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ORIGINAL ARTICLE

Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression

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Abstract The study was aimed at developing extended release matrix tablets of poorly water-soluble diclofenac sodium and highly water-soluble metformin hydrochloride by direct compression using cashew gum, xanthan gum and hydroxypropylmethylcellulose (HPMC) as release retardants. The suitability of light grade cashew gum as a direct compression excipient was studied using the SeDeM Diagram Expert System. Thirteen tablet formulations of diclofenac sodium (~100 mg) and metformin hydrochloride (~200 mg) were prepared with varying amounts of cashew gum, xanthan gum and HPMC by direct compression. The flow properties of blended powders and the uniformity of weight, crushing strength, friability, swelling index and drug content of compressed tablets were determined. *In vitro* drug release studies of the matrix tablets were conducted in phosphate buffer (diclofenac: pH 7.4; metformin: pH 6.8) and the kinetics of drug release was determined by fitting the release data to five kinetic models. Cashew gum was found to be suitable for direct compression, having a good compressibility index (ICG) value of 5.173. The diclofenac and metformin matrix tablets produced generally possessed fairly good physical properties. Tablet swelling and drug release in aqueous medium were dependent on the type and amount of release retarding polymer and the solubility of drug used. Extended release of diclofenac (~24 h) and metformin (~8–12 h) from the matrix tablets in aqueous medium was achieved using various blends of the polymers. Drug release from diclofenac tablets fitted zero order, first order or Higuchi model while release from metformin tablets followed Higuchi or Hixson-Crowell model.

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The mechanism of release of the two drugs was mostly through Fickian diffusion and anomalous non-Fickian diffusion. The study has demonstrated the potential of blended hydrophilic polymers in the design and optimization of extended release matrix tablets for soluble and poorly soluble drugs by direct compression.

1. Introduction

Hydrophilic polymers such as guar gum, pectin, chitosan, cashew gum, xanthan gum, HPMC and microcrystalline cellulose are pharmaceutical excipients which have been utilized individually or in blends to design hydrophilic matrix tablets to achieve controlled drug delivery (Maciel et al., 2006; Chivate et al., 2008; Nussinovitch, 2009; Vohra et al., 2012; Ali et al., 2013; Baviskar et al., 2013). Controlled-release dosage forms generally have reduced frequency of dosing, increased compliance, increased therapeutic effect, reduced side-effects, improved tolerability and reduced cost of treatment (Das and Das, 2003; Kamboj et al., 2009). Blending different hydrophilic polymers improves the physicochemical and release modifying properties of the resultant polymer leading to the design and formation of an optimized controlled-release product (Ofori-Kwakye et al., 2013) and the proper selection of polymers can help control the release profile of drugs (Fung and Saltzman, 1997). Hydrophilic matrix systems undergo swelling followed by gel formation, erosion and dissolution in aqueous media. In addition, such systems can sustain high drug loading and the excipients used are inexpensive and generally regarded as safe. They may however require optimal rate-controlling polymers for different active pharmaceutical ingredients (API's) and there could be challenges with scale-up of manufacture (Aulton, 2007).

Hydrophilic matrix tablets can be manufactured by wet granulation or direct compression techniques (Colombo et al., 2000). Direct compression is a simple technique of tableting a blend of powdered ingredients without granule formation or agglomeration process (Thakkar et al., 2009; Thoorens et al., 2014) and involves two sequential operations of powder mixing and tableting. The procedure requires the use of API's and or excipients with good flow and compressibility. As there is no involvement of heat and moisture in the process, direct compression is well-suited for heat and moisture-sensitive drugs and also enhances product stability (Aulton, 2007). The small number of operations involved in direct compression makes for reduced production cost making direct compression the most economical technique of manufacturing large batches of tablets (Thoorens et al., 2014). The major challenges associated with direct compression caused by the use of API's and excipients with poor physical attributes include poor flowability of powder blends, variability in tablet weight, poor content uniformity, tablets with poor mechanical strength and poor dissolution properties (Hentzschel et al., 2012; Thoorens et al., 2014).

Diclofenac sodium is a poorly water soluble (pKa = 4), Biopharmaceutics Classification System (BCS) class II (low solubility and high permeability), non-steroidal anti-inflammatory drug. It is commonly used in the treatment of mild to moderate post-operative or post-traumatic pain, menstrual pain and endometritis (Dastidar et al., 2000). Extended release diclofenac formulations are required for the treatment of chronic conditions such as rheumatoid arthritis, osteoarthritis, chronic pain, ankylosing spondylitis and actinic keratosis.

Metformin hydrochloride is a highly water soluble (> 300 mg/ml at 25 °C; pKa = 2.8 and 11.5), BCS class III (high solubility and low permeability) oral anti-diabetic drug in the biguanide class. It is a first line drug in the treatment of type-2 diabetes. Extended release metformin is needed for the long-term management and control of type-2 diabetes mellitus.

The aim of the current study was to design extended release oral matrix tablets of diclofenac sodium and metformin hydrochloride using varying blends of three hydrophilic polymers. The objective was to enhance the drug release modifying properties of the polymers leading to the formation of optimized formulations of the two model drugs with different water solubilities.

2. Materials and methods

2.1. Materials

Metformin HCl was a gift from Ernest Chemist Ltd. (Accra, Ghana). Diclofenac sodium BP was sourced from Hubei Prosperity Galaxy Chemical Co. Ltd. (China). Xanthan gum (SHL_PHXG980) was obtained from Luckystar Additives Co. Ltd. (Hong Kong). Microcrystalline cellulose (ACCEL 101) was sourced from Lavina Pharmaceuticals Pvt. Ltd., India. Glucophage® and voltaren retard® were purchased from retail pharmacies in Kumasi, Ghana. Potassium dihydrogen orthophosphate was obtained from Central Drug House Ltd. (New Delhi, India) and phosphoric acid and diethyl ether from Pokupharma Ltd. (Kumasi, Ghana). HPMC (Methocel E-15), magnesium stearate, ethanol, sodium hydroxide pellets, and hydrochloric acid were obtained from the Chemical store of the Pharmaceutics Department, KNUST, (Kumasi, Ghana). All other reagents used were of analytical grade. Crude cashew gum was collected from Bodokrom cashew plantation (Eastern Region, Ghana) and manually sorted into light and dark grades and the light grade cashew gum was purified as described elsewhere (Ofori-Kwakye et al., 2010). The purified light grade cashew gum (yield: 75.19%; moisture content 5.25 ± 0.35%, size range: 50–425 μm; swelling capacity: 3.33 (distilled water), 3.83 (phosphate buffer pH 6.8), 3.91 (phosphate buffer pH 7.4) (Mfoafo, 2013)) was employed as a direct compression excipient in the preparation of matrix tablets.

2.2. Preparation of blended powders

The compositions of various diclofenac sodium and metformin HCl matrix tablet formulations are presented in Tables 1 and 2,