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Improving the dissolution rate of a poorly water-soluble drug via adsorption onto pharmaceutical diluents

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ABSTRACT

The purpose of this study was to improve the dissolution rate of poorly water-soluble celecoxib (CXB) via a new adsorption method. CXB was dissolved in a co-solvent (ethanol:dichloromethane = 40:60 v/v) and then adsorbed on the surface of various diluent carriers by wet grinding. The physicochemical properties, such as the morphology and crystal structure, of the resulting adsorption powders were characterized. The adsorption powders were compressed into tablets after the wet granulation process. The *in vitro* dissolution rate of the CXB-loaded tablet was assessed in intestinal fluid (pH 6.8) containing 1% sodium lauryl sulfate. The differential scanning calorimetry and powder X-ray diffraction data showed that the crystallinity of CXB was maintained in the adsorption powders. Fourier transform infrared spectra indicated a molecular hydrogen-bonding between CXB and the adsorption carriers. Lactose monohydrate was the most effective at improving the dissolution rate of CXB via strong hydrogen bonding, followed by mannitol, Avicel® PH102, A-tab®, and Di-tab®. The CXB-loaded tablet was also stable during storage conditions (ambient: 25 °C, 60% RH, accelerated: 40 °C, 75% RH). Adsorption of CXB onto a hydrophilic diluent carrier provides an effective pharmaceutical strategy to enhance the dissolution rate of CXB-loaded tablets without changing drug crystallinity.

1. Introduction

Poorly water-soluble drugs formulation is one of the major current challenges in pharmaceutical industry. It has been reported that about 40% of oral immediate release formulations currently on the market contain poorly water-soluble drugs [1–3]. Poor solubility leads to low bioavailability, particularly for biopharmaceutical classification system (BCS) class II drugs, whose bioavailability is limited by their dissolution rate.

Celecoxib (CXB), a non-steroidal anti-inflammatory drug, is a specific cyclooxygenase-2 inhibitor used for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain [4–6], and has also been proved to lead to a better outcome in cancer treatment when used in combination with chemotherapeutic agents compared to chemotherapeutic agents alone [7]. However, CXB is a BCS II drug and has extremely low solubility in hydrophilic media [8,9]; its chemical structure is presented in Fig. 1. The solubility of crystalline CXB is approximately 3–7 μg/mL in water. With a pK_a of 11.1, the solubility of CXB is unaffected by pH over the physiologically relevant range of pH values [10]. Regarding the pharmacokinetic properties of CXB, the bioavailability is around 40%, the half-life is 11 h, protein binding is 97%, hepatic metabolism is mainly by CYP2C9, and excretion is via the renal (27%) and fecal (57%) routes [11].

Several formulation approaches have been investigated to improve the solubility and dissolution rate of CXB, thus improving the bioavailability. For instance, particle size reduction [12,13], solid dispersion [14–16], β-cyclodextrin complexation [17,18], nanosuspension [19], and co-crystal techniques [20] have been previously utilized to solubilize CXB. However, these techniques have been limited in terms of the unsatisfactory dissolution rate, low physicochemical stability and the manufacturing complexity of CXB-loaded formulations.

Herein, a new adsorption method was developed to enhance the dissolution rate of CXB without changing drug crystallinity and good stability during storage conditions. This is accomplished by dissolving the drug in an organic solvent and then adsorbing this

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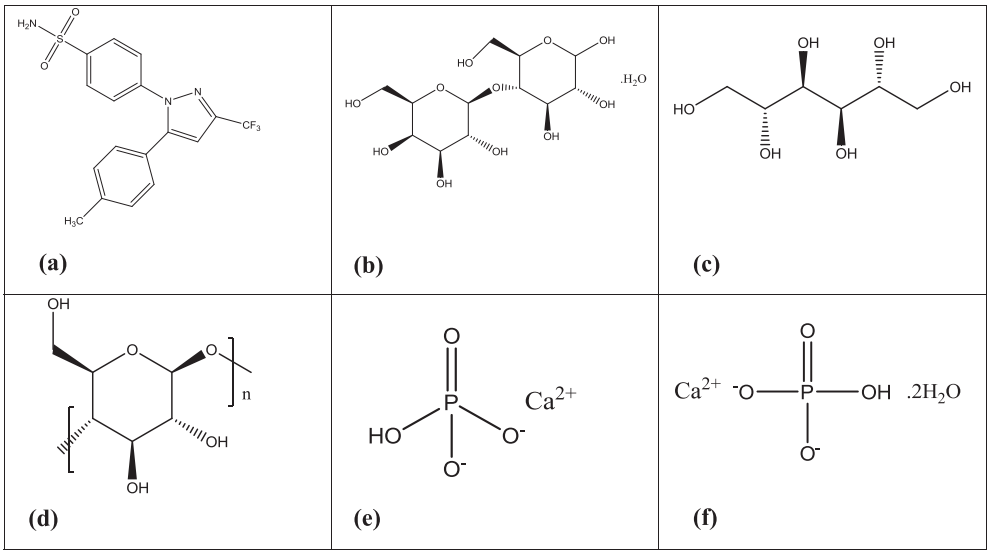

Fig. 1. Molecular structure of (a) celecoxib, (b) lactose monohydrate, (c) mannitol, (d) microcrystalline cellulose Avicel® PH102, (e) dicalcium phosphate anhydrous granular (A-tab®), and (f) dicalcium phosphate dihydrate granular (Di-tab®).

solution onto the carrier. The evaporation of the organic solvent results in the rapid precipitation of the drug on the surface of the adsorbent materials [21]. This is a simple and time-saving method that increases drug dissolution properties by reducing the drug particle size, thus improving the surface area of the drug available for contact with the dissolution medium. According to the Noyes–Whitney equation, when the surface area increases, the dissolution rate is in turn enhanced [22].

In this work, we found a new type of carrier and solvent system, which have never been used previously for enhanced dissolution of CXB via adsorption method. Various pharmaceutical diluents were investigated to adsorb model drug in a small quantity and newly found that lactose-based adsorbent system is very effective to be prepared and easy to design oral CXB tablet. Pharmaceutical diluents used as adsorption carriers included lactose monohydrate, mannitol, Avicel® PH 102, A-tab®, and Di-tab®. Their chemical structures are shown in Fig. 1.

Our new adsorption systems have novelties as compared with conventional ones. Firstly, as compared to solid dispersion in terms of preparation process, adsorption method is different from solvent-based solid dispersion method. In solid dispersion, both the drug and carrier were dissolved or dispersed in solvent, then this solvent was removed by drying process using spray drying or freeze drying [23]. Therefore, the amount of solvent used for making solid dispersion is typically large. In contrast, for our adsorption method, only drug was dissolved in optimally selected solvent and then the drug solution was adsorbed on the carriers by simple wet grinding. In other words, the carrier was not dissolved or dispersed in solvent. As a result, the amount of solvent used is much smaller than that of solid dispersion [21,24]. Secondly, unlike micronized drugs, which are more likely to agglomerate due to their hydrophobicity, thus reducing their available surface area [25,26], the adsorption method reduces the tendency to agglomerate. Hence, the increased dissolution rate achieved by the adsorption method is maintained during manufacturing process and storage. Finally, our system could be effectively applied a poorly water-soluble drug with high does strength like CXB (200 mg). Conventionally, common adsorbents such as fumed silica and crosslinked polyvinylpyrrolidone have been used with a large amount for adsorption studies but these systems are almost ineffective to be swallowed due to the large size of tablet and also induce stability problems [21].

Various physicochemical and molecular interactions were then characterized to elucidate the pharmaceutical mechanisms. The crystal structures of drug in adsorption mixture were characterized by using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). The morphology and particle size were also determined by using scanning electron microscopy (SEM). The molecular interaction between the drug and the carrier was examined by using Fourier transform infrared (FTIR) spectroscopy.

2. Materials and methods

2.1. Materials

CXB was purchased from Aarti Drugs Limited (Mumbai, India). Lactose monohydrate and mannitol were obtained from DFE Pharma (Tokyo, Japan). Microcrystalline cellulose (Avicel®PH102) was purchased from FMC (Philadelphia, USA). Dicalcium phosphate anhydrous (A-tab®) and dicalcium phosphate dihydrate (Di-tab®) were purchased form Whawon Pharm Ltd. (Seoul, Korea). Polyvinylpyrrolidone K30 (PVP K30) was obtained from BASF Chemicals (New Jersey, USA). Sodium lauryl sulfate (SLS) was purchased from Sigma-Aldrich (Missouri, USA). All other chemicals were of analytical grade. Water was purified by reverse osmosis.

2.2. Determination of celecoxib solubility

An excess amount of CXB was added to conical flasks containing 30 mL of various media, including distilled water, absolute ethanol, dichloromethane and cosolvent, pH 1.2, pH 6.8, pH 7.4, pH 6.8 with SLS (0.2%, 0.4%, 0.6%, 0.8% and 1%). The resulting samples were sonicated for 15 min then shaken in a shaking water bath (BS-06, JEIO Tech, Seoul, Korea) for 48 h at 37 °C (150 rpm). The contents of each conical flask were filtered through a 0.45-μm filter; the filtrate was subsequently diluted with media and then analyzed using high-performance liquid chromatography (HPLC). The solubility studies were carried out in triplicate.

2.3. Preparation of celecoxib adsorption mixture

The adsorption mixture was prepared by wet grinding. First, CXB (30 g) was dissolved in the co-solvent of absolute