clearly visible that the polymer beads have a loose structure of irregularly connected and small (ca. 45 nm in diameter, similar in size) microspheres (Fig. 1a) which form a continuous pore network. The high-resolution SEM image reveals that these microspheres are composed of very fine particles called nuclei (Fig. 1b). Such a complex internal structure is usually observed in porous copolymers [34].

The swelling of crosslinked polymers is a known phenomenon which has already been studied. Therefore, it is not surprising that after the ethanolic solution of naproxen has been added to the dry polymer beads, they swell easily, which results in the increase of their size. The porosity of the polymer contributes to its rapid swelling in an organic solvent, although it is the intermolecular interactions that are mainly responsible for the extent of swelling. It is worth noting that naproxen impregnated beads, P–INN, retain