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Research paper

In vitro prolonged gastric residence and sustained release of atenolol using novel clay polymer nanocomposite

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ABSTRACT

Atenolol (ATN) is a widely prescribed drug for the treatment of hypertension. Due to short biological half life, low oral bioavailability and poor absorption from the lower gastrointestinal tract, high doses are required to maintain its therapeutic level in the blood plasma which has undesirable side effects. It seems that an increase in gastric residence time may increase the extent of absorption and bioavailability of the ATN.

Therefore, to overcome the drawbacks associated with conventional oral delivery of ATN, a new drug delivery vehicle is required.

The purpose of the present research was to develop montmorillonite (Mt)-poly lactic-co-glycolic acid (PLGA) nanocomposites as sustained release oral delivery vehicle for ATN. The Mt–PLGA nanocomposites were prepared by w/o/w double emulsion solvent evaporation method by varying the ATN to Mt ratio at three levels using Pluronic F68 and PLGA as stabilizing agent and matrix material respectively. Effects of these compositions on interlayer spacing of Mt–PLGA nanocomposites, particle size, morphology and in vitro drug release were evaluated.

The in vitro release behavior of ATN from Mt–ATN–PLGA nanocomposites was found to be pH dependent and sustained as compared to ATN–PLGA nanoparticles, pure ATN and commercial formulation of Atenolol "ATEN-25" over a period of 24 h.

The developed clay polymer nanocomposites (CPN) show promising ability to prolong the gastric residence time of ATN and suggest the possibility of designing the sustained release formulations with improved bioavailability and patient compliance.

1. Introduction

Atenolol, is a cardio selective β1-adrenergic receptor blocking agent widely prescribed for the treatment of hypertension, cardiac arrhythmia and angina (Barrett et al., 1973; Majid et al., 1979; Frishman, 1982). The recommended adult oral dosage of conventional tablets of atenolol (ATN) is 25–100 mg twice daily for the effective treatment of hypertension (Wander et al., 2009). However, fluctuations of drug concentration in plasma may occur, resulting in side effects (nausea, stomach pain, low fever, loss of appetite, dark urine, jaundice, anxiety, depression, etc.) or a reduction in drug concentration at receptor side (Sastry et al., 1997; Vaithiyalingam et al., 2001).

ATN is considered a drug with short biological half life (6–7 h), low jejunal permeability and a low extent of absorption; with an oral bioavailability of about 50% (Fig. 1a). Thus, it seems that an increase in gastric residence time may increase the extent of absorption and bioavailability of the drug (Kulkarni and Bhatia, 2009; Barhate et al., 2011; Thomas and Khalil, 2011).

Therefore, an efficient oral drug delivery system is needed to overcome the drawbacks associated with conventional ATN tablets and improve the clinical treatment process which is capable of maintaining the therapeutic concentration of the drug at the desired absorption site over a longer period of time.

Several approaches have been reported on regulation of ATN release by formulations such as mucoadhesive, extended release and floating tablets, (Singh et al., 2006; Kulkarni and Bhatia, 2009; Barhate et al., 2011; Manivannan and Chakole, 2011; Thomas and Khalil, 2011), nanoparticles (Sabarikumar et al. 2012) hydrophilic matrices (Perez-Marcos et al., 1991; Vázques et al., 1996; Rouge et al., 1998) and transdermal drug delivery systems (Kim and Shin, 2004).

In recent years, the naturally occurring montmorillonite (Mt), a 2:1 layered clay mineral has been widely explored as fundamental constituents of several modified drug delivery systems, which had different purposes and acted through various mechanisms (Aguzzi et al., 2007; Wang et al., 2008; Depan et al., 2009; Yuan et al., 2010; Raghvendra and Saraswathi, 2012; Kaur and Datta, 2013; Seema and Datta, 2013a, b,c; Jain and Datta, 2014a,b; Kaur and Datta, 2014a,b; Seema and Datta, 2014). Structure of Mt consists of two silica tetrahedral sheets sandwiching an edge-shared octahedral sheet of aluminum, known as TOT layers (Fig. 1b). Its chemical formulae is $(Na,Ca)_{0.33}(Al,Mg)_2$

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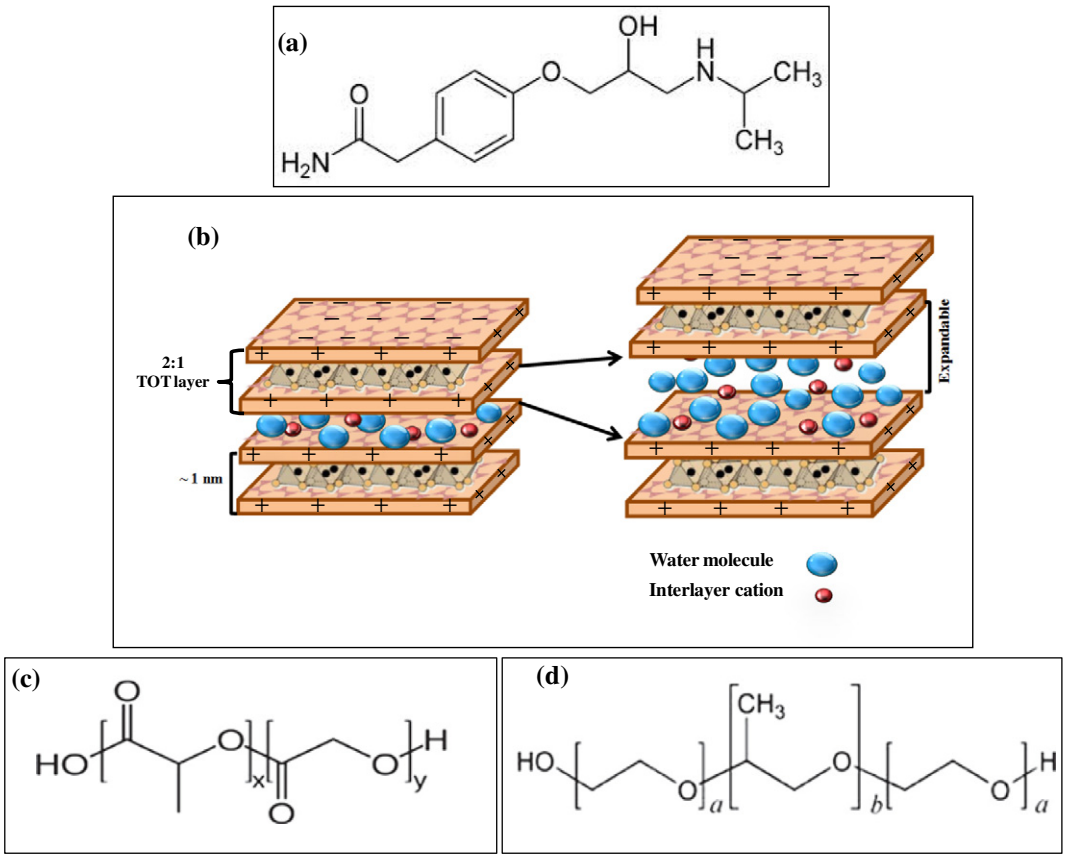

Fig. 1. Structural representation of montmorillonite (a), atenolol (b), poly lactic-co-glycolic acid (PLGA)x = poly (lactic acid) (PLA), y = poly (glycolic acid) (PGA); (c) and pluronic F68 (d).

$(Si_4O_{10})(OH)_2 \cdot nH_2O$. Water molecules are allocated in the interlayer space and are coordinated by the exchangeable cations (Calabresea et al., 2013). The size of the cations influences the basal spacing (001 plane) of the highly expandable clay mineral. The surface charge of Mt has been investigated in several studies (Abend and Lagaly, 2000; Janek and Lagaly, 2001; Penner and Lagaly, 2001; Ramos-Tejeda et al., 2003; Tombácz and Szekeres, 2004; Bergaya et al., 2006), showing that the faces of the layers of Mt have permanent negative charges owing to isomorphic substitutions, while pH-dependent charges develop on both the edge of the layer and in the interlayer space. Moreover, Mt has large specific surface area; and exhibits a good adsorption ability, swelling capacity, cation exchange capacity, standout adhesive ability and drug-carrying capability. Thus, the advantageous characteristic physico-chemical properties of Mt provide it all the properties of an ideal drug delivery vehicle (Aguzzi et al., 2007; Suresh et al., 2010; Rodrigues et al., 2013). It has also been demonstrated that Mt could effectively protect unstable bioactive molecules against harsh biological conditions and release them in a controlled manner, which finally contribute to enhance their efficacy (Fudala et al., 1999; Lin et al., 2002; Kollár et al., 2003; Park and Jonnalagadda, 2006; Zhang et al., 2006). Mt belongs to the GRAS list of FDA as an excipient material. It has been proved nontoxic by hematological, biochemical and histopathological analyses in rat models (Lee et al., 2005) and in human normal intestinal cells in short- and long-term exposures (Baek and Lee, 2012). It could be absorbed into the body within 2 h, but it did not significantly accumulate in any specific organ.

In order to modify drug release, a very interesting possibility is to use Mt–polymer nanocomposites. Although Mt and polymers were frequently used in their pure form as single drug carriers, this type of drug delivery vehicles often did not meet all the requirements. The preparation of clay–polymer nanocomposite (CPN) offered the possibility of improving the properties of each single component: those of the Mt particles alone (stability of the clay mineral dispersions and changes in its ion exchange behavior) and more frequently, those of the polymer (mechanical properties, swelling capacity, film forming abilities, rheological properties, bioadhesion or cellular uptake) (Viseras et al., 2008; Lambert and Bergaya, 2013).

Although few reports have been available for sustained delivery of ATN using polymeric materials (Srivastava et al., 2005; Dey et al., 2012, 2014; Raut et al., 2013) to the best of our knowledge, no report is available on the use of Mt–PLGA nanocomposites as a vehicle for oral and sustained release of ATN.

In the present study the efforts have been made to develop Mt based poly lactic-co-glycolic acid (PLGA) nanocomposites for oral and sustained release of ATN. PLGA (Fig. 1c) has been selected because it is FDA approved most extensively used biodegradable, biocompatible polymer with versatile degradation kinetics and safe degradation products (Jain, 2000; Miechel et al., 2004; Bhosale et al., 2013; Mirakabad et al., 2014).

Pluronic F-68[polyoxyethylene–polyoxy-propylene–polyoxyethylene (PEO–PPO–PEO) block polymer], an FDA approved a non-ionic surfactant (Fig. 1d), suitable for oral administration, widely used as wetting and solubilizing agent was employed in the present work as stabilizing agent (Kabanov et al., 2002; Adams et al., 2003; Artzner et al., 2007; Zhao et al., 2012; Seema and Datta, 2014).

2. Materials and methods

2.1. Materials

Montmorillonite KSF (Mt), PLGA 50:50 (molecular weight 40–75,000), Pluronic F-68 (PF-68) and ATN (purity > 99%) were ordered from Sigma Aldrich St. Louise USA. Analytical grade HCl, KCl, NaOH and potassium dihydrogen phosphate 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.