Journal of Analytical and Applied Pyrolysis 114 (2015) 91–99

Contents lists available at ScienceDirect

Journal of Analytical and Applied Pyrolysis

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

Thermal characterization of polymer-silica composites loaded with ibuprofen sodium salt

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ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form 10 April 2015
Accepted 9 May 2015
Available online 12 May 2015

Keywords:
Polymeric porous microspheres
Drug release systems
Thermal stability
Thermogravimetric analysis
TG/FTIR/MS

ABSTRACT

The study describes the thermal properties of a series of porous microspheres synthesized with 2-hydroxyethyl methacrylate (HEMA) and trimethylolpropane trimethacrylate (TRIM), their conjugates with ibuprofen sodium salt (IBS) and finally the polymer-drug-silica composites based on them. The poly(HEMA-*co*-TRIM) and pure poly(TRIM) permanently porous microspheres were synthesized via suspension-emulsion polymerization. The polymer-drug conjugates were produced by introduction of the IBS into the polymer beads by their swelling. The polymer–drug–silica composites were synthesized by the hydrolysis and condensation of silica precursor (tetraethoxysilane, TEOS) introduced into the conjugates. The transformation of TEOS was performed in the vapor phase of the acidic (A) or basic (B) catalyst. The conducted TG/FTIR/MS studies reveal that the initial decomposition temperature for organic matrices was dependent on the amount of HEMA monomer. Moreover, the thermal properties of the composites differ significantly from the pure polymer matrices. After the introduction of the drug and silica gel into the polymeric beads, the thermal stability of the composite materials was enhanced in comparison with the parent matrices, even at about 40 °C. This result was attributed to the shielding effect of IBS molecules and silica particles. FTIR and QMS analysis of the gases evolved during degradation indicates that the depolymerization, α- and β-hydrogen bond scission reactions went probably in parallel during the samples' thermal degradation.

1. Introduction

The systems prepared for controlled release of pharmaceutical ingredients due to the benefits arising from their use attracts growing interest in different fields, in biomedicine and pharmaceutics in particular. 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. Systems of controlled drug release have been constructed with the use of both organic and inorganic materials. Regardless of the type of the materials used, they should exhibit biocompatibility, biodegrability, environmental sensitivity or responsiveness, sufficient mechanical resistance and many other specific properties. The integral components of drug delivery systems are usually high molecular weight organic carriers, such as nano- and microparticles [1], nano- and micro-capsules [2], capsosomes, micelles, and dendrimers [3], in which the drug is embedded or covalently bound. Hence, the drug is protected from interacting with the environment, which could cause a change in its chemical structure and further cause losing its pharmaceutical action. If a polymeric carrier is to be used, its structure will permit obtaining the desired release conditions. However, in many polymeric systems, a high initial delivery of the entrapped drug is observed immediately upon immersion into the released medium [4,5]. To overcome problems connected with the so-called burst effect into the polymer-drug systems other ingredients are added. Among them, silica gel can be distinguished as an attractive material [6,7]. The strategy of the fabrication of polymer-drug-inorganic nanocomposites, based on the physical swelling of the preformed porous polymeric template in a properly selected inorganic precursor has proved to be an excellent technique for gaining polymer-silica nanocomposites and silica gel [8]. It was reported that introduction of the silica nanoparticles dispersed homogeneously within the preformed polymer matrix with embedded drug molecules significantly changes the material's porosity and has an impact on the drug diffusion rate [10,11].

It should also be noticed that appropriate choice of the drug form is also very important from the point of view of formulation, phar-

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http://dx.doi.org/10.1016/j.jaap.2015.05.004
0165-2370/

maceutical storage and handling. In our research the salt form of ibuprofen was chosen. From previous research it is known that the dihydrate form of sodium ibuprofen, which is the commercialized one, may be considered the more stable form in normal storage conditions. It was proved that the in reversion from the hydrated form to the anhydrous one and vice versa is easy, however, thermodynamic parameters showed that the reversion to the hydrate form is more favored [12].

The aim of this study is to present the thermal properties of a series of multicomponent polymer-drug-silica composites prepared for controlled drug release. The study describes the thermal properties of a series of porous microspheres synthesized with 2-hydroxyethyl methacrylate (HEMA) and trimethylolpropane trimethacrylate (TRIM), their conjugates with ibuprofen sodium salt (IBS) and finally the polymer-drug-silica composites based on them. Furthermore, the project also shows the influence of drug and silica gel embedding on the thermal stability of polymeric matrices.

2. Experimental

2.1. Materials

2-hydroxyethyl methacrylate (HEMA), trimethylolpropane trimethacrylate (TRIM), α, α′-azoisobisbutyronitrile (AIBN), sodium lauryl sulfate (SDS) and tetraethoxysilane (TEOS) were obtained from Sigma–Aldrich Chemie (Steinheim, Germany). Solvents were purchased from POCh (Gliwice, Poland). All reagents were analytical grade and used as received.

2.2. Preparation porous microspheres

The poly(TRIM) and poly(HEMA-*co*-TRIM) microspheres were prepared via suspension-emulsion polymerization according to the previously described procedure [13]. Polymerization experiments were performed in aqueous solution of sodium dodecyl sulfate, using toluene as a pore-forming agent. The homopolymer poly(TRIM) was prepared only with trimethylolpropane trimethacrylate monomer, whereas poly(HEMA-*co*-TRIM) copolymers were obtained with the functional 2-hydroxyethyl methacrylate and TRIM in the molar ratio of HEMA:TRIM 1:1 and 2:1. The fragment of the copolymers' chemical structure is shown in Fig. 1. The volume ratio of monomers to toluene was 1/1.5. The radical polymerization was carried out in 80 °C for 18 h, then the obtained microspheres were filtered, extracted with acetone in Soxhlet apparatus to remove any unreacted monomers and dried. The obtained poly(TRIM) resin was denoted as HT01 and poly(HEMA-*co*-TRIM) copolymers with the molar ratio of HEMA:TRIM 1:1 and 2:1 as HT11 and HT21, respectively. Dry materials were hermetically sealed, stored at ambient conditions and used as polymer matrices for the loading of the drug.

The polymer-drug conjugates were prepared by loading ibuprofen sodium salt (IBS) into polymer matrices (HT01, HT11 and HT21) following the swelling method. Firstly, a drug solution was prepared by dissolving IBS in anhydrous ethanol (34 mg mL^{-1}). Next, freshly prepared alcoholic solution was added drop by drop to polymer beads. The amount of the IBS solution was adjusted so that it was fully absorbed during the polymer swelling. Afterwards, the polymer beads swollen in IBS were immediately hermetically sealed and left for 3 h at room temperature. Then the solid product was dried at 50 °C under vacuum for 6 h. The polymer-drug conjugates were labeled as the HT01-D, HT11-D and HT21-D, respectively. The final loading efficiency of the drug was 51 mg g^{-1} for HT01-IBS and 55 mg g^{-1} for HT11-D and HT21-D, taking into account the mass of the total carrier system.

The prepared conjugates were saturated with the silica precursor tetraethoxysilane using the swelling method [7,10,11]. The TEOS-saturated conjugates were exposed to catalyst vapours at autogenous pressure and room temperature for 24 h, analogically to the one reported in [14]. Following the TEOS gellation, the ternary polymer-drug-silica gel composites were labelled as HT01-DA (acid set HT01- ibuprofen sodium salt-SiO_2 composite) and HT01-DB (base set HT01- ibuprofen sodium salt-SiO_2 composite), respectively. All polymer-drug-silica gel composites were labelled analogously using an appropriate name of the organic support used.

2.3. Methods of analysis

Scanning electron microscopic (SEM) studies were conducted on FEI Quanta 3D FEG instrument operating at 30.0 keV. SEM images of the investigated materials were taken in the dry state.

Parameters characterizing the porosity of all the investigated materials were determined by nitrogen adsorption at −196 °C using a Micromeritics ASAP 2420 analyzer. Before measurements samples were degassed at 60 °C under vacuum. The specific surface areas, S_{BET}, were evaluated using the standard BET method [15] for the adsorption data in the relative pressure range p/p_o from 0.04 to 0.25. The total pore volumes, V_p, were estimated from a single adsorption point at the relative pressure of 0.985. The pore size distributions (PSD) were obtained from the desorption branch of the isotherm using the Barrett–Joyner–Halenda (BJH) procedure [16].

ATR-FTIR spectra were recorded on a Tensor 27 (Bruker) spectrometer equipped with a diamond crystal. The spectra were recorded in the spectral range of 600–4000 cm^{-1} with the resolution of 4 cm^{-1} and 50 scans.

Thermogravimetric analysis of materials was carried out with a Netzsch STA 449 F1 Jupiter thermal analyzer (Germany) at the heating rate of 10 K min^{-1}, in the temperature range of 20–850 °C, with the sample mass of 10 mg in helium atmosphere. The gas flow was 20 mL min^{-1}. The gas composition which evolved during the decomposition process was detected and analyzed by a quadrupole mass spectrometer QMS 403C Aëolos (Germany) as well as an FTIR Tensor 27 Bruker (Germany) spectrometer coupled on-line to an STA instrument. The mass spectrometer was connected on-line to the STA instrument by a quartz capillary heated to 300 °C. The QMS was operated with an electron impact ionizer with the energy of 70 eV. The measurements were performed in scan mode for *m/z*, where *m* is the mass of the molecule and *z* is the charge of the molecule in electron charge units in the range of 10–100 amu.

Calorimetric measurements were carried out with the Netzsch DSC 204 calorimeter (Germany) operating in the dynamic mode. The dynamic scans were performed at the heating rate of 10 K min^{-1} from room temperature to the maximum of 550 °C under helium (30 mL min^{-1}) atmosphere in two stages. Since obtained porous materials were able to adsorb water from air, the first scan was performed from room temperature to the maximum of 120 °C to remove any adsorbed moisture. The second scan was conducted between 20 °C and 550 °C. The mass of the sample was 10 mg. As a reference an empty aluminium crucible was used.

3. Results and discussion

Polymeric microspheres synthesized from functional monomer HEMA crosslinked with TRIM were obtained via suspension-emulsion polymerization. The toluene usage made it possible to get these materials with developed permanently porous structure (Table 1). As can be seen from the analysis of the shape of nitrogen adsorption–desorption isotherms together with the data collected in Table 1, a decrease in the amount of TRIM reduces the parameters characterizing the porosity of the final copolymers. Furthermore,