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Original article

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

portions were chosen so that the amount of drug was the same and equaled at about 7 mg per portion. At predetermined time intervals, 5 cm^3 of buffer was taken out for analysis of the drug concentration which was carried out at a wavelength of 222 nm. The taken aliquot was replenished with a fresh dissolution medium. To determine the mechanism of ibuprofen salt release from the polymer and polymer-silica materials, the first 60% of drug release data were analyzed in accordance with the Korsmeyer-Peppas model (the so-called power law) (Korsmeyer et al., 1983; Siepmann and Peppas, 2001): $M_t/M_\infty = Kt^n$, where M_t/M_∞ is the fraction of the drug released at time 't', 'K' is the rate constant and 'n' is the release exponent used to characterize the transport mechanism. It is an empirical equation developed to analyze both Fickian and non-Fickian release of drug from swelling as well as nonswelling polymeric delivery systems.

Drug release kinetics was determined using the zero order, the first order, the Higuchi and the Hixson-Crowell models. The zero order rate refers to the systems in which the drug release is independent of the concentration of the drug and can be represented as $Q = K_0 \times t$, where 'Q' is the amount of the drug released in time 't', 'K_0' is the zero order rate constant expressed in the units of concentration (Hadjiioannou et al., 1993). The first order equation: Log Q = Log Q_0 - Kt/ 2.303 (where 'Q' is the amount of the drug released in time 't', 'Q_0' is the initial amount of the drug and 'K' is the first order rate constant) refers to the systems in which the drug release rate depends on the concentration of the drug (Bourne, 2002). The Higuchi model, which can be simplified to $Q = K_H\, t^{1/2}$, (where 'Q' is the amount of the drug released in time 't', 'K_H' is the Higuchi dissolution constant) describes the drug release as a diffusion process based on the Fick's law, square root time dependent (Higuchi, 1963). The Hixson-Crowell cube root law: $Q_0^{1/3} - Q_t^{1/3} = K_{HC}t$ (where 'Q_t' is the amount of drug remaining in the tablet in time 't', 'Q_0' is the initial amount of the drug in the tablet, and 'K_{HC}' is the rate constant incorporating the surface–volume relation) describes the release from systems in which there is a change in the surface area and diameter of particles or tablets (Costa and Sousa Lobo, 2001).

2.3. Characterization methods

The morphology of ternary composite beads was characterized with the use of scanning electron microscope (SEM, FEI Quanta 3D FEG) working at 30 kV. The low temperature nitrogen adsorption/desorption was measured with a volumetric adsorption analyzer ASAP 2405 (Micromeritics, Norcros, GA) to determine parameters characterizing the porosity of materials. The specific surface area, S_{BET}, was established by BET (Brunauer-Emmett-Teller) method (Brunauer et al., 1938). The plots of the corresponding pore size distribution were obtained from the adsorption and desorption branches of the isotherms by using BJH (Barrett-Joyner-Halenda) model (Barrett et al., 1951). The total pore volume, V_p, was estimated from single point adsorption at $p/p_0 = 0.996$. A thermal analyzer, Netzsch STA 449 F1 Jupiter (Germany), was used to estimate the content of inorganic residues within the samples. A thermogravimetric analysis was carried out at a heating rate of 10°/min in the temperature range of 20–800 °C with the sample mass of 15 mg in air flow. The gas flow was 20 mL/min.

3. Results and discussion

3.1. Physicochemical characterization of the investigated materials

The solid dispersion of ibuprofen sodium within polymer beads exhibits the ability to swell in tetraethylsilane, the silica gel precursor to a different extent depending on the type of matrices. Hence, a significant difference between the swelling ratios (S%; 50% for HP-D and 5% for CP-D) of solid dispersions is observed; it stems from the difference in the degree of double bonds conversion in organic matrices, which is much higher in the case of CP (Kierys et al., 2015a). This, in turn, regardless of the presence of drug dispersion in matrix, results in the copolymer having a lower tendency to swell in TEOS and confirms that the unmodified CP matrix is cross-linked to a greater extent than the HP one. The swelling method was used to prepare solid dispersions saturated with TEOS; their subsequent exposure to HCl or NH_3 vapours results in TEOS hydrolysis and condensation, and, in consequence, leads to the deposition of the silica gel within polymer-drug beads (Fig. 1). SEM images of the representative collection of composites (Fig. 2a and d) confirm that such ternary composites preserve the spherical shape. Since their size is within the range from 0.25 (HP-DA & HP-DB) to 0.7 mm (CP-DA & CP-DB), therefore, they exhibit potential in the formulation of an oral multiparticulate drug release dosage.

Interestingly, the fine-grained structure of beads interior, typical for the crosslinked polymers (Kierys, 2014; Okay, 2000), is still preserved even after the introduction of silica gel species. Regardless of the applied gelling conditions, the interior of composites based on poly(TRIM) consists of tiny and smooth species which are closely packed (Fig. 3a and b), whereas, the internal structure of composites based on poly(HEMA-*co*-TRIM) is more rough and inhomogeneous, as well as loosely packed (Fig. 3c and d). Unlike the internal structure of CP-DA and CP-DB, the external surface of their beads is smooth and compact (Fig. 2b and c). On the other hand, fine particles can be easily distinguished in the SEM images of the external surface of the beads of the composites based on poly(TRIM) (Fig. 2e and f).

It should be emphasized that the silica species are indistinguishable in the SEM images. Thus, the place of the silica gel location within beads cannot be indicated precisely. On the other hand, the thermogravimetric measurements along with the N_2 sorption data (Table 1 and Fig. 5) clearly indicate the successful deposition of silica gel. According to the TG results (Fig. 4), the residual mass

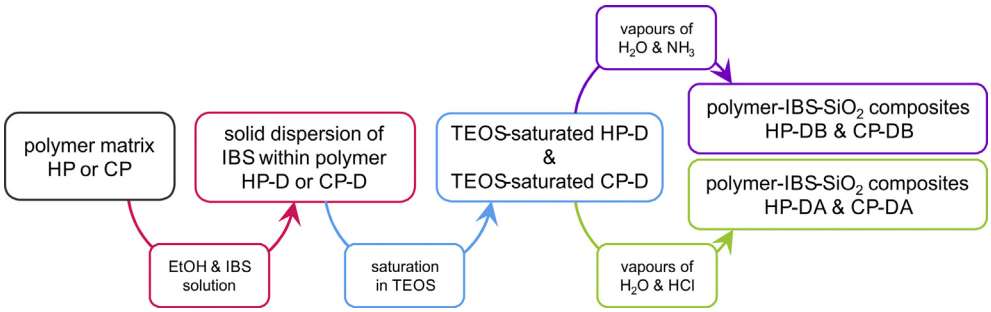

Fig. 1. Scheme for the synthesis of the ternary composites.

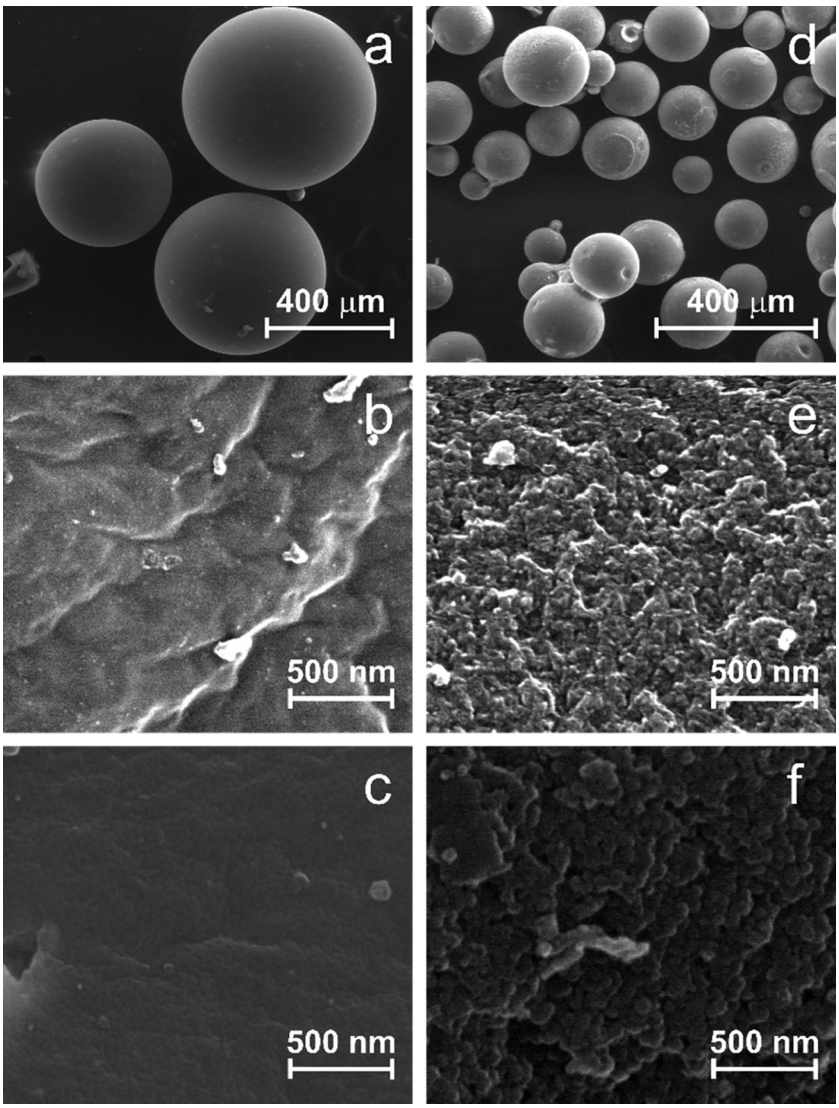

Fig. 2. SEM micrographs of beads of the CP-DB (a) and HP-DA (d) and micrographs of the surface of representative bead of CP-DA (b), CP-DB (c), HP-DA (e) and HP-DB (f).

after degradation of ternary composites at 800 °C is 27% for composites based on poly(TRIM), whereas for CP-DA is 31.7% and 28.7% for CP-DB. Nevertheless, to determine the actual contents of silica gel within composites, it should be taken into account, that residues are also obtained after the combustion of solid dispersions. Their amount equals about 3.7% and 5.4%, for composites based on poly(TRIM) and poly(HEMA-*co*-TRIM) respectively. Thus, the actual content of SiO_2 equals 23.3% for composites based on poly(TRIM) (i.e. HP-DA, HP-DB) and CP-DB, and 26.3% for CP-DA, taking into account the total mass of composites. This is in good agreement with the theoretical quantity of silica gel which could be obtained from the amount of introduced TEOS into the solid dispersions.

According to N_2 adsorption-desorption data (Table 1), the values of parameters characterizing the porosity of ternary composites decrease in comparison to solid dispersions of drug as well as unmodified organic matrices. These changes clearly indicate the successful introduction of the additional component i.e. silica gel into the solid dispersions. At this point, it is worth noting that of the range in which the parameters change depends on the applied conditions of TEOS gelation (Table 1).

The biggest decrease in the specific surface area is observed for composites in which the gelling of TEOS took place in the presence of acid catalyst vapours. S_{BET} lowering by about 80% for CP-DA and by about 90% for HP-DA (in comparison to S_{BET} of the corresponding solid dispersions) is accompanied by the decrease of the total pore volume by about 80% and by about 70%, respectively. When TEOS transformation takes place in alkaline conditions, the lowering of both S_{BET} and V_p is less pronounced regardless of the type of the used polymer matrix. Following on from Table 1, S_{BET} decreases by 56% and by 36% for CP-DB and HP-DB, respectively, whereas the total pore volume is reduced by 57% for CP-DB and by 54% for HP-DB (in comparison to S_{BET} and V_p of the corresponding solid dispersions). From the analysis of the micropore volume assessed by the application of the t-method, it follows that the contribution of the micropores volume is negligibly small in the total pore volume for the set of samples based on poly(HEMA-*co*-TRIM), whereas, the micropores volume of poly(TRIM) which is about 0.03 $cm^3\ g^{-1}$ decreases after the introduction of the drug and silica gel (up to 0.01 $cm^3\ g^{-1}$).

A very similar direction of the porosity parameters changes has been previously illustrated for composites based on the XAD7HP polymer (Halasz et al., 2015). Therefore, it can be assumed that the applied conditions of TEOS gelation are responsible mainly for the structural differences between composites. The reasons should be sought in the mechanism of TEOS solidification in the

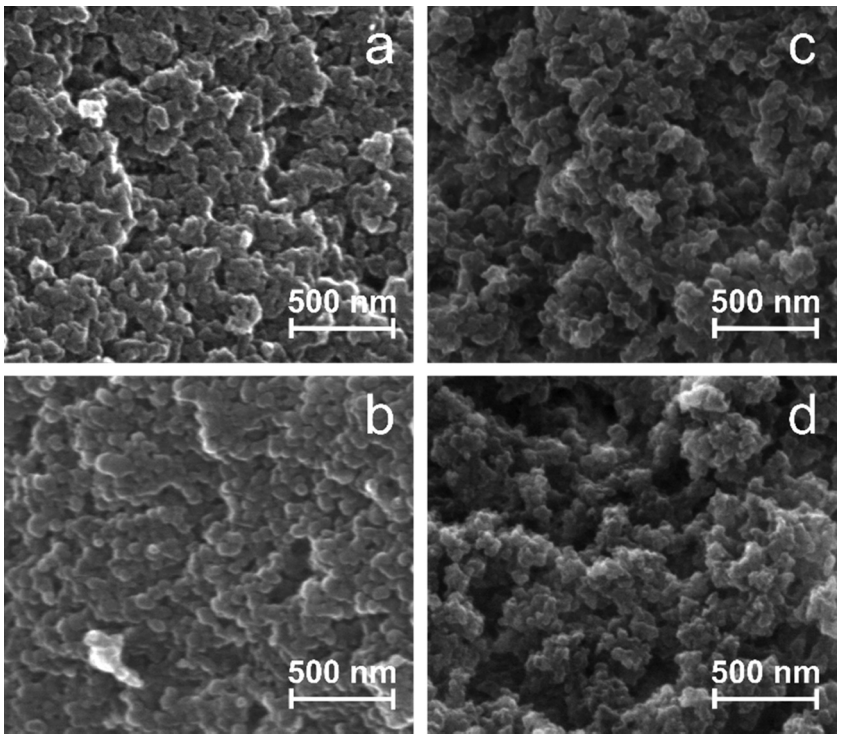

Fig. 3. SEM micrographs of the interior of the HP-DA (a), HP-DB (b), CP-DA (c) and CP-DB (d) Composites.

Table 1
The parameters characterizing the porosity of the samples obtained from N_2 adsorption/desorption at 77 K: the specific surface area S_{BET}, the total pore volume V_p and the pore diameter at the peak of PSD, D_p.

Sample	S_{BET} (m^2/g)	V_p (cm^3/g)	D_{p1} (nm)	D_{p2} (nm)
HP	530	0.78	3.8	15.3
HP-D	451	0.76	3.7	17.1
HP-DB	290	0.35	3.7	10.0
HP-DA	42	0.12	–	13.2
CP	223	0.60	3.8	33.3
CP-D	175	0.56	3.8	36.3
CP-DB	77	0.26	3.8	56.7
CP-DA	40	0.15	–	52.9

pores of solid dispersions, as well as in the molecular constitution of the precipitated silica gel. On the other hand, although HP-D and CP-D contain a low dosage of the drug, the transformation of ibuprofen sodium into sodium chloride and the acid form of ibuprofen under the acidic environment should be taken into consideration (Kierys et al., 2015b). This process, together with additional components appearing within solid dispersions, may influence the structure and the location of newly created inorganic component. It may also contribute to the clogging of the pores. All these, in turn, cause the effective prevention of N_2 adsorption.

On the other hand, it is surprising that the introduction of silica gel into both solid dispersions only marginally affects the shape of N_2 isotherms, and in consequence, the isotherms of the resulting ternary composites are similar in shape to the isotherms of the parent matrices (Fig. 3a and b). Obviously, they differ significantly in the nitrogen adsorption. This is all the more surprising, given that synthesis of the ternary composites includes several stages during which the polymer matrices swell or shrink, respectively. During wetting of the resins in the alcoholic ibuprofen sodium solution, they swell, whereas when being dried, they shrink. Furthermore, the saturation of solid dispersions with TEOS also causes their swelling. Finally, gel formation during hydrolytic oligomerization of TEOS results in the shrinking of polymer-drug beads with the simultaneous release of ethanol and water. These products of TEOS transformation certainly favour the relocation of drug molecules within polymer matrices. Moreover, different conditions have been employed to initiate TEOS transformation, and, as it was previously presented, there are differences between polymer-silica composites prepared under acidic and basic conditions (Halasz et al., 2015). Therefore, it seems evident that the formation of the additional inorganic phase within solid dispersions should trigger significant rearrangement of the internal structure. Indeed, it is reflected in the shape of PSDs of the composites derived from the corresponding adsorption and desorption data. The pore size distributions calculated from the adsorption branches of the isotherm of poly(TRIM) and poly(HEMA-*co*-TRIM), as well as solid dispersion based on them, cover a broad range from micro-through meso-to macropores (Fig. 5c and d). The introduction of SiO_2 shifts the PSD peaks towards the mesoporous regime and it is more pronounced in the case of acid set composites (CP-DA and HP-DA).

On the other hand, from the inverse size exclusion chromatography it follows that the pore size distribution of TRIM-based copolymers is of bimodal character (Grochowicz and Gawdzik, 2013). Furthermore, the results of positron annihilation lifetime spectroscopy (PALS) indicate the presence of mesopores of a diameter of about 3 nm (Zaleski et al., 2011). Thus, analyzing also the changes in the pore size distributions derived from the desorption branches of isotherm seems to be very interesting. Obviously, the mechanism of N_2 desorption in such a complex pore system as in the presented materials may involve pore blocking and cavitation effects, which are widely discussed in the literature of the subject (Reichenbach et al., 2011; Thommes, 2010) and thus, the results need to be carefully interpreted. As it follows from Fig. 5e and f, PSD of ternary composites with the basic set silica gel, i.e. HP-DB and CP-DB preserve their bimodal character, and, what is more, exhibit an almost unchanged peak of PSD centered at D_p = 3.7 nm. This peak is also visible in the parent matrices (HP and CP) and it may be assigned to the pores between the nuclei (Kierys et al.,

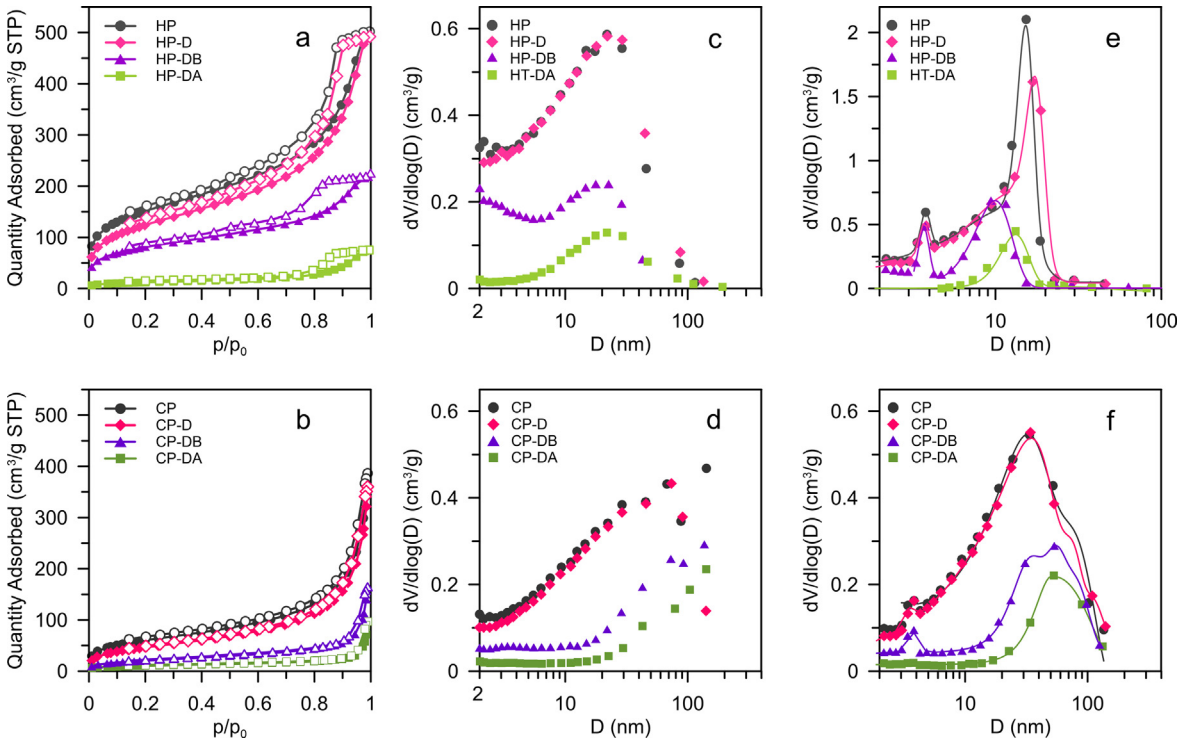

Fig. 5. N_2 adsorption (solid points) and desorption (open points) isotherms (a and b) and pore size distributions determined by applying the BJH method to the adsorption (c and d) and desorption isotherm (e and f) under study of the series of the investigated materials. In the figure of PSDs, the lines are provided for convenience.

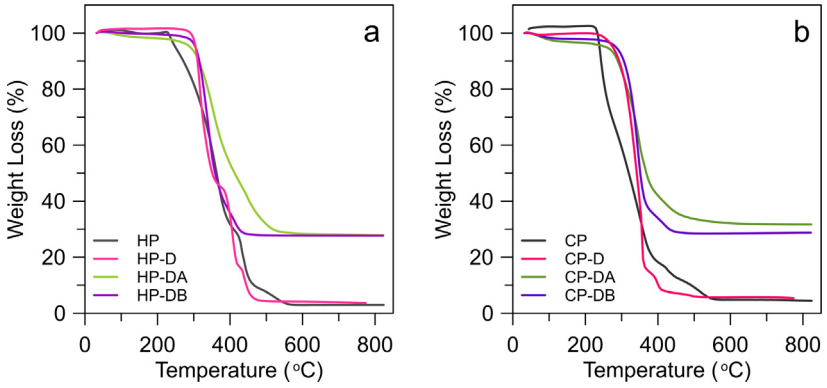

Fig. 4. TG curves of the investigated materials: (a) Series of HP and (b) Series of CP.

2015a). The second group of pores of larger dimensions (mean pore diameter D_p = 36.3 nm) shifts towards macropores regime after TEOS treatment of CP-D. The opposite effect is observed for the HP-DB, where the PSD peak shifts towards mesoporous regime after the introduction of SiO_2. Interestingly, after the exposure to vapours of acid of TEOS-saturated HP-D and CP-D, the mesopores of smaller dimensions seem to disappear, whereas the second group of pores shifts analogously to the HP-DB and CP-DB. Regardless of the presented changes in the shape of PSD, it should be concluded that PSDs prove the structural heterogeneity of the investigated samples, which is in line with the presented SEM micrographs.

Considering the presented results, as well as thermogravimetric analysis of composite materials (Grochowicz and Kierys, 2015), it may be concluded that the applied conditions of TEOS-saturated solid dispersion treatment influence the characteristics of composites, since they affect the silica gel species morphology and their location within the solid dispersions as well as drug transformation.

3.2. Drug release

The drug release profiles are very interesting, and give further insight into the changes within solid dispersions after precipitation of silica gel species. First of all, according to ibuprofen sodium release profiles provided in Fig. 6, the drug desorbs most effectively in the case of the CP-D solid dispersion, reaching almost 100%, and it is at about 40% higher than HP-D. On the other hand, CP-D suffers from prominent burst release which manifests itself in leaching more than 60% of the precipitated drug within the first fifteen minutes. Therefore, it can be said that the type of polymer matrix used in the preparation of the solid dispersion plays a significant role and influences both the rate of the drug desorption and the efficiency of the release process.

Secondly, processing of solid dispersions which involves the saturation with TEOS, and the subsequent exposure to vapours of catalysts, which results in the deposition of silica gel, heavily influences the rate and the efficiency of the drug desorption. The use of

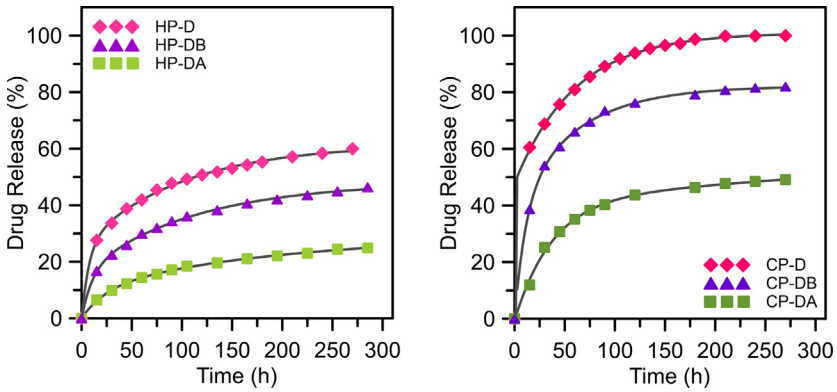

Fig. 6. Ibuprofen sodium release from the solid dispersions (HP-D and CP-D), acid set samples (HP-DA and CP-DA) and base set samples (HP-DB and CP-DB) measured in the phosphate buffer solution at 37 °C. In the figure, the lines are provided for convenience.

Table 2
Values of correlation coefficient for release kinetics of ibuprofen sodium salt.

Sample	Zero-Order	First-Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	R^2	n
HP-D	0.6816	0.8063	0.9021	0.7673	0.8588	0.3401
HP-DA	0.8288	0.8589	0.9784	0.8492	0.9773	0.0939
HP-DB	0.7550	0.8298	0.9478	0.8063	0.9113	0.2387
CP-D	0.5601	0.9792	0.6671	0.9494	–	–
CP-DA	0.6871	0.7656	0.8949	0.7404	0.9192	0.2142
CP-DB	0.5546	0.7784	0.8084	0.7076	0.9709	0.0577

acid vapours promotes two processes which occur simultaneously within solid dispersions, i.e. (1) the transformation of silica precursor into the silica species and (2) an irreversible transformation of ibuprofen sodium into sodium chloride and a derivative of propanoic acid (Kierys et al., 2015b), which is poorly soluble in the phosphate buffer at pH 7.4. Both of them affect the efficiency of the drug desorption (Fig. 6). However, taking into account that the silica gel exists also within HP-DB and CP-DB, it may be assumed that the transformation of the drug into the poorly soluble acid is the main reason for the drug release restrictions. Obviously, the presence of silica gel and its influence on the drug desorption cannot be ignored. It is likely that silica gel exists in the form of a dense mass or some kind of a membrane which not only clogs pores (Table 1) but also impedes the drug desorption and/or the infiltration of the dissolution medium. This is due to the fact, that silica gel stiffens the internal structure of the solid dispersions and reduces their ability to swell in the used buffer solution.

To better understand the mechanism of ibuprofen sodium release from the investigated systems, the dissolution data were fitted with the Korsmeyer–Peppas model. Additionally, kinetic data were analyzed by models widely used in literature, i.e. the zero order, the first order, the Higuchi and the Hixson-Crowell.

The model which gave the highest coefficient of determination (R^2 collected in Table 2) was considered to be the most suitable kinetic model for describing the release of ibuprofen sodium from the systems.

Taking into account the values of R^2 and 'n' exponent, which indicates the mechanism of drug release, it is clear that the power law can only give limited insight into the exact release mechanism of the drug. Firstly, 'n' lies below 0.43 for all investigated systems which is beyond the limits of the power law for spheres. Secondly, all systems present poor fitting to this model. What is more, the same applies to other mentioned models. Generally, none of the considered kinetic models can be used for an unambiguous description of the drug release from investigated systems. Furthermore, as it is presented, the release is usually more complicated than the simplified models, since it can involve various interactions among the solvent, drug and polymer. In the case of the investigated systems, it is related both to the complex internal structure and to the composition of the analyzed samples. Therefore, the change in the rate of drug release should be interpreted in terms of the chemical character of the network of composites and its alteration after the silica nanoparticles are incorporated into the solid dispersions. It may also be associated with the restricted swelling of the composites in the buffer solution. Also, the transformation of the ibuprofen sodium salt into the acidic form of drug and its possible slow release may also affect the drug desorption from the acid set composites.

Of course, if comparing R^2 for the Higuchi model, it follows that the best fitting is for samples based on the poly(TRIM). Since this model describes diffusion-controlled mechanism of the release of water soluble drug, it appears reasonable, that ibuprofen sodium release may involve the diffusion process. Similarly, taking into account the high value of R^2 for CP-D, the drug desorption may be posited according to the first order release kinetic. Nevertheless, this model relates to conditions in which there is no change in the shape of the solid during the dissolution process (i.e. the surface area remains constant). Hence, the mentioned model cannot be used in the case of CP-D because this solid dispersion is based on the copolymer matrix, which easily swells, and, in consequence, its surface area changes after immersion in the dissolution medium.

4. Conclusions

The present article has demonstrated the preparation of polymer-drug-silica composites in which silica gel is deposited from the vapour phase of an appropriate catalyst (i.e. HCl or NH_3) on the solid dispersion of ibuprofen sodium within the permanently porous poly(HEMA-*co*-TRIM) or poly(TRIM) resins. In the course of the study, it was revealed that both of resins loaded

with drug exhibit the ability to swell in the silica gel precursor (TEOS). Regardless of the presence of drug dispersion in the matrix, the poly(HEMA-*co*-TRIM), which has a higher degree of crosslinking, swells in TEOS to a lesser extent than a poly(TRIM)-drug sample. TEOS gelation in the presence of an acidic and basic catalyst in the vapour phase has been demonstrated as an efficient method of introducing the silica gel into both of the solid dispersions. The great advantage of the vapour-phase method stems from the ability to precipitate inorganic phase within polymer matrix loaded with water soluble drug without the loss of the drug due to the leaching, which may happen in conventional sol-gel processes occurring in the solution. Obviously, the internal structure is significantly rearranged after the introduction of SiO_2 and, in consequence, the porosity of ternary composites differs in comparison to the corresponding solid dispersions and the host polymers. However, it should be strongly emphasized that the total porosity of the ternary composites depends on the catalyst which was used for silica precursor gelation. It was presented that parameters characterizing the porosity of both acid set composites (HP-DA and CP-DA) are much lower than the parameters of the base set composites (HP-DB and CP-DB). Therefore, it can be concluded that the created acid set silica gel is poorly condensed and thoroughly clogs up the pores of solid dispersions. From the presented studies, it also follows that 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. Furthermore, the efficiency of drug release is mainly affected by the chemical character of the polymeric carrier but it is also associated with the restricted swelling of the composites in the buffer solution after precipitation of silica gel. To summarize, the presented approach is a promising method for the production of oral multiparticulate dosage forms of water-soluble nonsteroidal anti-inflammatory drugs. An extension of the presented experiments to other drugs as well as other ternary composites is in progress and will be reported in due course.

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