Effect of Hydroxypropyl Methylcellulose and Hydrogenated Castor Oil on Naproxen Release From Sustained-Release Tablets

M. Helena Amaral*, J.M. Sousa Lobo and D.C. Ferreira

Centro de Tecnologia do Medicamento, Faculty of Pharmacy, University of Oporto,
Rua Aníbal Cunha, 164, 4050-Porto, Portugal

ABSTRACT The effect of the concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC]) and hydrophobic (hydrogenated castor oil [HCO]) products, fillers (lactose and dibasic calcium phosphate), and buffers (sodium bicarbonate, calcium carbonate, and sodium citrate) on naproxen release rate was studied. Matrix tablets were prepared by double compression, and *In vitro* dissolution tests were performed. The dissolution results showed that an increased amount of HPMC or hydrogenated castor oil resulted in reduced drug release. The inclusion of buffers in the HPMC matrix tablets enhanced naproxen release. For HCO tablets, only sodium bicarbonate enhanced naproxen release. The presence of lactose on HPMC matrix tablets did not show a significantly different result from that obtained with the formulation containing dibasic calcium phosphate as a filler. However, for the tablets containing HCO, the presence of lactose significantly enhanced the naproxen release rate. The matrix-forming materials in this study were suitable for use in sustained-release tablets containing naproxen. The drug release can be modulated by adding suitable amounts of diluents and buffers.

*Corresponding Author: M. Helena Amaral, Centro de Tecnologia do Medicamento, Faculdade de Farmácia do Porto, Rua Aníbal Cunha, 164, 4050 Porto, Portugal; Telephone: 222078900; Facsimile: 222003977; E-mail: hamaral@eudoramail.com

INTRODUCTION

Naproxen, (S)-2-(6-methoxynaphth-2-yl)propionic acid, is one of the most potent nonsteroidal anti-inflammatory agents; it also presents analgesic and antipyretic properties. The anti-inflammatory effects of naproxen, and most of its other pharmacological effects, are generally thought to be related to its inhibition of cyclooxygenase and consequent decrease in prostaglandin concentrations [1].

Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form. For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimal variations. Sustained-release products have become important for the oral administration of many drugs because they give more consistent blood levels [2]. One of the most commonly used methods of modulating tablet drug release is to include it in a matrix system. The classification of matrix systems is based on matrix structure, release kinetics, controlled-release properties (diffusion, erosion, swelling), and the chemical nature and properties of employed materials [3]. Matrix systems are usually classified in 3 main groups: hydrophilic, inert, and lipidic.

In this study, a hydrophilic polymer, hydroxypropyl methylcellulose (HPMC), and a lipidic product, hydrogenated castor oil (HCO), were used in 3 percentages: 32%, 16%, and 8%.

HPMC is a semisynthetic nonionic cellulose ether, which is widely used in controlled-release dosage

forms because of its nontoxic nature, its capacity to accommodate high levels of drug loading, and its non-pH dependence. Drug release from hydrophilic matrix tablets is controlled by a hydrated viscous layer formed at the tablet periphery; this gel layer acts as a barrier to drug release.

HCO is a white to slightly yellow fine powder obtained by hydrogenating castor oil using a catalyst. HCO has been used in pharmaceutical formulation or technology as a sustained-release coating material and hardening agent [4]. When tablet components are compressed, HCO forms a thin coating on the surface of the particles; thus, HCO may function as a binder.

To obtain suitable tablet formulations, the presence of other excipients, such as fillers and lubricants, is usually required. In this work, several studies were also undertaken to verify the effects of various fillers (lactose and dibasic calcium phosphate) and buffering agents (sodium bicarbonate, calcium carbonate, and sodium citrate) on naproxen release rate.

MATERIALS AND METHODS

Materials

Naproxen was generously supplied by Janssen-Cilag, Lisobon, Portugal. Hydroxypropyl methylcellulose (methocel K100m, nominal viscosity 100 000 cP) was generously supplied by Univete, (Lisbon, Portugal). Hydrogenated castor oil (Cutina HR) was supplied by Henkel International, Dusseldorf, Germany. Silicon dioxide (Aerosil 200), stearic acid, lactose, dibasic calcium phosphate (Emcompress), sodium bicarbonate, calcium carbonate, and sodium citrate were supplied by J.V.P. (Lisbon, Portugal). All reagents used in chromatographic analysis were reagent grade obtained from Merck (Darmstadt, Germany).

Solubility Studies

Aqueous solubility is a useful preformulation parameter mainly for poorly water-soluble drugs such as naproxen. Bioavailability problems are often present when the aqueous solubility of a drug is less than 10 mg/mL over the pH range 1-8 [5]. Zecchi et al demonstrated that the dissolution rate represents the limiting factor in the bioavailability of naproxen in solid dosage forms [6].

Naproxen solubility at 37°C in 7.4 buffer phosphate solution was determined by preparing saturated naproxen solutions that were maintained at 37.0°C ± 0.5°C in a water bath and continually shaken until saturated. Withdrawn samples were filtered through a millipore filter (Millipore Corp., Bedford, Massachussets) (pore size 0.45 mm), and assayed by high-performance liquid chromatography (HPLC) using the chromatographic analysis conditions described below.

Tablet Preparation

Sixteen formulations corresponding to the 2 types of matrix tablets (8 hydrophilic and 8 lipidic matrix tablets) were studied. Tablet formulations containing 160 mg of naproxen, binder agents, fillers, and lubricants were prepared by double compressing the blended powders, using a single-punch compression machine KORSH 9048-71 (Maschinenfabrik, Berlin, Germany), and 12-mm diameter punches. Tablets compositions are given in **Table 1**.

To obtain acceptable tablet compacts and the desired drug release rates, besides the drug and binder agent, the presence of other excipients may be required. In this study, the effect of soluble (lactose) and insoluble (dibasic calcium phosphate) fillers was studied. The additives that modify the matrix pH were also used to regulate the drug release rate. In this study 3 buffer agents, namely sodium bicarbonate, calcium carbonate, and sodium citrate, were added to hydrophilic and lipidic matrix formulations. The quantitative composition of the prepared tablets is shown in **Table 1**. Compositions IX-XVI are identical to their corresponding formulas I-VIII, except that HCO replaces the HPMC in each case.

Weight Variation and Hardness Determination

To study tablet weight variation, 20 tablets of each formulation were weighed using a METTLER AE 200 balance (Mettler Toledo, Switzerland). For each formulation the hardness of 10 tablets was also evaluated using an ERWEKA TBT 28 apparatus (Erweka GmbH, Germany).

Table 1. Naproxen Tablet Composition (mg)*

Formulations	I	II	III	IV	V	VI	VII	VIII
Naproxen	160	160	160	160	160	160	160	160
HPMC K100m	160	160	160	80	40	80	80	80
Dibasic calcium phosphate		160						
Lactose			160	240	280	230	230	230
Sodium bicarbonate						10		
Calcium carbonate							10	
Sodium citrate								10
Silicon dioxide	15	15	15	15	15	15	15	15
Stearic acid	5	5	5	5	5	5	5	5
Formulations	IX	X	XI	XII	XIII	XIV	XV	XVI
Naproxen	160	160	160	160	160	160	160	160
HCO	160	160	160	80	40	80	80	80
Dibasic calcium phosphate	160							
Lactose			160	240	280	230	230	230
Sodium bicarbonate						10		
Calcium carbonate							10	
Sodium citrate								10
Silicon dioxide	15	15	15	15	15	15	15	15
Stearic acid	5	5	5	5	5	5	5	5

*HCO indicates hydrogenated castor oil; HPMC, hydroxypropyl methylcellulose.

Release Studies

"*In vitro*" dissolution tests were used to simulate the gastrointestinal tract physiological conditions. For dissolution and drug release studies, the US Pharmacopoeia Paddle method II was used. The dissolution medium consisted of 1000 mL 0.1 m, pH 7.4, phosphate buffer solution [7], maintained at 37.5°C ± 0.5°C and stirred at 100 rpm. Samples (5 mL) were withdrawn at predetermined time intervals (30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes), and immediately replaced with equal volumes of dissolution medium. Samples were filtered to remove suspended, insoluble tablet components and assayed by HPLC.

The drug release study was performed for 8 hours because the total gastrointestinal transit time of nutrients and dosage forms in humans is approximately 8 hours.

HPLC Analysis

The HPLC system consisted of a pump (VARIAN model 9012, Varian Chromatographic Systems, Palo Alto, California), a variable wavelength detector (VARIAN model 9050), and a 20-μL loop. A WATERS reversed-phase column (Waters Corp., Milford, Massachussets) (15 cm x 4.6 mm, 5 μm) was used. The mobile phase was a mixture of acetonitrile:water:glacial acetic acid (50:49:1, vol/vol/vol) at a flow rate of 1.0 mL/min, and the detector was set to 331 nm. The drug concentrations were determined by measuring the peak area and comparing them with the peak area of known naproxen standard solutions. The reported data are the mean of at least 3 determinations.

Data Analysis

To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations:

Zero-order equation: $Q = k_0 t$

Where Q is the amount of drug released at time t, and k_0 is the release rate;

First-order equation: $\ln(100-Q) = \ln 100 - k_1 t$

Where Q is the percent of drug release at time t, and k_1 is the release rate constant;

Higuchi's equation [8]: $Q = k_2 t^{1/2}$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

RESULTS AND DISCUSSION

In vitro drug release depends on several factors, such as the manufacturing process, the type of excipient, and the amount of drug. In this work the effect of some excipients on naproxen release was studied.

Drug solubility is an important parameter of the preformulation studies. Naproxen is a weak acid with greater solubility in alkaline than in acidic media; therefore, its release profiles are pH dependent and its solubility is higher when pH is increased. The naproxen

equilibrium solubility in pH 7.4 phosphate buffer solution determined at 37°C was 6.0 mg/mL. Thus, sink conditions existed for naproxen release at this pH.

Tablets with acceptable physical properties were obtained in all formulations studied. The tablet batches complied with the weight variation and hardness requirements stated in the European Pharmacopoeia [9]. The naproxen release rates from tablets containing 32% HPMC as hydrophilic polymer and dibasic calcium phosphate or lactose (formulations II and III) as fillers, and 32% of HCO (formulations X and XI) and the same fillers, were compared to that of matrix tablets without filler (formulation I for HPMC tablets and formulation IX for HCO tablets). As it can be seen in **Figure 1**, no significant differences between the drug release rates of formulations containing HPMC, lactose, or dibasic calcium phosphate were observed. **Figure 2** shows that for HCO matrices the presence of lactose enhanced significantly the naproxen release rate. However none of the formulations shown in **Figure 1** and **2** released as much as 50% drug in 8 hours.

The use of HPMC (formulations III, IV, and V) and HCO (formulations XI, XII, and XIII) matrices in different concentrations (32%, 16%, and 8%) wherein lactose, a soluble filler, replaces the insoluble filler of formulations II and X, was studied. As shown in **Figure 3** (HPMC matrix tablets) and **Figure 4** (HCO matrix

tablets), for both matrices a decrease in HPMC/lactose or HCO/lactose ratio caused an increase in the cumulative percentage of drug released. More complete drug release over 8 hours is shown in these figures compared to **Figure 1** and **2**.

Naproxen is a weak acid, making it more soluble in basic conditions. Buffering agents have been included in tablet formulations to increase the dissolution and to decrease the gastric irritation of weak acid drugs, such as naproxen. Buffers can compete for the water of hydration and reduce the hydrophilic matrix integrity. Morgan et al [10] showed that trisodium citrate enhanced the permeability of the HPMC surface gel layer, which at higher concentrations resulted in the pseudogel failing as a diffusion barrier and in its ability to control release. The effect of buffers (2%) on naproxen release from HPMC matrix tablets was studied. As can be seen in **Figure 5**, inclusion of buffers (sodium bicarbonate, calcium carbonate, and sodium citrate) in the HPMC matrix increased the release of the weakly acidic drug naproxen. **Figure 6** shows that the inclusion of sodium bicarbonate produced complete naproxen release within 60 minutes from HCO matrix tablets. Calcium carbonate or sodium citrate produced a retardant effect on naproxen release from the HCO matrix.
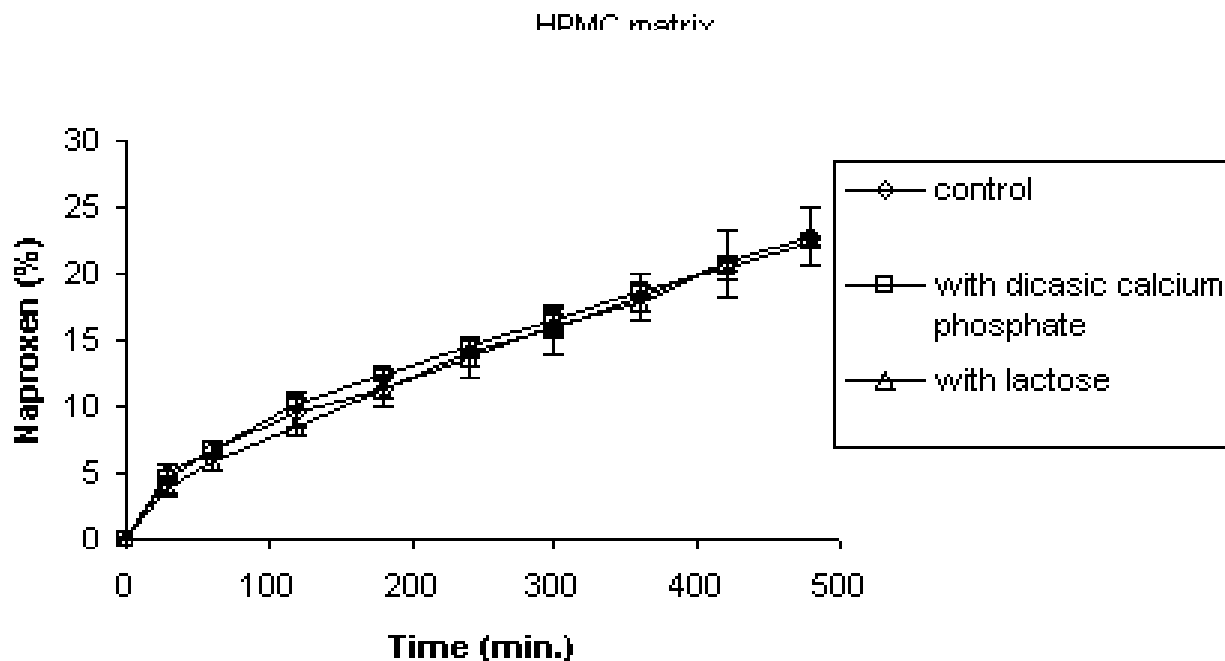
HPMC matrix

Figure 1. Cumulative percentage of naproxen released from formulations I (control), II (with dibasic calcium phosphate), and III (with lactose).
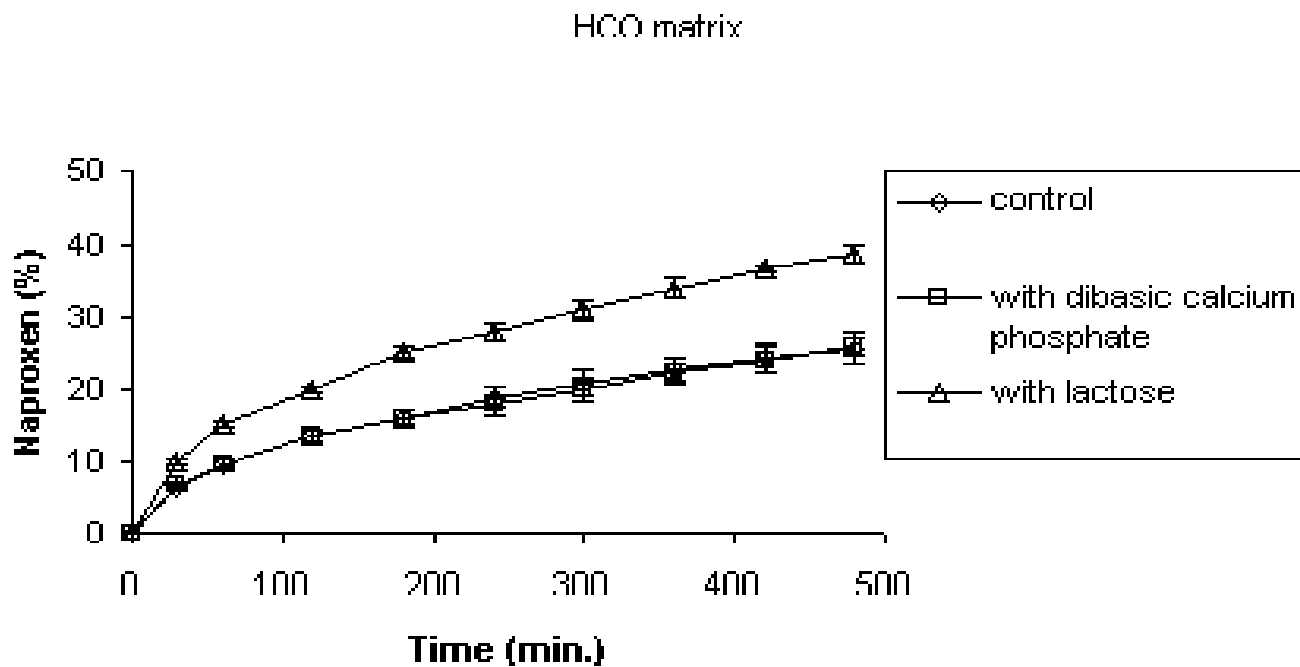
HCO matrix

Figure 2. Cumulative percentage of naproxen released from formulations IX (control), X (with dibasic calcium phosphate), and XI (with lactose).
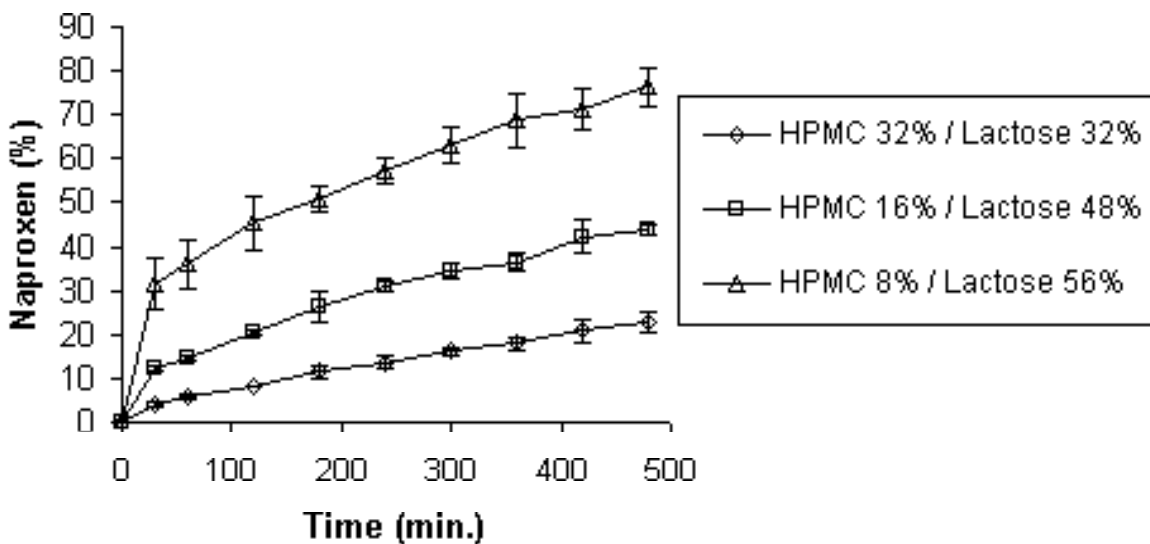

Figure 3. Cumulative percentage of naproxen released from formulations III (HPMC 32%/lactose 32%), IV (HPMC 16%/lactose 48%), and V (HPMC 8%/lactose 56%).
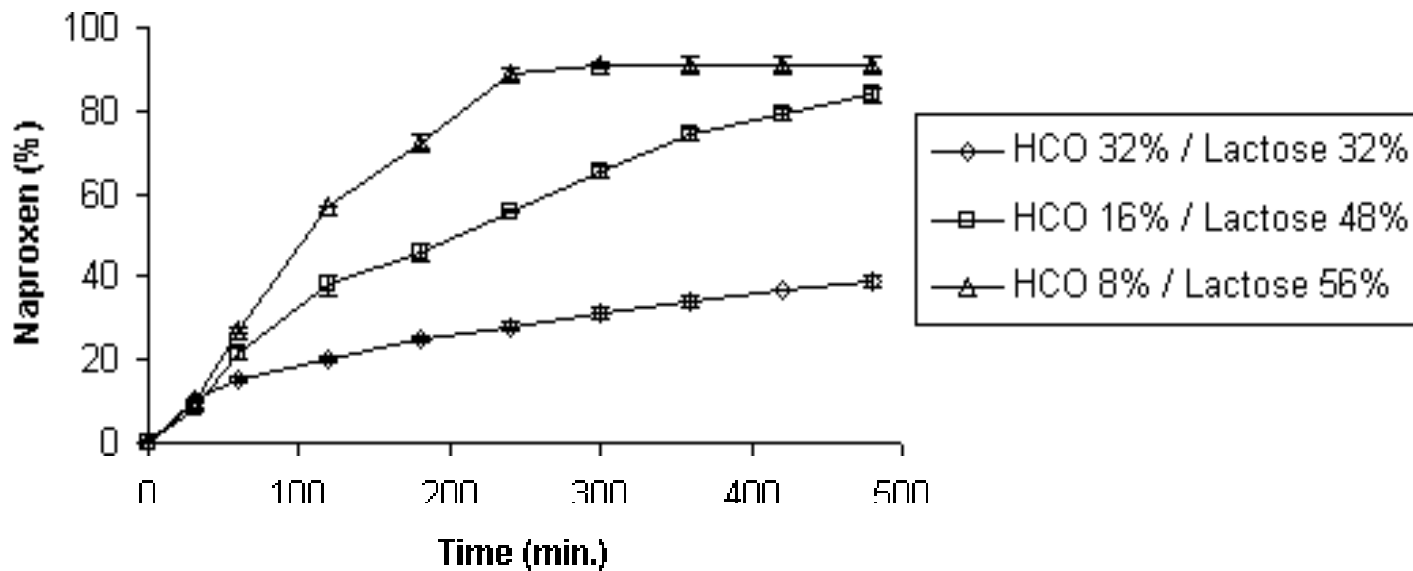
Figure 4. Cumulative percentage of naproxen released from formulations XI (HCO 32%/lactose 32%), XII (HCO 16%/lactose 48%), and XIII (HCO 8%/lactose 56%).
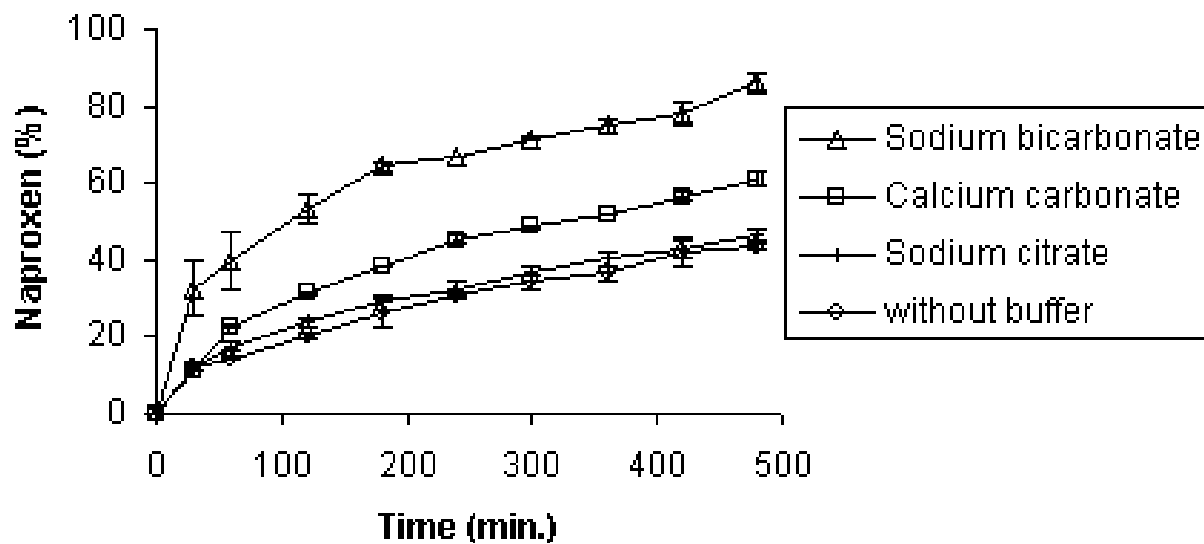

Figure 5. Effect of buffer presence on naproxen release from formulations VI (sodium bicarbonate), VII (calcium carbonate), and VIII (sodium citrate).
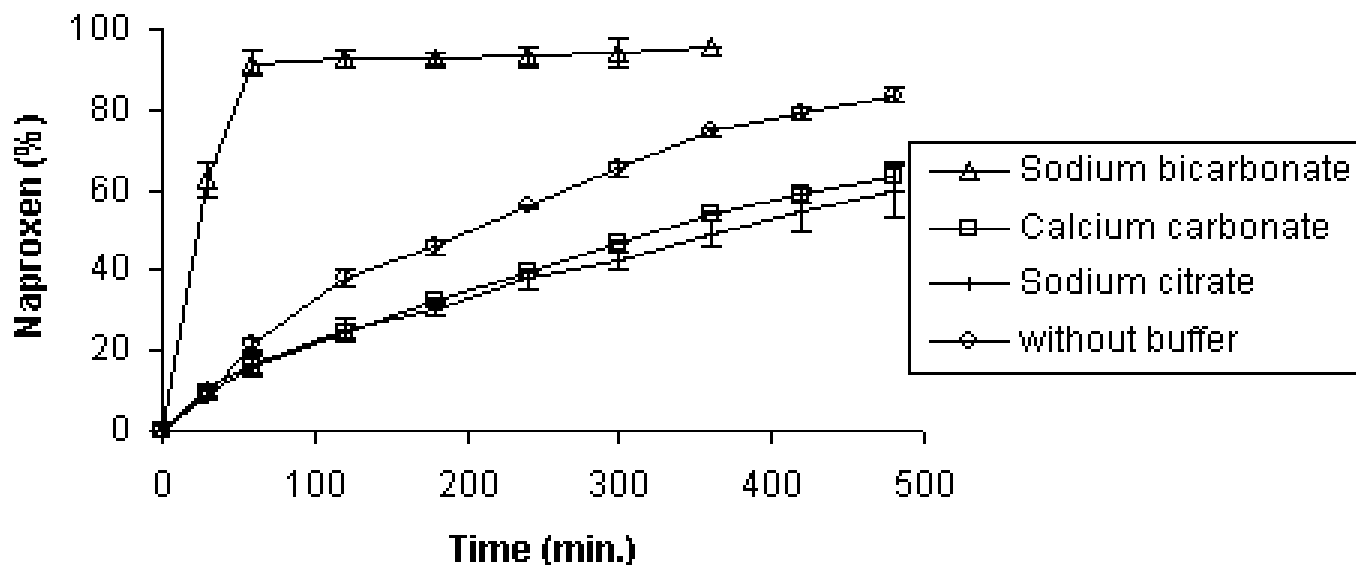
Figure 6. Effect of buffer presence on naproxen release from formulations XIV (sodium bicarbonate), XV (calcium carbonate), and XVI (sodium citrate).

CONCLUSIONS

The modification of naproxen release rates from 2 types of matrix systems was studied. The presence of soluble (lactose) or insoluble (dibasic calcium phosphate) fillers did not affect the naproxen release rate from the hydrophilic (HPMC) matrix tablets (all formulations released about 22% of naproxen over 8 hours). A decrease in the HPMC:lactose ratio produced an increase in naproxen release. Tablets containing 1:1 (formulation III), 1:3 (formulation IV), and 1:7 (formulation V) HPMC:lactose ratios released, respectively, 22.0%, 43.8%, and 76.3% of naproxen over 8 hours.

Naproxen is a weak acid, so it is more soluble in alkaline media. The inclusion of sodium bicarbonate and calcium carbonate in the HPMC matrix improved the naproxen dissolution; however, including sodium citrate did not produce any effect on naproxen dissolution. Using 16% of HPMC, 46% of lactose, and 2% of sodium bicarbonate (formulation VI), calcium carbonate (formulation VII), or sodium citrate (formulation VIII), the amount of drug released was 86.1%, 61.2%, and 46.3%, respectively, over 8 hours.

For lipidic (HCO) matrix tablets, the inclusion of an insoluble diluent (dibasic calcium phosphate) did not change the amount of naproxen released (26.2% over 8 hours). However, the presence of a soluble diluent (lactose) produced an increase in naproxen release rate (38.9% over 8 hours). Lactose dissolution may create void spaces in the lipidic structure that result in increased naproxen release.

A reduction in the HCO:lactose ratio resulted in an increase in the percentage of naproxen released. Tablets with the lowest HCO:lactose ratio (formulation XIII) released almost 90% of their naproxen content after 4 hours. For the intermediate HCO:lactose ratio (formulation XII), however, the naproxen release was prolonged for 8 hours or longer.

For the HCO matrix, substituting 2% of lactose with sodium bicarbonate (formulation XIV) produced rapid tablet disintegration and a relatively rapid naproxen release (almost 100% in 1 hour). However, including the same amount of calcium carbonate (formulation XV) or sodium citrate (formulation XVI) produced decreased naproxen release over 8 hours (63.5% and 59.7%, respectively).

ACKNOWLEDGEMENTS

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