Applied Clay Science 80–81 (2013) 85–92

Contents lists available at SciVerse ScienceDirect

Applied Clay Science

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

Research paper

Clay–polymer nanocomposites as a novel drug carrier: Synthesis, characterization and controlled release study of Propranolol Hydrochloride

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ARTICLE INFO

Article history:
Received 25 May 2012
Received in revised form 17 May 2013
Accepted 1 June 2013
Available online xxxx

Keywords:
Clay–polymer nanocomposites,
Montmorillonite
Controlled drug delivery
Antihypertensive drug

ABSTRACT

Short half life of Propranolol Hydrochloride (PPN), an antihypertensive drug is a prime requirement to develop a formulation which could extend the release of PPN in the human body and also eliminate daily multiple dosage of PPN. In this study, a system of PPN loaded Montmorillonite–Poly lactic-co-glycolic acid (Mt–PLGA) nanocomposites has been developed. PPN incorporated PLGA nanoparticles have been compared with Mt–PPN–PLGA nanocomposites. Mt was used as sustained release carrier for PPN with addition of biodegradable polymer PLGA by preparing Mt–PPN–PLGA nanocomposites by double emulsion solvent evaporation method. The drug encapsulation efficiency and drug loading capacity of synthesized products were estimated with HPLC including suitable analytical techniques to confirm the formation of clay–polymer nanocomposites (CPN). The release profile of encapsulated PPN in CPN shows pH dependent release in simulated gastrointestinal fluid for a period of 8 h. This study suggests that the methodologies used are suitable for the synthesis of Mt based PLGA nanocomposites with high drug encapsulation efficiency and controlled drug release characteristics and indicates that the Mt–PPN–PLGA nanocomposites are supposed to be better oral controlled drug delivery system, for a highly hydrophilic low molecular weight antihypertensive drug PPN to minimize the drug dosing frequency and hence improving the patient compliance.

1. Introduction

Drug delivery systems have been of great interest for the past few decades to realize the effective and controlled drug delivery and minimize the side effects in the field of pharmaceutics. Oral controlled drug delivery system is an essential part of the development of new medicines. The carriers used for control drug release were mainly biodegradable polymers (Langer et al., 1999) and porous inorganic matrix (Suresh et al., 2010; Aguzzi et al., 2007).

In recent years, drug intercalated smectite, especially Montmorillonite (Mt) pharmaceutical grade clay mineral has attracted great interest of researchers (Joshi et al., 2009a,b). Mt has large specific surface area, exhibits good adsorption ability, cation exchange capacity, and drug-carrying capability. Mt is hydrophilic and highly dispersible in water and can accommodate various protonated and hydrophilic organic molecules along the (001) planes which can be released in controlled manner by replacement with other kind of cations in the release media (Bergaya et al., 2006; Chen et al., 2010; Iliescu et al., 2011). Therefore the Mt is suggested to be a good delivery carrier of the hydrophilic drugs. Mt is a potent detoxifier with excellent adsorbent properties due to its high aspect ratio. It can adsorb excess water from feces and thus act as anti-diarrhoeic. Mt can also provide mucoadhesive capability for the nanoparticles to cross the gastrointestinal barrier (Dong and Feng, 2005; Feng et al., 2009). It has also been used as a controlled release system. Mt has been proved to be nontoxic by hematological, biochemical and histopathological analyses in rat models (Lee et al., 2005). Mt is utilized as a sustained release carrier for various therapeutic molecules, such as 5 Fluorouracil (Lin et al., 2002), sertraline (Nunes et al., 2007), vitamin B1 (Joshi et al., 2009a,b), promethazine chloride (Seki and Kadir, 2006) and buspiron hydrochloride (Joshi et al., 2010).

Propranolol Hydrochloride [(2RS)-1-(1-Methylethyl) amino-3-(naphthalen-1-yloxy) propan-2-ol monohydrochloride] an antihypertensive drug is a nonselective, beta-adrenergic receptor-blocking agent (Dollery, 1991). It is a white crystalline solid, highly soluble in water. The dose of Propranolol Hydrochloride (PPN) ranges from 40 to 80 mg/day. Due to shorter half life (3.9 h) the drug has to be administrated 2 or 3 times daily so as to maintain adequate plasma levels of the drug (Chaturvedi et al., 2010). Thus, the development of controlled release dosage forms would clearly be advantageous (Sahoo et al., 2008). Sanghavi et al. (1998), prepared matrix tablets of PPN using hydroxypropyl methylcellulose which exhibited first order release kinetics. Velasco-De-Paola et al., 1999, described dissolution kinetics of controlled release tablets containing PPN prepared using eudragit. Some other researchers have also formulated oral controlled release products of PPN by various techniques (Gil et al., 2006; Mohammadi-Samani et al.,

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http://dx.doi.org/10.1016/j.clay.2013.06.009

2000; Paker-Leggs and Neau, 2009; Patel et al., 2010; Patra et al., 2007). However, many researchers in the development of PPN sustained release dosage forms were met with problems, such as the difficulty to control the release of the drug due to the high aqueous solubility of PPN. Sánchez-Martin et al. (1981) and Rojtanatanya and Pongjanyakul (2010) have reported the interaction of PPN with Mt and magnesium-aluminium-silicate mineral (MAS, a mixture of Mt and saponite) respectively. PPN can intercalate into the interlayer space of MAS and the obtained complexes showed control of the release of PPN.

However no report has been available in the literature for the combination of a biodegradable polymer Poly lactic-co-glycolic acid (PLGA) and Mt for controlled release of PPN. In this study we have tried to obtain the synergism of biodegradable and biocompatible polymer which has already been widely explored for controlled drug release properties, with pharmaceutical grade Mt to produce the oral and controlled drug delivery formulations for PPN. Being a highly hydrophilic drug molecule, it is very difficult to encapsulate a high amount of PPN within the hydrophobic polymer matrix. Therefore, in the present study a modified double emulsion solvent evaporation technique has been developed to entrap a substantial amount of drug in the synthesized formulations.

PPN–PLGA nanoparticles and Mt–PPN–PLGA nanocomposites were prepared by w/o/w double emulsion/solvent evaporation method by using biodegradable polymer PLGA and non-ionic Pluronic F68 (a triblock co-polymer selected as an emulsifier and stabilizing agent for the formation of PPN–PLGA nanoparticles and Mt–PPN–PLGA nanocomposites).

The synthesized products were characterized for interlayer structural changes in the solid by XRD, surface morphology and particle size by SEM and TEM with EDX, physical status of the drug and Mt by thermal studies and drug loading by HPLC technique. The drug release profile of the synthesized PPN–PLGA nanoparticles and Mt–PPN–PLGA nanocomposites was investigated in simulated gastrointestinal fluid. The Mt–PPN–PLGA nanocomposites obtained were intercalated and partially exfoliated in nature, spherical in shape with about 50–300 nm in size, the favorable size range for intestinal mucosal membrane uptake. DSC results clearly indicate the degradation of the drug encased within synthesized PPN–PLGA nanoparticles and Mt–PPN–PLGA nanocomposites. The drug release profile of Mt–PPN–PLGA nanocomposites shows up to 14% of the drug was released in simulated gastric fluid whereas in simulated intestinal fluid it shows up to 72% of drug release in a period 8 h. Thus we can suggest that Mt–PLGA nanocomposites can be used as a potential drug carrier for the controlled drug delivery of the low molecular weight cationic hydrophilic drugs like PPN.

2. Materials and methods

2.1. Materials

Mt KSF, PLGA 50:50 (molecular weight 40–75,000), Pluronic F-68 and drug PPN (purity >98%) were ordered from Sigma Aldrich St. Louise USA. HCl, KCl, NaOH, potassium dihydrogen phosphate of analytical grade for simulated gastric fluid HCl (pH 1.2) and simulated intestinal fluid (PBS, pH 7.4) preparation were ordered from MERCK (Germany). HPLC grade methanol and water were used for drug estimation by HPLC technique. All other reagents whether specified or not were of analytical grade. Double distilled water was used throughout the experimental work.

2.1.1. Synthesis of PPN–PLGA nanoparticles

In this study, the water/oil/water (w/o/w) double emulsion solvent evaporation method has been selected to encapsulate highly hydrophilic drug PPN in the nanoparticles. PPN–PLGA nanoparticles were synthesized in two steps. First, PPN was dissolved in water and emulsified in a solution of methylene chloride containing PLGA under magnetic stirring followed by sonication. In the second step, the primary w/o emulsion was emulsified in the external aqueous phase of Pluronic F68 (0.2%, w/v) to form a w/o/w-emulsion. The middle organic phase separated the internal water droplets from each other as well as from the external aqueous continuous phase. After solvent evaporation the PPN–PLGA nanoparticles were isolated by centrifugation and washed with double distilled water before freeze-drying.

2.1.2. Synthesis of PPN–PLGA–MMT nanocomposites

The synthesis of Mt–PPN–PLGA nanocomposites involved the emulsification of first w/o emulsion in Pluronic F-68 and Mt aqueous dispersion (Fig. 1) followed by the same procedure as discussed in Section 2.1.1.

2.2. Characterizations

Powder X-ray diffraction (PXRD) measurements of samples were performed on a powder X-ray diffractometer (XPERT PRO Pananlytical, model (PW3040160, Netherland) the measurement conditions were a Cu K α radiation, generated at 40 kV and 30 mA as X-ray source 2–40° (2θ) and step angle 0.01°/s. The differential scanning calorimetric studies were conducted on a DSC instrument (DSC Q200 V23.10 Build 79). The samples were purged with dry nitrogen at a flow rate of 10 ml/min and the temperature was raised at 10 °C/min. The effect of Mt content on thermal stability of the Mt–PPN–PLGA nanocomposites was assessed by the thermogravimetric analyzer (TGA 2050 Thermal gravimetric Analyzer). The surface morphology and particle size of the synthesized products were examined with the Scanning Electron Microscope (Zeiss EVO 40) and high resolution transmission electron microscope (TECNAI G2 T30, U-TWIN) with an accelerating voltage of 300 kV.

2.3. Estimation of drug loading and encapsulation efficiency with high pressure liquid chromatography (HPLC technique)

2.3.1. HPLC apparatus and conditions

The HPLC system consisted of a Shimadzu Model DGU 20 A5 HPLC pump, a Shimadzu-M20A Diode Array Detector, Shimadzu column oven

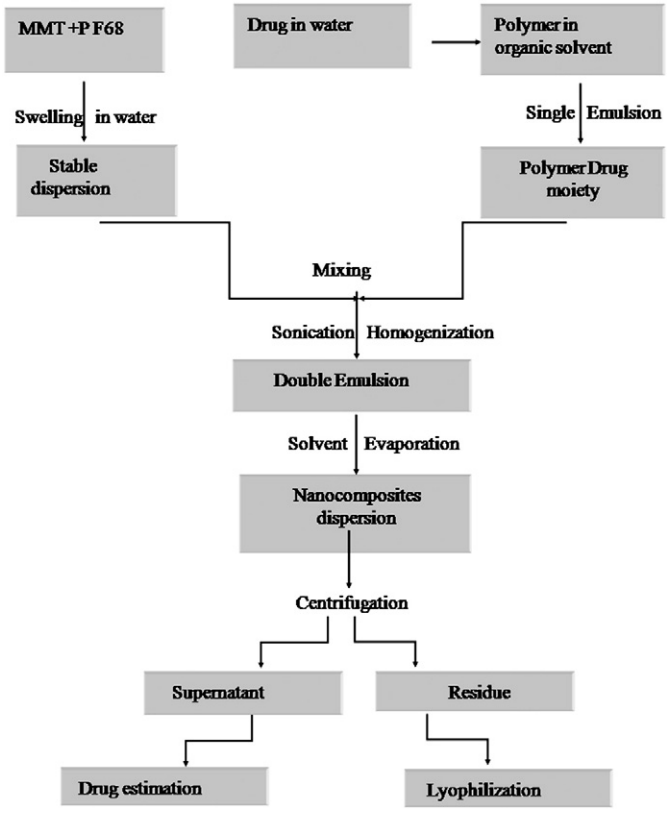

Fig. 1. Schematic representation of clay–polymer–drug nanocomposite synthesis.