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Research paper

Swelling, erosion and drug release characteristics of Sodium Diclofenac from heterogeneous matrix tablets

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ABSTRACT

The aim of this study was to investigate the effect of combination lipophilic (Acryl-EZE®) and hydrophilic (HPMC) polymers on the release of Sodium Diclofenac (DS) from a tablet. The microgranules were prepared using a fluidized bed followed by direct compression. Swelling and erosion studies of polymer matrix tablets were carried out in various media. The matrix tablets formed a continuous gel layer while in contact with the aqueous medium undergoing a combination of swelling and erosion. The swelling action of matrices was controlled by the rate of its hydration in the medium. The in vitro release was examined with and without rat caecal contents. Release studies showed that the swelling and erosion influenced the drug release. The good fit to Higuchi equation, the n values from Korsmeyer equation and the prevalence of kd over kr in Peppas-Sahlin equation revealed a drug release mechanism controlled mainly by diffusion.

1. Introduction

With the aim of maximizing the bioavailability of conventional drugs and reducing side effects, controlled or sustained release delivery systems can be used as a tool for optimizing therapeutic effect. These systems include matrix tablets, which are considered to be the easiest strategy for controlled-release systems [1]. Matrix tablets can be formulated by using hydrophilic polymers as the release material.

Hydroxypropyl methylcellulose (HPMC) is frequently used as matrix former in oral controlled release tablets [2–5]. It is well known that the mass transfer can affect drug release kinetics and control thereof through highly complex processes [6,7]. Release of drugs from HPMC systems is influenced by polymer concentration, drug: polymer ratio, polymer particle size, and polymer degree of substitution [8,9].

Upon contact with the aqueous contents of the gastro intestinal tract, water penetrates into the systems, resulting in polymer chain relaxation, drug dissolution, drug diffusion through the hydrated polymeric network, polymer chain disentanglement, matrix erosion and moving boundaries. Initially the system increases in size due to swelling; at a later time the tablet decreases in size due to polymer dissolution.

The conditions for drug diffusion permanently change, since the water content in the polymeric tablet strongly depends on time and position and determines the mobility of the macromolecules. Major efforts have been made to gain insight on the various phenomena that influence the control of drug release from HPMC-based matrix tablets [10,11]. Modulation of drug release from hypromellose matrices has been widely studied [12–14].

Much research is focused nowadays on the formulation of gastro intestinal and sustained-release dosage forms because some therapeutic molecules require the release in intestinal medium.

Methacrylate polymers are highly preferred because they prevent the release of drug in gastric environment. However, the pH in the caecum is usually about one pH unit lower than terminal ileum [15] and this will have an influence on the value of pH dependent polymers for colonic delivery [16].

In this study, a Sodium Diclofenac (DS) tablet formulation was developed. It is a non-steroidal anti-inflammatory drug with pronounced analgesic and antipyretic properties. Its half-life in plasma has been reported to be 1–2 hrs. DS produces side effects in about 20% of patients. Gastro intestinal effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen. Due to the

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short biological half-life and associated adverse effects it is considered as an interesting candidate for controlled drug release formulations.

Therefore, this study was aimed to study the effect of the combination of both hydrophilic (HPMC) and lipophilic (Acryl EZE®) polymers on swelling, erosion and drug release from matrix tablets. The effect of dissolution medium with and without rat caecal contents was also investigated.

2. Materials and methods

2.1. Materials

All raw materials are supplied by pharmaceutical manufacturing company Saidal (Algeria): Sodium Diclofenac (China Meheco Corporation- China), Hydroxypropyl Methyl-Cellulose (Methocel K15M, Shin-Etsu Chemicals Ltd. Japan), Cellulose microcrystalline (CMC) (Avicel PH101. SEPPIC - France), Povidone (PVP K90, International Specialty Products - USA), Acryl EZE® (Aqueous acrylic enteric system, Colorcon-France).

2.2. Preparation of microgranules by fluidization

The microgranules were prepared in the first step by wet granulation, using HPMC K15M as hydrophilic matrix at concentrations of 20 and 40%, PVP K90 as binder, and microcrystalline cellulose as diluent. The composition is described in Table 1.

Ingredients were de-agglomerated by sieving the powders through a 1 mm mesh screen and added into the container. The powder blends were granulated using a fluidized bed granulator (GPCG-1, Glatt GmbH, Binzen, Germany) by top spraying. During granulation, the inlet-air temperature was set to 60 °C and the outlet was in the range of 20–40 °C. The fluidizing air flow rate is set to 30 m^3/hr. The bed temperature was maintained at 45 °C ± 2 °C. The spray rate of binder was set at 22 ml/min with 2 bar atomization air pressure.

The microgranules were coated in the second part using the Acryl EZE at concentrations of 3, 5 and 7%. The coating was performed using a fluidized bed coater (GPCG-1, Glatt GmbH, Binzen, Germany) equipped with a Wurster column. The inlet air temperature was set to 50 °C and the outlet temperature was in the range of 20–40 °C. The atomizing pressure was 2.0 bar and the spray rate was 1.1 g/min.

2.3. Preparation of tablets containing microgranules

The matrix tablets containing microgranules were prepared by direct compression in tablet press (FROGERAIS type 1 B, France) using 8-mm diameter biconcave punch with a compression force equal to 6 kN. Total tablet weight was 250 mg. The tablet composition and Acryl- EZE compound used in this study are respectively detailed in Table 1.

Table 1
Formulation composition (%).

Ingredients (%)	Formulation code			
	F1	F2	F3	F4
Diclofenac	40	40	40	40
HPMC	40	20	20	20
Avicel PH 101	18	38	38	38
PVP K90	2	2	2	2
Acryl- EZE	5	3	5	7
HPMC: Acryl- EZE ratio	8:1	4:0.6	4: 1	4: 1.4

2.4. Swelling or water uptake studies

The rate of dissolution medium uptake by the tablets was determined by equilibrium or gravimetric analysis methods [17,18]. The dry matrices containing different concentrations of polymer were accurately weighed (W_0), placed in dissolution baskets and soaked in vessels containing dissolution medium of simulated gastric fluid USP without pepsin (pH 1.2), or simulated intestinal fluid (acetate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.2) at 37 ± 0.5 °C and rotating at 200 rpm. After 2, 5, 10, 20, 60 and 120 min, each container was removed, the tablet with the pre-weighted mesh was withdrawn from the medium and lightly blotted with tissue paper to remove excess test liquid and then reweighted (W_1) on an analytical balance (model AG204, Mettler-Toledo, Greifensee, Switzerland). The experiment was performed in triplicate for each time and fresh samples were used for each individual time. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time from the following equation.

$$Water\ uptake(\%) = \frac{W_1 - W_0}{W_0} * 100 \quad (1)$$

2.5. Matrix erosion studies

Matrix erosion studies were performed by equilibrium or gravimetric analysis methods [17,18]. After the swelling studies, the wet samples were respectively dried in an oven at 80 °C for a 24 hrs time period, and cooled in desiccators; finally the samples were weighed until constant weight was achieved (final dry weight, W_2). The experiment was performed in triplicate for each time. The tablet erosion (E) at different times was estimated from the following equation:

$$Matrix\ erosion(\%) = \frac{W_0 - W_2}{W_0} * 100 \quad (2)$$

2.6. Drug release study

Drug release studies were conducted using the USP basket method (apparatus I) at 100 rpm and 900 mL of dissolution fluid at 37 ± 0.5 °C. The dissolution tests were performed in HCl pH 1.2, phosphate buffer solution pH 6.0 and 7.2, respectively. Samples were collected at predetermined time points, analyzed for DS content using a UV-spectrophotometer (Optizen 2120 UV, Korea) at 275 nm. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, pH 6.0, and pH 7.2, were sequentially used, referred to as the sequential pH change method. These media were chosen to mimic the conditions in the stomach, duodenum, lower small intestine and colon, respectively, summarized in Table 2 pH 6.0, and pH 7.2 media were 0.05 mol/L phosphate buffer solution. When performing release experiments, the pH 1.2 medium was first used for 2 hrs, then removed, and the fresh pH 6.0 dissolution medium was added. After 1 hr, the medium was

Table 2
Dissolution conditions of DS.

pH	Time (hr)	Simulated GI region
1.2	2	Stomach
6.0	1	Duodenum
7.2	5	Lower small intestine and colon