Journal of Pharmaceutical and Biomedical Analysis 54 (2011) 711–716

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Evaluation of powder mixtures and hydrophilic gastroretentive drug delivery systems containing zinc acetate and sodium bicarbonate

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ARTICLE INFO

Article history:
Received 28 July 2010
Received in revised form 13 October 2010
Accepted 29 October 2010
Available online 9 November 2010

Keywords:
Zinc acetate dihydrate
Sodium bicarbonate
Water uptake
Disintegration
Floating
Dissolution

ABSTRACT

The aim of this study was to develop and study floating controlled drug delivery systems consisting of a model drug (zinc acetate dihydrate), different forms of a matrix-forming polymer (Metolose 90 SH) and sodium bicarbonate as an effervescent component. The proportions of Metolose and bicarbonate were varied, and the effects of the different ratios on the properties of the resulting powders and tablets were determined. The water uptakes of different powder mixtures were initially evaluated. These tests indicated the interaction of the active and effervescent agent, this phenomenon leading to an unpredicted increase in the amount of liquid taken up. This interaction was evaluated as concerns the degradation of the hydrophilic matrix system. The disintegration of tablets with different compositions revealed that this interaction increases the time required for the disintegration of these systems. The study demonstrated that the interaction of the components induced significant changes in the parameters of this new sensitive delivery system. In the last steps, the buoyancy and dissolution properties of tablets that appeared appropriate for the formulation of a controlled drug delivery system were investigated.

1. Introduction

Zinc acetate has a wide range of medical and dietary applications, e.g. as a dietary supplement, as an adstringent [1] or in lozenges used to treat the common cold [2]. Zinc salts, e.g. the sulfate, gluconate or acetate, can also be used to treat zinc deficiencies. As an oral daily supplement, this metal ion is used for the treatment of Wilson disease, an inherited, copper accumulation disorder that affects about 30 individuals per million people [3]. It is due to a dysfunction of a copper-transporting ATPase [4,5], leading to an accumulation of copper, mainly in the liver, but also in the brain, cornea and kidney, and causing progressive hepatic and nervous system damage. In the treatment of this disease, different active agents and their combinations can be applied, depending on the severity of the symptoms [6]. Zinc was first used by Schouwink in The Netherlands in the early 1960s [7,8]. Zinc interferes with the uptake of copper from the gastrointestinal tract, and removes stored copper [9]. Zinc may also act by inducing elevated levels of metallothionein [10–12]. Dosing is in the order of milligrams of zinc: the necessary amount is 150 mg of zinc per day. Thus, zinc sulfate, for instance, should be administered in a dose of 220 mg/day three times daily [13]. The actual salt used does not make a difference with respect to efficacy, but may affect tolerability [14]. Acetate may cause the least gastrointestinal distress, and gluconate may be more tolerable than sulfate. In the case of active agents with a short elimination half-life in the plasma, administration two or three times a day is necessary, but the compliance and tolerability of patients can be increased by developing a sustained-release system.

The primary site of absorption of exogenous zinc in the human is thought to be in the proximal small bowel [15,16]. In order to develop a desired sustained-release dosage form for zinc acetate, it is necessary to optimize both the residence time of the system in the gastrointestinal (GI) tract and the rate of release of the drug. Various approaches are used to increase the GI residence time, including mucoadhesive systems [17,18], swellable systems [19] and flotation systems [20,21]. Floating drug delivery systems (FDDSs) remain buoyant in the stomach for a prolonged period of time because of their lower bulk density as compared with that of the aqueous medium. These systems can involve the use of carbonates and bicarbonates, for example [22–24]; when these come into contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the system to float. An FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine [25]. These systems help in releasing the active agent continuously before it reaches the absorption window, thereby ensuring optimum bioavailability [26].

In our work, hydrophilic floating matrix tablets were prepared by direct compression. Compressed hydrophilic matrix tablets are

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doi:10.1016/j.jpba.2010.10.026

commonly used as oral drug delivery systems because of their good compactibility. Drug release from these systems is controlled by the formation of a viscous layer around the tablet, which acts as a barrier by opposing the penetration of water into the tablet. The overall drug release is influenced not only by the drug solubility, but also by the physical and mechanical properties of the gel barrier. Besides the mechanism of drug release, the extents of matrix swelling and erosion, and the diffusion of the drug determine the kinetics [27].

For FDDSs, rapid hydration is a basic requirement. It is well known from the literature that Metolose matrices hydrate rapidly only at the surface [28], retaining the bubbles developing from sodium bicarbonate and extending flotation during 8 h. The addition of sodium bicarbonate expands the volume of the matrices due to the gas bubbles formed after reaction with the acidic dissolution medium [29] and with the active agent, increasing their hydration volume.

In this study, a new FDDS based on the gas formation technique was developed. The tablets were prepared by direct compression, containing different ratios of an effervescent component (sodium bicarbonate) and different types of hydroxypropyl methylcellulose as matrix former. Zinc acetate dihydrate (Zn-ac), which is predominantly absorbed in the upper part of the GI tract, was used as active compound. It is known that interaction may occur between bicarbonates and Zn-ac [30]; accordingly, the objective of this work was to prepare a controlled drug delivery system and to investigate the effects of the ingredients and their possible interaction on the properties of powder mixtures (water uptake) and tablets (disintegration, floating and dissolution). In this part of our work, only the technological aspects were studied. The chemical relevance and the background will be discussed later. Our aim was an evaluation of the effects of the components on the functioning and erosion of this hydrophilic floating system.

2. Materials and methods

2.1. Materials

Zn-acetate (Zn-ac) (Merck KGaA, Darmstadt, Germany) was chosen as active agent. Forms of hydroxypropyl methylcellulose (Metolose 90 SH 100 SR, 4000 SR, 100,000 SR, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) with different viscosities were used as matrix-former. This component is frequently utilized to form floating matrix systems [24,31]. The notations for the different (low, medium and high) viscosities of the Metolose used in this work were as the follows: 100 SR – LV, 4000 SR – MV and 100,000 SR – HV. Sodium bicarbonate ($NaHCO_3$, Solvay S.A., Brussels, Belgium) was applied as gas-forming agent. Lactose monohydrate (Ph. Eur., Hungaropharma Plc, Budapest, Hungary) was used to substitute Zn-ac in the second part of the work.

2.2. Preparation of powder mixtures

As a preliminary step, the Zn-ac and $NaHCO_3$ were size-reduced in a mortar (Retsch RM 100, Retsch GmbH, Haan) for 10 min. Particle sizes were determined with an analytical sieve (Retsch GmbH, Haan) and particles with diameters of 100–200 μm were used in the study. The drug and the excipients were mixed in a rotating shaker mixer (Turbula, Willy A. Bachofen Maschinenfabrik, Basel) at 50 rpm for 10 min. The amount of active agent was calculated on the basis of the zinc requirement, which is equivalent to 500 mg of Zn-ac a day. The mass of the tablets prepared was 1 g. Powder mixtures in every case contained 50% Zn-ac, while the ratio of $NaHCO_3$ and Metolose was varied as follows: 10:40%, 15:35%, 20:30% and 25:25% (w/w).

2.3. Evaluation of water uptake

The Enslin number, a simple semiquantitative measure of the water uptake of a powder, is the amount of fluid absorbed by 1 g of the powder (in ml/g). An Enslin apparatus with a glass filter and a pipette with 0.01 ml accuracy were used for these experiments [32]. 0.1 g of the different forms of Metolose, 0.25 g of each powder mixture and 0.5 g each of Zn-ac and $NaHCO_3$ were tested; 5 parallel experiments were performed in every case.

2.4. Preparation of matrix tablets

Tablets were prepared with a hydraulic press (Specac Inc., Graseby, England); round and flat punches 13 mm in diameter were used. 1 g of powder mixture was compressed at 3×10^8 Pa with a dwell time of 10 s. Additional excipients (lubricant and glidant) were not applied. In the second part of the work, powder mixtures containing lactose monohydrate instead of Zn-ac were prepared; the ratio of the components was not changed.

2.5. Study of matrix disintegration

The disintegration of tablets was evaluated with a disintegration tester (Erweka ZT 71, Erweka GmbH, Heusenstamm, Germany), tablets were stored in a desiccator for 24 h before the test. The test liquid was gastric fluid (pH 1.2, Ph. Eur.) and the temperature was 37 °C. Twelve parallel experiments were performed. Each test was carried out for a maximum of 8 h, as floating systems with a residence time in the stomach longer than 8 h are not reasonable [33].

2.6. Buoyancy

The buoyancy of the tablets was studied at 37 ± 0.5 °C, in 150 ml of gastric fluid at pH 1.2 (Ph. Eur.). The floating lag times (the duration of the period between the placing of the tablet in the medium and the tablet floating) and durations of tablet floating were determined by visual observation. Tablets were stored in a desiccator for 24 h before the test.

2.7. Dissolution study

The rates of *in vitro* release of Zn-ac from the matrix tablets were determined in 900 ml gastric acid (pH 1.2, Ph. Eur.) by the paddle method (Ph. Eur.). Tablets were stored in a desiccator for 24 h before the test. The paddle rotation speed was kept at 50 rpm, and the temperature at 37 ± 0.5 °C. Dissolution tests were carried out under sink conditions. The motor activity of the stomach in the fed state is induced 5–10 min after the ingestion of a meal; the larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h, or more typically, 3–4 h. The phasic contractions are similar to those seen during phase 2 of the interdigestive myoelectric motor complex (IMMC) in the fasting state [34]. Thus, the dissolution study was carried out for 4 h. Three millilitre samples were withdrawn at 0.5, 1, 1.5, 2, 3 and 4 h, and the Zn contents were measured by X-ray fluoresence analysis (Philips MiniPal PW 4025, Philips Analytical, Almelo, The Netherlands). During the measurements, the conditions applied were 12 kV and 100 μA, with a kapton filter and an air purge. The samples were measured during 60 s, repeated in triplicate for each sample.

The concentrations of zinc (ppm) were calculated by means of linear calibration ($r^2 = 0.9945$) from the intensities of the K_α lines of the detected radiation. The dissolved drug concentration was calculated on the basis of the zinc content of Zn-ac.