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RESEARCH PAPER

Naproxen Availability from Variable-Dose and Weight Sustained-Release Tablets

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ABSTRACT

The aim of this work was to compare the naproxen availability from hydroxypropyl methylcellulose (HPMC) matrix tablets containing the same dose and a 2-fold weight variation (160 mg of naproxen in tablets weighting 250 and 500 mg) or with the same weight and a 2-fold dose variation (500 mg of weight and 160 or 320 mg of naproxen). The 2-fold weight variation in tablets with the same dose and also the 2-fold dose variation in tablets with the same weight did not affect the naproxen release. In addition, the release rate of two tablets of the same formulation and one tablet with a 2-fold dose and weight variation was not significantly different at the first minutes of the dissolution assay.

KEY WORDS: Naproxen; Sustained-release; Hydroxypropylmethylcellulose.

INTRODUCTION

Naproxen is an anti-inflammatory drug that also has analgesic and antipyretic properties. Naproxen is extensively bound to plasma albumin (1), so it may be more efficient to deliver this drug as a sustained-release dosage form.

One of the most commonly used methods to modulate tablet drug release is to include it on a hydrophilic matrix such as hydroxypropyl methylcellulose (HPMC). A large number of studies have been reported in the literature to investigate the drug release from HPMC tablets (2–4). The mechanism of release from swellable matrix systems is complex and is not completely understood. In general, on contact with an aqueous medium, the initially glassy polymer undergoes a relaxational process that is observed macroscopically as gelation and swelling. As a result of these processes, two fronts are established. At the swelling front (glassy polymer/gel interface), the hydration, swelling, and coalescence of individual polymer particles occur. The gel layer so formed swells as additional water is absorbed. At the eroding front (gel/dissolution medium interface), polymer chain disentanglement and concomitant dissolution of the hydrated matrix occur. The distance between the swelling and the eroding fronts is the gel layer thickness and has been called the diffusion layer

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thickness. This distance is dependent on the drug solubility and the relative rates at which the swelling and the eroding fronts move in relation to each other. The drug-release mechanism of matricial sustained-release tablets can be rationalized as being attributable to a coupling of diffusion and erosion release mechanisms, with the relative contribution of each being determined, in part, by the drug solubility. Drugs with low water solubility are more likely to exhibit contribution of drug release owing to erosion because solid drug particles may exist in the hydrated matrix near the eroding front (4).

In this study we intended to compare the naproxen availability from HPMC matrix tablets containing the same dose and a 2-fold weight variation (160 mg of naproxen in tablets weighting 250 and 500 mg) or with the same weight and a 2-fold dose variation (500 mg of weight and 160 or 320 mg of naproxen). We also intended to verify whether, for the same therapeutic dose, it was advantageous to administer two tablets (250 mg of weight and 160 mg of naproxen) instead of one tablet with a 2-fold dose and weight variation (500 mg of weight and 320 mg of drug).

The in vitro naproxen availability depends on a number of factors, such as manufacturing process, amount of active substance, and excipients nature. It is well known that excipients play a very important role on drug availability, thus, their choice must be careful. In this study, HPMC Methocel® K100M, was used as the rate-controlling polymer in the naproxen controlled-release tablet formulation. This polymer was chosen because of its nontoxic nature and its capability to accommodate high levels of drug loading (5).

MATERIAL AND METHODS

Materials

Naproxen was a kindly provided by Janssen-Cilag, Portugal. HPMC (Methocel K100M) was provided by UNIVETE, Portugal. All the other excipients were obtained from J.V.P., Portugal. Reagents used in liquid chromathography were reagent grade from Merck.

Granulometric Studies

Drug granulometry could influence its dissolution properties. Naproxen particle size was determined using the Coulter Counter MULTISIZER II, an apparatus that counts and sizes particles suspended in an electrolyte. This method is primarily used in particle size characterization and has been applied to dissolution studies of pharmaceutical powders (6).

Solubility Studies

It is has been recognized that the rate of dissolution often controls drug bioavailability, in particular, poorly soluble drugs in which dissolution could be the rate-limiting step. Zechi et al. (7) showed that the dissolution rate represents the limiting factor in the bioavailability of naproxen in solid dosage forms. Naproxen solubility studies at 37°C in pH 7.4 buffer phosphate solution were performed. For these studies, an excess of the drug was added to 10 mL of pH 7.4 buffer phosphate solution maintained at 37°C in a water bath and continually shaken for 24 hr. Withdrawn samples were filtered through a Millipore filter (pore size, 0.4 μm) and assayed using HPLC. The HPLC system consisted of a pump (VARIAN model 9012) and a variable wavelength detector (VARIAN model 9050) set at 331 nm. A reversed-phase column (ODS2, 15 cm $\times$ 4.6 mm; 5 μm) was used. The eluent used was a mixture of acetonitrile:water:glacial acetic acid (50:49:1, v/v/v), the flow rate was 1.0 mL/min, and the injection volume was 20 μL.

Tablets Preparation

Three naproxen sustained-release formulations (Table 1) were prepared. The powders were blended manually, and tablets were made by double compression using an alternative compression machine (KORSH 9048-71) with 12-mm-diameter punches.

Tablets weight variation and hardness were evaluated using a METTLER AE 200 balance and an ERWEKA TBT/S apparatus, respectively.

Pure naproxen powder was also compressed using the same punches described above.

Table 1.

Naproxen Tablet Composition (mg)

Formulation	1	2	3
Naproxen	160.0	160.0	320.0
Methocel K100M	80.0	80.0	160.0
Lactose	—	240.0	—
Aerosil	7.5	15.0	15.0
Stearic acid	2.5	5.0	5.0

Dissolution Studies

For dissolution and drug release studies, the USP Paddle Method II was used. pH 7.4 phosphate buffer solution (1000 mL), maintained at 37.5 ± 0.5°C and stirred at 100 rpm, was used as the dissolution medium. Samples (5.0 mL) were withdrawn at predetermined time intervals (30, 60, 120, 180, 240, 300, 360, 420, and 480 min), filtered, and assayed using HPLC (liquid chromatograph VARIAN).

Dissolution tests of pure naproxen powder and pure naproxen tablets (without excipients) were also performed to evaluate the effect of compression on the dissolution process.

RESULTS AND DISCUSSION

The mean particle size of powdered naproxen determined by the Coulter counter method was 47 μm. Several studies showed that the dissolution rate represents a limiting factor in the bioavailability of naproxen in solid dosage forms. Naproxen solubility at 37°C is 6 mg/mL.

Fickian diffusion is the driving force for mass transfer from the solid to the liquid phase. In the film theory, a stagnant liquid film of calculable length is postulated to exist adjacent to the dissolving solid surface. The carboxylic acid, naproxen, dissolves at the solid surface and instantaneously and reversibly reacts throughout the film.

As shown in Figure 1, pure powdered naproxen showed a higher dissolution rate than did pure compressed naproxen. This may be explained by the irregular compressed naproxen wettabillity attributable to the formation of slightly soluble small agglomerates (8). Solid/liquid contact surface area seems to be the cause for the different dissolution rate. Duru et al. (9) showed that a decrease in the solid/liquid contact surface area of compressed theophylline gave rise to a decrease in the drug dissolution rate.

Table 2.

Tablets Thickness (mm) and Surface Area (mm^2)

Formulation	1	2	3
Thickness (mm)	3.0	5.0	5.0
Surface area (mm^2)	339.3	414.7	414.7

The produced tablet batches complied with the hardness and weight variation requirements outlined in the European Pharmacopoeia (10). Table 2 presents tablet thickness and surface area of the prepared formulations.

Figure 2 shows that despite its higher surface area, the naproxen dissolution rate of formulation 2 does not differ significantly from the dissolution rate of formulation 1.

As shown in Figure 3, the naproxen dissolution rate of formulation 1 does not differ significantly, up to 420 min, from the dissolution rate of formulation 3 with a 2-fold dose and weight variation.

To verify whether, for the same therapeutic dose, it was advantageous to administer two tablets instead of one with a 2-fold dose and weight variation, data from dissolution assays of two tablets of formulation 1 and one tablet of formulation 3 were compared. As shown in Figure 4, the dissolution rate of two tablets weighting 250 mg (formulation 1) did not differ significantly up to 240 min, from that of one tablet with a 2-fold weight and dose variation (formulation 3).

The process of drug release from an HPMC-drug matrix is a complex. The overall drug release is affected

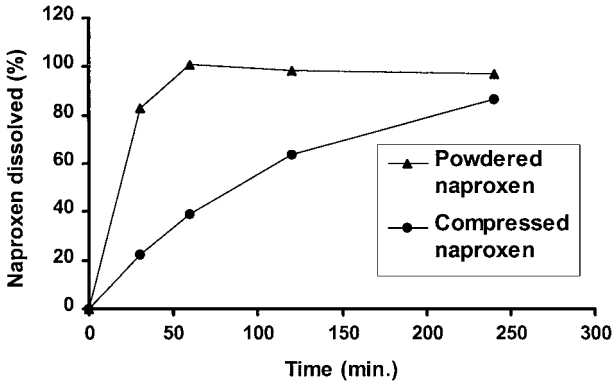

Figure 1. Pure naproxen powder and pure naproxen tablets dissolution profile.

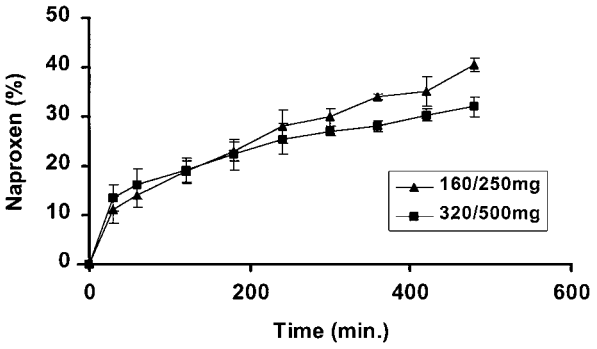

Figure 2. Naproxen released from formulation 1 (160/250 mg) and formulation 2 (160/500 mg).

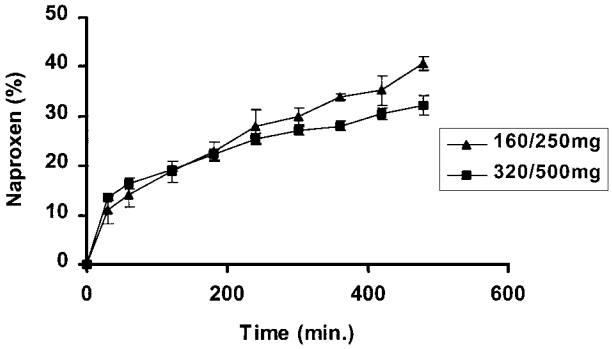

Figure 3. Naproxen released from formulation 1 (160/250 mg) and formulation 3 (320/500 mg).

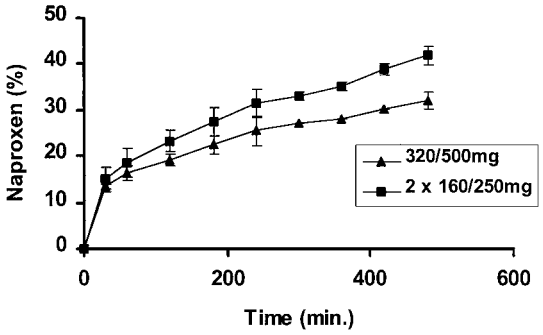

Figure 4. Naproxen released from formulation 3 (320/500 mg) and two tablets from formulation 1 (160/250 mg).

by the rate of water uptake and the diffusion rate of the drug through the swollen gel. Water uptake rate into the matrix is enhanced in the presence of HPMC because of its high hydrophilicity. However, like all swellable polymers, HPMC swells as it absorbs water. The thickness of the gel layer formed varies with the polymer content.

To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order [Eq. (1)], first-order [Eq. (2)], and Higuchi (11) [Eq. (3)] equations:

$$Q = k_0 t \tag{1}$$

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

$$\ln(100 - Q) = \ln 100 - k_1 t \tag{2}$$

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

$$Q = k_2 t^{1/2} \tag{3}$$

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

Table 3 shows the mathematical model applications to the dissolution results.

Plots of percent of dissolved drug versus square root of time shows regions of good linearity. As shown in Table 3, for the applied models, the Higuchi model was the one that best describes the naproxen release from the formulations studied.

CONCLUSIONS

The increase of solid/dissolution medium contact surface causes an increase in pure naproxen dissolution rate. However, for the formulations studied, the 2-fold weight variation in tablets containing the same dose of naproxen did not affect the release rate of the drug. The 2-fold dose variation in tablets containing the same weight did not affect the release rate of naproxen. In addition, the dissolution rate of two tablets of the same formulation and one tablet with a 2-fold dose and weight variation was not significantly different, up to the first 240 min of the assay. Tablet/dissolution medium contact surface does not seem to produce a significant effect on naproxen release from sustained-release dosage forms.

For the applied mathematical models, the Higuchi model was the one that best described the naproxen release from the formulations studied. The square root of

Table 3.

Mathematical Model Applications to the Dissolution Results

	Zero Order		First Order		Higuchi Model	
Formulation	k	R^2	k	R^2	k	R^2
1	0.0626	0.9844	0.0027	0.9253	1.7503	0.9895
2	0.0716	0.9815	0.0028	0.9176	2.0079	0.9927
3	0.0397	0.9677	0.0018	0.9179	1.1240	0.9963

time analysis is consistent with a diffusional mechanism of release. However, matrix dissolution is not considered in the Higuchi model.

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