Journal of Industrial and Engineering Chemistry 20 (2014) 4094–4101

Contents lists available at ScienceDirect

Journal of Industrial and Engineering Chemistry

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

Preparation and characterization of polymer/layered silicate pharmaceutical nanobiomaterials using high clay load exfoliation processes

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ARTICLE INFO

Article history:
Received 7 August 2013
Accepted 30 December 2013
Available online 10 January 2014

Keywords:
Montmorillonite
Nanocomposites
Organophilic clays
Layered silicates
Exfoliation process

ABSTRACT

The purpose of this study was to prepare and characterize lamellar silicate nanocomposites using exfoliation processes, high clay load and polyvinylpyrrolidone (PVP), ethylcellulose (EC) and polyquaternium-H (PQH). The clays (sodium montmorillonite, Viscogel S4™, S7™ and B8™) were pre-treated with ultrasonic energy in order to increase clay exfoliation yields. Polymeric nanocomposites were characterized by XRPD, DSC, TGA, DLS and NMR. The results revealed a new exfoliation method and new intercalated nanocomposites. High clay load was used to obtain the nanocomposites, which enables its application at an industrial scale. These nanocomposites could be broadly applied across the pharmaceutical, medical and food industries.

1. Introduction

Nanotechnology has emerged as one of the most promising approaches for the development of new biomaterials, especially for those related to the pharmaceutical industry [1–3]. The combination of biocompatible polymers and layered silicates are ideal for such purposes. These biocompatible polymers are highly absorptive and possess increased internal surface area that can react with silicate [4–8]. For these reasons, mineral clays have been investigated for development of modified release matrices, nanocarrier systems and tissue replacement materials that have evident pharmaceutical and medical applications [8–13].

According to the literature, a promising alternative for the production of new modified release and drug delivery systems involves the utilization of layered silicates such as sodium montmorillonite (MMTNa) combined with pharmaceutical polymers [8,10,14]. These materials can still be used in guiding tissue regeneration and other medical applications [15–17]. MMTNa, a hydrophilic clay, is classified as a 2:1 smectite type possessing two tetrahedral sheets and a central octahedral sheet. The negative MMTNa layers are naturally balanced by exchangeable Na^+ which is hydrated in the presence of water [18,19]. The organoclay derivatives of MMTNa are obtained by the cation exchange reaction of MMTNa sodium with quaternary ammonium salts, which allows the absorption of hydrophobic organic compounds [6,20,21]. The occurrence of this cationic substitution alters several of the initial properties of the clay. These alterations can be explained by changes to the superficial hydrophilic character of the MMTNa lamellae and a potential increase in their basal spacing [22]. Hydrophilic polymers including PVP, chitosan and methylcellulose and especially amino polymers exhibit high affinity for MMTNa and organophilic clays such as Viscogel B8, S4 and S7. The predominant differences found between Viscogel group organoclays result from the type of organic modifier employed in the organophilization process including: VB8 [bis(hydrogenated tallow alkyl) dimethyl ammonium (BHTADMA)-2-propanol (10%)], VS4 [bis(hydrogenated tallow alkyl) dimethyl ammonium (BHTADMA), and VS7 [dimethyl benzyl hydrogenated tallow ammonium (DMBHTA)] [23].

The formation of nanocomposites depends on several factors including experimental conditions and the type of polymer structure and layered silicate utilized [24–27]. Furthermore, polymer-layered silicate nanocomposites are classified as

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http://dx.doi.org/10.1016/j.jiec.2013.12.110

exfoliated or intercalated based on their structural differences. Intercalated nanocomposites are characterized by their regularly alternating clay and polymer layers and increased distance between platelets, generally up to 2–5 nm, due to the addition of polymer within interlayer areas. Whereas nanocomposites have exfoliated clay structures with no longer identifiable silicate sheets that are completely delaminated and have randomly dispersed polymer chains [28,29]. In the presence of exfoliated clay, the nanoscale dispersed silicate layers improve thermal stability [5,30,31], mechanical properties [5,30,32], gas barrier characteristics [31,33], tensile properties [30,32,34], rheological properties [34,35], crystalline structure and isothermal crystallization kinetics [32,34] more effectively than when obtained from non-exfoliated structures. This is likely due to homogeneity of the high phase which contributes to increased surface area contact, resulting in better clay dispersion in the polymer matrix and consequently improvement of the performance properties [35,36]. Despite their established importance, the use of intercalated polymeric nanocomposites it is of great interest that nanobiomaterials and nanocarriers are further developed for the production of new pharmaceutical formulations [8,14,37]. In addition, several studies have emphasized the fundamental importance of these nanomaterials for developing sustained release systems [8,12,37], tablet film coatings [38] and nanocarrier transport based upon drug delivery systems [6,9,11,12,39].

In recent years, the formation of nanocomposites based on montmorillonite (MMT) and biodegradable polymers as poly(vinyl alcohol) [40]; poly(L-lactide) and poly(3-caprolactone) [30]; polyurethane [41]; chitosan [42]; PVP [29,43,44] among other nanobiomaterials has been extensively described in the literature. It has been previously demonstrated by our research group that the intercalation reaction of PVP and EC with different clays [45,46] resulted in the production of materials with novel properties (sustained release matrix, enhanced dissolution and coating materials for the oral administration of solid dosage forms). These materials also demonstrated significant changes in microstructure, thus producing a real nanocomposite. However, few reports describe the preparation of exfoliated nanocomposites containing high loads of clay. Koo and coworkers [44] reported that PVP:MMTNa nanocomposites prepared by attrition ball milling and the solution intercalation method resulted in exfoliation of MMTNa. Futhermore, PVP and MMTNa nanocomposites were produced by Zabska and coworkers [29] through the solution–intercalation technique, resulting in the formation of exfoliated structures. The solvent also plays an important role in exfoliation as it can be considered an "exfoliation aid". Obtaining the correct balance between hydrophilic and hydrophobic character of the solvent is the key to nanoclay dispersion. Long alkyl chains of quaternary-ammonium-ion-exchanged montmorillonite become more swollen by apolar solvents, such as toluene, than the primary-ammonium-ion-exchanged form. The most effective organic solvents for producing exfoliated nanocomposites were those combining polarity with a high organophilic character [47]. Swelling occurs as a two-step process: the solvents first diffuse in the spaces between the platelets and coat the platelets inside and outside without increasing the interlayer spacing, and the second step when the organic ions become solvated and the Van der Waals interactions that exist between the ammonium ions are destroyed [48]. In addition, the use of MMTNa and its organophilic derivatives for the production of exfoliated nanocomposites was described only with the use of small amounts of lamellar silicate around 1.0% to 7.0% w/w [31,49–51], however obtaining nanocomposites with a high load of clay would enable their use for industrial scale applications.

For these reasons, the aim of the present work was to use the solution technique to develop and characterize exfoliated polymer nanocomposites using a high clay load. In this work a new nanocomposite was prepared using the hydrophilic clay MMTNa intercalated with PQH. The exfoliation process was tested by screening a number of organophilic clays (Viscogel S4, S7 and B8) and MMTNa combined with different hydrophilic polymers (PVP, PQH and EC) currently used in the pharmaceutical industry.

2. Materials and methods

2.1. Materials

Polyquaternium H (Polyquart H™) was supplied by Cognis (United Kingdom), ethylcellulose (Ethocel 100™) and polyvinylpyrrolidone K-30, Mw 40.000 was obtained from Sigma Aldrich (United States). Purified MMTNa, Viscogel B8™ (VB8—trimethyloctadecyl ammonium salt), Viscogel S4™ (VS4—ditallow dimethyl ammonium salt) and Viscogel S7™ (VS7—tallow benzyl dimethyl ammonium salt) were purchased from Bentec (Italy). Dichloromethane and toluene were obtained from Tedia (Brazil). Ethyl alcohol and acetone was purchased from Vetec (Brazil). All other chemicals used were of analytical reagent grade and obtained from Vetec (Brazil). Distilled water was utilized in the solutions used in the preparation of MMTNa nanocomposites.

2.2. Preparation of intercalated PQH:MMTNa nanocomposites

Considering our previous successful intercalation studies conducted with PVP and EC [45,46], in this work we only tested the previously unstudied polymer (PQH) for the production of nanomaterials by solution technique with VB8, VS4, VS7 and MMTNa at 2:1, 1:1 and 1:2 (polymer:clay) mass ratios. Water was selected as the solvent for MMTNa reaction while dichloromethane was used for VB8, VS4 and VS7 reactions. Polymeric dispersions were homogenized by magnetic stirring and reaction times were used (15, 30, 45 min and 1, 24, 48, 72 h) at room temperature. The resultant reaction medium was centrifuged (4000 rpm) for 1 h, while the pellet obtained was washed 3 times using the same reaction solvent. In the cases when dichloromethane was used as solvent, water was added to the reaction medium for the centrifugation process. The precipitated materials were placed in a vacuum desiccator to ensure complete drying. Intercalation yields were indirectly calculated in the supernatant by Ultraviolet–visible spectrophotometry (UV–Vis) using a Perkin Elmer Lambda 35 spectrophotometer (United States). The polymer concentration was determined using the linear regression equation and calculated from the calibration curve. The calibration curve was established for the PQH polymer at the concentrations 0.6, 1.2, 2.4, 3.6, 4.8 mg/mL, using distilled water as the solvent at a wavelength of 210 nm. Afterwards, the samples were crushed, gridded through a 70 mesh sieve and then characterized to determine the best experimental conditions for the preparation of the nanocomposites.

2.3. Characterization of intercalated PQH:MMTNa nanocomposites

Raw materials and their respective physical mixtures were used as negative controls for the evaluation of nanocomposite formation. Initially, all samples were characterized by X-ray powder diffraction (XRPD) (Rigaku Miniflex diffractometer; Tokyo, Japan) to evaluate changes in interlamellar spacing of the studied clays and thus evaluate the success of the intercalation process [45]. XRPD analyses were carried out, using a 30 mA current and a voltage of 40 kV while operating at the Cu$K\alpha$ wavelength (1.542 Å). Bragg's equation was used to measure basal spacing. The formation of intercalated nanocomposites was also assessed by different techniques, including differential scanning calorimetry (DSC) and