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Vapour-phase method in the synthesis of polymer-ibuprofen sodium-silica gel composites

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ABSTRACT

The study discusses the synthesis of polymer-silica composites comprising water soluble drug (ibuprofen sodium, IBS). The polymers selected for this study were poly(TRIM) and poly(HEMA-*co*-TRIM) produced in the form of permanently porous beads via the suspension-emulsion polymerization method. The acid and base set ternary composites were prepared by the saturation of the solid dispersions of drug (poly (TRIM)-IBS and/or poly(HEMA-*co*-TRIM)-IBS) with TEOS, and followed by their exposition to the vapour mixture of water and ammonia, or water and hydrochloric acid, at autogenous pressure. The conducted analyses reveal that the internal structure and total porosity of the resulting composites strongly depend on the catalyst which was used for silica precursor gelation. The parameters characterizing the porosity of both of the acid set composites are much lower than the parameters of the base set composites. Moreover, the basic catalyst supplied in the vapour phase does not affect the ibuprofen sodium molecules, whereas the acid one causes transformation of the ibuprofen sodium into the sodium chloride and a derivative of propanoic acid, which is poorly water soluble. The release profiles of ibuprofen sodium from composites demonstrate that there are differences in the rate and efficiency of drug desorption from them. They are mainly affected by the chemical character of the polymeric carrier but are also associated with the restricted swelling of the composites in the buffer solution after precipitation of silica gel.

1. Introduction

Oral multiparticulate dosage forms which consist of microparticles or nanoparticles offer great advantages since they make it possible to achieve a reproducible drug-release rate and to improve drug bioavailability (Nidhi et al., 2016; Siepmann et al., 2006). Obviously, the aqueous solubility of the drugs entails the necessity of using certain strategies to control their release. One very interesting method is to use of ion-exchange resins as carriers of water soluble drugs having acidic or basic groups in their chemical structure (Fazal Ur and Khan, 2012; Guo et al., 2009). However, the process of ion-exchange, i.e. drug release, begins almost immediately after immersion of a drug–resin complex in a dissolution medium. Moreover, prolonged oral administration of large quantities of ion-exchange resin can disturb the ion strength in body fluids and cause harmful side effects, e.g. reduced potassium and calcium levels in the blood (Ranade and Hollinger, 2004). As an alternative solid drug carrier, which does not cause such side effects may be considered crosslinked polymeric microspheres. They are permanently porous, insoluble in GI fluids (Oh et al., 2008) and able to swell in different solutions, and this, in turn, is highly desirable during preparation of solid dispersion of drug (Li and Chase, 2010; Murillo-Cremaes et al., 2014; Wu et al., 2012). Selecting an appropriate material for covering solid dispersion of a drug within the polymer makes it possible to obtain a desired drug release rate. Therefore, microencapsulation with the use different polymers, such as polymethylmethacrylate, Eudragits, cellulose or polystyrene (Halder and Sa, 2006; Rodríguez et al., 1998; Sriwongjanya and Bodmeier, 1997; Tummala et al., 2015) has been proposed as a one of the effective method to modify the drug release rate. On the other hand, not only polymeric materials but also inorganic ones e.g. a silica gel can be used as an effective covering of solid dispersion. Admittedly, an unmodified silica gel does not form a uniform, continuous film but rather a nanoporous phase, since it

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is composed of primary particle of SiO_2, but its presence modifies the drug desorption rate from the formulation (Kierys, 2014; Kierys et al., 2016; Koubková et al., 2014; Niemirowicz et al., 2015). Moreover, the silica gel is an attractive modifier since it is produced under mild conditions which make it possible to obtain the silica gel immobilized with drug without any loss in its integrity and pharmacological activity (Avnir et al., 2006; Han et al., 2016; Prokopowicz et al., 2004). Therefore, it prompts to introduce the silica gel into the solid dispersion of drug within porous beads.

The purpose of this study was to investigate the influence of the silica species on the drug release from ternary composites comprising a water soluble drug, and also the influence of SiO_2 on the physical characteristics of composites. For the present study, the sodium salt form of ibuprofen (α-methyl-4-(isobutyl)phenylacetic acid; a nonsteroidal anti-inflammatory drug (NSAID)) was chosen as it is known that the drug in its acidic form has several disadvantageous formulation properties, such as poor water solubility (<1 mg/mL at 25 °C), a low melting point of 77 °C, and possible esterification in the presence of excipients containing a hydroxyl group (Censi et al., 2013; Zhang et al., 2007). The ibuprofen sodium, similarly to other NSAIDs, is used due to its analgesic and antipyretic properties. However, its long-time use is associated with the risk of having a gastrointestinal irritation and other side effects, which are dose-dependent (Brayfield, 2014). Therefore, the development of controlled release administration of NSAIDs is very important and highly advantageous. The polymers selected as drug carriers for this study are poly(TRIM) and poly(HEMA-*co*-TRIM) produced by the suspension-emulsion polymerization method. Poly(TRIM) was prepared only with trimethylolpropane trimethacrylate monomer (TRIM), whereas poly(HEMA-*co*-TRIM) copolymers were obtained with the functional 2-hydroxyethyl methacrylate (HEMA) and TRIM (Grochowicz and Kierys, 2015). They were selected on the grounds of the reports on the excellent properties of systems consisting of poly(HEMA) cross-linked with TRIM and their possible use as materials with the enhanced resistance to protein adsorption and cell adhesion with potential for artificial cornea applications (Lai et al., 2012); and vehicles for immobilization and capsulation of 5-fluorouracil, an antimetabolic drug commonly used in cancer chemotherapy (Garcia et al., 1997). Both of these matrices are in the form of permanently porous beads. However, they differ in the chemical character, porosity, the degree of crosslinking, and hence, the swelling ratio (Kierys et al., 2015a). To introduce silica gel into the solid dispersion of ibuprofen sodium within poly(TRIM) and/or poly(HEMA-*co*-TRIM), the swelling method has been applied (Kierys et al., 2010). Firstly, TEOS was introduced into solid dispersions, which were subsequently exposed to the vapour mixture of water and ammonia, or water and hydrochloric acid, at autogenous pressure and room temperature; this ensured the mild conditions of TEOS gelation. The resulting acid and base set polymer-drug-silica composites were investigated by the means of the low temperature nitrogen sorption and scanning electron microscopy (SEM). The conducted studies provide insight into the changes and rearrangement of the internal structure of the solid dispersions as a result of the silica gel introduction obtained at different conditions. Furthermore, the in vitro examination of the drug release rate from these composites is presented in order to determine the kinetic model and the mechanism of drug release.

2. Experimental

2.1. Materials

2-hydroxyethyl methacrylate (HEMA), trimethylolpropane trimethacrylate (TRIM), α,α′-azobisisobutyronitrile (INB), sodium dodecyl sulfate (SDS), ibuprofen sodium (IBS) and tetraethoxysilane (TEOS) were obtained from Sigma Aldrich. Solvents were purchased from POCh (Poland), and di-sodium hydrogen phosphate and sodium dihydrogen phosphate were obtained from Chempur (Poland). All reagents were analytical grade and used as received.

2.1.1. Synthesis of solid dispersion of ibuprofen sodium within resins

Firstly, the homopolymer poly(TRIM) and the copolymer poly(HEMA-*co*-TRIM) were synthesised according to the procedure which has recently been described in detail in Ref. (Grochowicz and Kierys, 2015). Trimethylolpropane trimethacrylate monomer was only used to prepare the poly(TRIM), whereas the copolymer was obtained with the functional 2-hydroxyethyl methacrylate and TRIM in the molar ratio of HEMA:TRIM 2:1. The volume ratio of monomers to toluene equalled 1/1.5. Following the polymerization, resins in the form of beads were extracted with acetone and dried at 80 °C under vacuum for 8 h. The unmodified poly(TRIM) and poly(HEMA-*co*-TRIM) were labelled as HP and CP, respectively and were used as matrices for the preparation of the solid dispersion of ibuprofen sodium. The drug was loaded by the saturation of HP or CP with the freshly prepared alcoholic solution (35 mg IBS/1 ml EtOH). The solid dispersion of ibuprofen sodium within poly(TRIM) was designated as HP-D, whereas the same within the copolymer poly(HEMA-*co*-TRIM) was labelled CP-D. The final loading efficiency of the drug was estimated to be 53 mg/g for HP-D and 62 mg/g CP-D, taking into account the mass of the total carrier system.

2.1.2. Synthesis of polymer-drug-silica composites

Prior to the preparation of ternary composites, volumetric swelling measurements of solid dispersions in TEOS were carried out. Accordingly, 4 cm^3 of TEOS was poured into a graduate cylinder with 1 cm^3 of HP-D and/or CP-D bed. After 1 h, the final volumes of swollen samples were noted. Swelling ratios (S%) were calculated from equation: $S\% = (V_F - V_I)/V_I \times 100\%$, where: V_I – the initial volume of bed before swelling in TEOS, V_F – the final volume of the swollen bed (Tuncel and Piskin, 1996). For HP-D (S%) ratio was 50% and for the CP-D sample was 5%.

Polymer-drug-silica composites were prepared by the swelling method (Kierys et al., 2010) which involve saturation of the organic matrix with a silica gel precursor (here TEOS), and next its transformation into the silica species. At this juncture, the vapour mixtures of water and hydrochloric acid (A) or water and ammonia (B) were used to initiate the hydrolysis and condensation of TEOS (Halasz et al., 2015).

1 g of HP-D and/or CP-D saturated with TEOS (1.13 g of TEOS per 1 g of HP-D and 1.44 g of TEOS per 1 g of CP-D) were exposed to the vapour mixtures of water and ammonia (20 cm^3 of a freshly prepared 6.68 M NH_4OH) or water and hydrochloric acid (20 cm^3 of a freshly prepared 5.87 M HCl) at autogenous pressure and room temperature for 1 day. Afterwards, the composites were dried at 80 °C under vacuum for 8 h. The final polymer-drug-silica composites prepared in the presence of acid catalyst were labelled as HP-DA and CP-DA, whereas those prepared in the presence of alkaline catalyst, as HP-DB and CP-DB. The drug contents in ternary composites, taking into accounts the mass of the total carrier system, were estimated to be 39 mg/g for HP-DA, 39 mg/g for HP-DB, 42 mg/g for CP-DA and 44 mg/g for CP-DB.

2.2. Release of ibuprofen salt

The ibuprofen sodium desorption was measured under stirring at 250 rpm in a thermostated bath. As a dissolution medium phosphate buffer at pH 7.4 maintained at 37 ± 0.5 °C was used. For the test, a portion of each sample containing the drug was placed in the vessel with 50 cm^3 of the dissolution medium. The masses of

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