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Layered bionanocomposites as carrier for procainamide

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ABSTRACT

The study deals with the intercalation of procainamide hydrochloride (PA), an antiarrythmia drug in montmorillonite (MMT), as a new drug delivery device. Optimum intercalation of PA molecules within the interlayer space of MMT was achieved by means of different reaction conditions. Intercalation of PA in the MMT galleries was conformed by X-ray diffraction (XRD), Fourier transform infrared spectra (FT-IR), and thermal analysis (DSC). In order to retard the quantity of drug release in the gastric environment, the prepared PA–MMT composite was compounded with alginate (AL), and further coated with chitosan (CS). The surface morphology of the PA–MMT–AL and PA–MMT–AL–CS nanocomposites beads was analyzed by scanning electron microscope (SEM). The in vitro release experiments revealed that AL and CS were able to retard the drug release in gastric environments, and release the drug in the intestinal environments with a controlled manner. The release profiles of PA from composites were best fitted in Higuchi kinetic model, and Korsmeyer–Peppas model suggested diffusion controlled release mechanism.

1. Introduction

For controlled drug delivery systems, the optimal concentration of drug should be maintained without reaching a higher toxic level or dropping below the minimum effective level. Recently, the field of polymer layered silicate composites has attracted much attention for drug delivery applications (Pongjanyakul, 2009). The unique properties of the polymer layered silicate composites such as easy degradation, biocompatibility and tunable mechanical properties are essential for pharmaceutical applications (Pongjanyakul, 2009). Montmorillonite (MMT), smectite family clay is a promising layered silicate as delivery carrier for various drug molecules. Smectite clays have a layered structure and layer is constructed from tetrahedrally coordinated silica atoms fused into an edge-shared octahedral plane of aluminum. (Mohanambe and Vasudevan, 2005; Patel et al., 2006; Depan et al., 2009). Moreover, the positively charged edges on the layers of MMT could interact with anionic polymer like alginate (AL) to form unique polymer layered silicate materials having a large inter-planar spacing; and superior capability to intercalate drug molecules into the interlayer space of the (0 0 1) plane. Involvement of MMT to AL composites decreases the drug release rate due to an increase in the adsorption capacity for the incorporated compound by the matrix (Gerstl et al., 1998; Lin et al., 2002; Pongjanyakul, 2009).

Alginate (AL) is widely used as a drug delivery vehicle for control release of therapeutic agents (Shilpa et al., 2003). The capability of AL to form gel in the presence of multivalent ions has been exploited to prepare multi-particulate systems, incorporating numerous drugs, proteins, cells, or enzymes. AL is a linear, naturally occurring polysaccharide extracted from brown sea algae containing D-mannuronic (M) and L-guluronic (G) acids which are arranged in homopolymeric MM or GG blocks separated by blocks with an alternating sequence (Tonnesen and Karlsen, 2002). The distinctive properties of AL, e.g. hydrophilicity, biocompatibility, mucoadhesiveness, nontoxicity, and inexpensiveness makes it a potential drug delivery carrier. AL shrinks at low pH (gastric environment) and the encapsulated drugs cannot be released in the stomach, this phenomenon leads to site-specific delivery (Shilpa et al., 2003). The hydrogel of AL have attracted increasing attention due to their unique properties of pH-sensitivity as drug carrier (Shilpa et al., 2003). Due to increase in pH as the hydrogels pass down the intestinal tract, the degree of swelling increases which facilitate its rapid disintegration and drug releases at preferred sites (Tonnesen and Karlsen, 2002). The chitosan (CS), copolymer of D-glucosamine and N-acetyl glucosamine derived from chitin deacetylation process has a special feature of adhesion to the mucosal surface and transiently opening of tight junction between epithelial cells therefore quiet appropriate for drug carriers (Denkbas and Ottenbrite, 2006; Wang et al., 2008). Compared to other biopolymers, AL and CS offer additional advantage in terms of safety, biocompatibility and low cost.

Although several drugs have been extensively investigated using alginate, chitosan and synthetic peptide as carriers, but

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the use of layered silicate along with AL and CS as carrier is inadequate. Lin et al. (2006) have modified the MMT gallery by trimethylammonium cation (HDTMA) and used it as DNA carrier. Poly(D,L-lactide-co-glycolide)/MMT nanoparticles for targeted breast cancer chemotherapy of paclitaxel have been reported (Dong and Feng, 2005; Sun et al., 2008). Various drug molecules such as BSA (Wang et al., 2008), timolol maleate, vitamin B_1 and vitamin B_6 (Joshi et al., 2009a,b,c; Kevadiya et al., 2009), carbofuran (Manuel Fernandez-Perez et al., 2000), ibuprofen (Zheng et al., 2007), donepezil (Park et al., 2008) have been studied to execute controlled drug delivery using smectite clays. Procainamide hydrochloride (PA, an antiarrythmia drug), has a short half-life in vivo and it must be dosed in every 3–4 h (Danielly et al., 1994; Sintov and Levy, 1997; Ellenbogen et al., 1998; Markland et al., 1999; Lee et al., 2005; An et al., 2009).

The present communication deals with the intercalation of PA molecules into the interlayer of MMT at different reaction environment such as time, temperature, pH, and initial concentration. In order to control the release of PA in the gastric environments, PA–MMT composites were compounded with natural polymers, AL and CS. The in vitro drug release studies were performed using buffer solutions of pH 1.2 and 7.4. Higuchi and Korsmeyer–Peppas kinetic models were applied to elucidate the drug release kinetics in a superior way.

2. Materials and methods

2.1. Materials

Alginic acid sodium salt (viscosity: 20.0–40.0 CP in 1% water, MW: 7334), procainamide hydrochloride (PA), chitosan (medium molecular weight) and cellulose acetate dialysis tube (MW: 07014) were purchased from Sigma–Aldrich, USA. Sodium chloride, fused calcium chloride, hydrochloric acid, potassium chloride, potassium dihydrogen orthophosphate and sodium hydroxide were procured from S.D. fine chemicals, India and were used as received. The montmorillonite (MMT) rich bentonite clay was collected from Akli mines, Barmer district, Rajasthan, India. Deionized water was obtained from Milli-Q Gradient A10 water purification system.

2.2. Preparation of PA–MMT composites

2.2.1. Purification of MMT

300 g of raw bentonite dispersed in 3 l of 0.1 M NaCl solution was stirred for 12 h. To obtain Na-MMT, the slurry was treated with NaCl for three times. Finally, the slurry was centrifuged and washed with Milli-Q water until free from chloride ion as tested by $AgNO_3$ solution (Bergaya et al., 2006). Na-MMT was purified by sedimentation technique as described earlier (Patel et al., 2007a). The cation exchange capacity of MMT (91 mequiv./100 g of MMT on dry basis, dried at 110 °C) was measured by the standard ammonium acetate method at pH 7 (Bergaya et al., 2006).

2.2.2. Intercalation kinetics

20 ml aqueous solution of PA (120 mg of PA) was mixed with 100 mg of MMT powder in 100 ml conical flask. The experiments were performed with continuous shaking (Julabo shaking water bath, SW23) at 40 °C, and different time intervals ranging from 1 to 24 h. The reaction mixtures were filtered and analyzed for PA by UV–visible spectrophotometer at λ_{max} = 278 nm. The amount of PA intercalated per gram of MMT was calculated by the difference of the PA concentration before and after the intercalation process.

2.2.3. Effect of temperature

100 mg of MMT was dispersed in 20 ml of deionized water containing 120 mg of PA. The suspensions were shaken for 5 h, and at 30, 40, 50, 60, 70, and 80 °C. The reaction mixtures were filtered, and the concentration of PA in the filtrate was determined spectrophotometrically.

2.2.4. Influence of pH environment

The relation between pH and the intercalation amount of PA in MMT was studied at optimized time (5 h), temperature (40 °C), and fixed concentration of PA (120 mg). 20 ml aqueous solution of PA and 100 mg of MMT powder were taken in a 100 ml flask, and was shaken. The pH was adjusted from 2 to 12 by HCl and NaOH solutions. The remaining concentrations of PA in the filtrates were measured by UV absorbance.

2.2.5. Equilibrium isotherms

To study the effect of PA concentration on the intercalation of PA into MMT, reactions were carried out at different initial concentration of PA at constant time, temperature, and pH. 20 ml aqueous solution of PA containing different amount of PA were treated with 100 mg of MMT powder for 5 h, at pH 4 and 40 °C in a 100 ml conical flask with continuous shaking. The reaction mixtures were filtered and absorption of PA in the filtrates was determined by UV–visible spectrophotometer. The entire intercalation studies were performed in triplicate and the average values were utilized in data analysis.

2.2.6. Characterization

Powder X-ray diffraction (PXRD) analysis were carried out with a Phillips powder diffractometer X'Pert MPD using PW3123/00 curved Ni-filtered Cu Kα (λ = 1.54056 Å) radiation with scanning of 0.3°/s in 2θ range of 2–10°. Fourier transform infrared spectra (FT-IR) were recorded on PerkinElmer, GX-FT-IR as KBr pellet over the wavelength range 4000–400 cm^{-1}. Differential scanning calorimetric (DSC) studies were carried out in the range of 30–400 °C at the rate 10 °C/min under nitrogen flow (10 ml/min) using Mettler-Toledo, DSC-822e, Switzerland. The morphology of composites beads was observed by scanning electron microscope (SEM), LEO-1430VP, UK. The UV–visible absorbance of procainamide hydrochloride solutions were measured on UV–visible spectrophotometer (Shimadzu, UV-2550, Japan) equipped with a quartz cell having a path length of 1 cm.

2.3. Preparation of PA–MMT–AL composites

The site-specific delivery of PA was attained by compounding the prepared PA–MMT composite with AL, and further coated with CS. The appropriate amount of AL (1.0 g) dissolved in deionized water (50 ml) and stirred for 6–8 h to obtain homogeneous solution. The required quantity of calcium chloride dihydrate was dissolved in deionized water to prepare 100 mmol solutions. PA–MMT–AL nanocomposite beads were prepared by the means of gelation technique (Shilpa et al., 2003; Pasparakis and Bouropoulos, 2006; Dai et al., 2008). Appropriate amount of PA loaded MMT (0.7 g) was added to the AL solution, and stirred for 5 h to obtain homogeneous suspension. The resulting solution was then slowly added to the 200 ml calcium chloride solution by dripping it from the tip of a 20-guage hypodermic needle (falling distance 2 cm, pumping rate 2.5 ml/min) attached to a peristaltic pump (Master flex L/S 7518-00, Cole-Parmer, USA). In this approach the spherical shape of the drop was retained by the gelled suspension. The beads were allowed to cure in the calcium chloride solution for 20 min, and then separated by filtration. The prepared beads were washed thrice with deionized water, and dried at room temperature. The filtrate was used to calculate the encapsulation efficiency of the beads. The mean diameter of the dry beads was determined by measuring 50 beads with the help of micrometer screw (Mitutoyo, Japan), and mean value was used for data analysis. The PA–MMT composite: alginate