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Research paper

Design and preparation acid-activated montmorillonite sustained-release drug delivery system for dexibuprofen *in vitro* and *in vivo* evaluations

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ABSTRACT

Montmorillonite (Mt) plays a very important role in controlling drug delivery. In this paper, the hydrochloric acid (HCl) treated Mt. was exploited to obtain composites, which were able to enhance dexibuprofen (IBU) loading and achieve to sustain release drug. The textural properties of the Mt. were strongly dependent on the treatment of HCl. The drug loading of pristine Mt. was 190 mg/g, while it was increased to 298 mg/g for Acid-Mt. *In vitro* release showed that the IBU was released about 92% from IBU/Acid-Mt within 12 h, while the pure IBU was released all within 4 h in simulated intestinal fluid, which meant that the IBU/Acid-Mt were able to retard the drug release with a controlled manner. The release profiles of IBU from composites were fitted by *Higuchi* and *Korsmeyer-Peppas* equations, which manifested that diffusion sustained release dominated the main mechanism. Meanwhile, *in vivo* pharmacokinetics studies in rats displayed that the IBU/Acid-Mt exhibited better gradual drug release than the commercial IBU suspension. For the IBU/Acid-Mt composites, the area under the plasma concentration-time curve from 0 to 24 h ($AUC_{0–24}$) and mean residence time ($MRT_{0–24}$) were 644.49 ± 73.26 μg/h/mL and 7.65 ± 0.48 h, both of which were significantly larger than commercial IBU suspension ($AUC_{0–24}$ of 439.88 ± 84.41 μg/h/mL and $MRT_{0–24}$ of 3.10 ± 0.38 h), respectively ($P < 0.05$). The relative bioavailability of IBU/Acid-Mt was 154.11% ± 27.41% compared to commercial IBU suspension. As a result, the IBU/Acid-Mt is expected to achieve sustained release and extend residence time in plasma.

1. Introduction

Dexibuprofen (IBU) is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties (Dziadkowiec et al., 2017). It is widely used for the treatment of osteoarthritis and rheumatoid arthritis (Chantaburanan et al., 2017). The molecular structure of IBU is shown in Fig.1. Although this drug exhibits strong anti-inflammatory actions, treatment with IBU frequently leads to side effects due to the reported gastrointestinal toxicity of this drug (Bae et al., 2005; Talelli et al., 2010; Zhan et al., 2011). IBU contributes to topical injuries of the gastric mucus, what decreases mucus resistance to acidic environment, pepsin and some exogenous factors, such as the drug itself (Diego-Taboada et al., 2013; Oh et al., 2013; Rabiei et al., 2016). Since IBU is low water-soluble, short biological half-life ($t_{1/2}$ 2.1 h), and high frequency of dosing (2–4 times daily), it increases gastrointestinal complications (Hama Aziz et al., 2017). Therefore, it is necessary to develop an IBU carrier system to overcome the oral administration problem in clinical applications.

Montmorillonite (Mt) is a kind of clay mineral, which has been used in various industrial and pharmaceutical fields based its unique features, such as, swelling and adsorption (Ghadiri et al., 2015). The high adsorption capacity of Mt. contributes to increase drug entrapment and sustained-release of drugs (Joshi et al., 2009). Mt. generally sustains drug release in many formulations by strongly adsorbing to the drug, and it enhances the dissolution rate and bioavailability of hydrophobic drugs (Dening et al., 2016; Fini et al., 2017). Thus, Mt. can be applied to formulate diverse drug delivery systems to control and/or improve the pharmaceutical properties of drugs, including solubility, dissolution rate, and absorption. The drug molecules can be adsorbed on the surface, edges, or interlayer spaces of Mt., which greatly increase the surface area available to the dissolution medium. It is effectively enhanced the *in vitro* dissolution rate of non-ionic and acidic insoluble drugs (Aguzzi et al., 2007). There are many mechanisms that can be involved in the interaction between Mt. and drug molecules, such as hydrogen bonding, hydrophilic/hydrophobic interaction, ion exchange, van der Waals interaction and so on (Huang et al., 2017; Krupskaya

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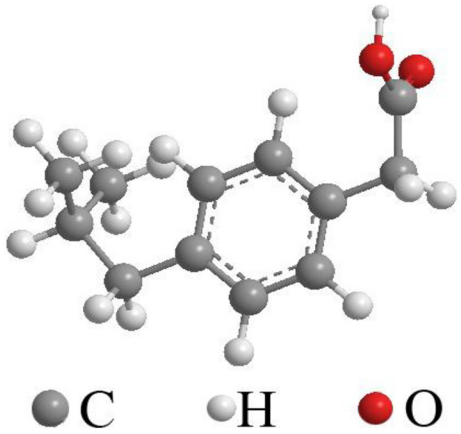

Fig. 1. IBU molecule structure.

et al., 2017; Mao et al., 2016). Moreover, it is important to note that Mt. proved with low toxicity by biochemical and histopathological studies in rat models (Hou et al., 2016; Namazi and Belali, 2016). Mt. has been widely used in the treatment of colitis, diarrhea, hemorrhoids, stomach ulcers, intestinal problems, acne, anemia, and a variety of other health issues (Cirri et al., 2017; Seetharaman et al., 2017). Hence, Mt. can be an excellent candidate carrier in controlled drug release system.

In our previous work, we had synthesized hydrochloric acid treatment Mt. (Acid-Mt), which exhibit a larger surface and a high specific pore volume (T. Li et al., 2017). This feature could encapsulate more drug molecules and provide a sustained release. The aim of this work is to use Acid-MMT to develop the IBU sustained release system. The properties of this composites were characterized by X-ray diffraction (XRD), fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM) and Brunauer-Emmett-Teller (BET) analyzer. In order to further investigate the release behavior of IBU, *in vitro* release characteristics and release kinetics were evaluated in stimulated gastrointestinal fluids. *In vivo* pharmacokinetics (PK) were measured in animal model of Sprague-Dawley (SD) rats, which was conducted in close comparison with the commercial IBU suspension.

2. Materials and methods

2.1. Materials

Pure IBU was supplied by Baikehengdi Pharmaceutical Co., Ltd. (Hubei, China). Na–montmorillonite was purchased from Zhejiang Sanding Science and Technology Co., Ltd. The cation exchange capacity (CEC) was around 110 meq per 100 g clay. The chemical composition of Na–montmorillonite wt%: SiO_2 65.14, Al_2O_3 17.05, Fe_2O_3 3.12, TiO_2 0.77, K_2O 1.52, MgO 3.12, CaO 0.35, Na_2O 2.15, and loss on ignition (LOI): 6.52. All other reagents were all of analytical grade.

2.2. Preparation of acid-Mt supported IBU

The Acid-Mt supported IBU by solution intercalation methods, and the synthetic scheme of the drug carrier system was described in Fig.2. HCl-acidified the Mt. was prepared by adding 4 g of the Mt. into a 250 mL three necked round bottom flask, and 10% HCl (wt%) was added in it. The resulting dispersion was stirred at 40 ± 5 °C for 8 h. After cooling, the supernatant liquid was discarded and the Mt. was repeatedly washed with deionized water until free from Cl^- ion ($AgNO_3$ test). The Mt. was recovered, dried in an air oven at 50 ± 5 °C over night to obtain the solid products and ground in a mortar pastel to powder form (Elfadly et al., 2017).

1.3 g Acid-Mt was separated into 100 mL beakers, then 50 mL IBU ethanol solution (0.5–2.5 mg/mL) was slowly added into the acid-Mt under vigorous stirring for 6 h at the room temperature. The mixture was separated by centrifugation at 10000 rmp, and this filtrate was treated as the sample solution. Simultaneously, the same amount of acid-Mt was added into ethanol without IBU, and stirred, centrifuged, and filtered at the same conditions, as the reference solution. The acid-Mt supported IBU was dried at 40 °C under vacuum for 24 h and maintained in a desiccator. The loaded amount of IBU was determined by UV–visible spectroscopy at λ_{max} = 264 nm with the reference solution as blank control. The entire studies were performed in triplicate and the average values were selected in the research. Drug loaded amount (mg/g) can be calculated by the equation

$$D(mg/g) = \frac{(C_0 - C) \times V_{IBU}}{M_{Acid-Mt}} \times 1000 \quad (1)$$

where D is the drug loaded amount (mg/g), C_0 is the IBU initial concentration (mg/mL), C is the equilibrium concentration of IBU in solution (mg/mL), V_{IBU} is the volume of IBU (mL), and $M_{Acid\text{-}Mt}$ is the Acid-Mt amount (mg).

2.3. Characterization of IBU/acid- Mt. composites

X-ray diffraction (XRD) patterns were obtained by a diffractometer (Rigaku D/MAX, Japan) with Cu Kα radiation (λ = 1.5418 Å, voltage of 40 kV, a generator current of 40 mA, a scan rate of 2°/min and the angle (2θ) was 4° – 40°).

N_2 adsorption–desorption isotherms were measured with Micromeritics ASAP 2020 instrument. The samples were degassed in vacuum for 4 h before measurement. The specific surface area was calculated by the Brunauer-Emmett-Teller (BET) method, and the pore size and pore volume were determined on the basis of the Barrett–Joyner-Halenda (BJH) method using the adsorption branches.

Fourier transform infrared (FT-IR) spectroscopy (Perkin-Elmer 1730 spectrometer, American) analysis was conducted on a Nicolet Avatar 360 spectrometer. FT-IR spectras in the transmittance mode were recorded from the range of 400–4000 cm^{-1} at a solution of 4 cm^{-1}, using the standard KBr-pressed disc method.

The particle size and zeta potential were analyzed by dynamic light scattering (DLS) analyzer (Nano ZA, Malvern Instruments). Samples were suspended in deionized water at room temperature and diluted to 0.1 wt%. The resulting suspension was measured 4 times.

Scanning electron microscopy (SEM) images were obtained on a Philips-FEI model Quanta 200.

2.4. In vitro release studies of IBU/acid-Mt composites

In vitro release studies of IBU/Acid-Mt composites were carried out in USP six stage dissolution test apparatus by dialysis technique in the simulated gastric acid fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) (Rivera et al., 2016). The weighted pure IBU and IBU/Acid-Mt composites were placed in dialysis membrane bag, which was immersed in 500 mL release medium. The temperature was maintained at 37 ± 0.5 °C with the rotation frequency maintained at 100 rpm. At specific time intervals, 5 mL of the dissolution medium were taken from the solvent medium and immediately replaced with the same volume of fresh medium. The concentration of the drug released into the solvent medium and was determined by UV spectrometer. The cumulative release rate of IBU was calculated as

$$M_t = \frac{V_e \sum_{i}^{n-1} C_i + V_0 C_n}{m_{drug} D} \times 100\% \quad (2)$$

where M_t is the cumulative release quantity (%), V_e is the displaced volume of release medium (mL), V_0 is the initial volume of release medium (mL), C_i is the drug concentration of the *i-th* medium (mg/mL), C_n is the drug concentration of the *n-th* medium (mg/mL), m_{drug} is the