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CONTROLLED-RELEASE MATRIX TABLETS OF KETOPROFEN

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ABSTRACT

To obtain a prolonged-action dosage form of ketoprofen, 3 different techniques for delaying drug release from hydrophylic matrices of hydroxypropylmethylcellulose were evaluated. They were: the incorporation of glyceryl monostearate, as a release retardant; the partial coating with an impermeable covering of cellulose acetate phthalate; the pan-spray coating with a mixture of insoluble (Eudragit) and soluble (PEG 400) polymers. The in vitro release profiles of each formulation were studied using the USP basket method. Pan-spray coating with the Eudragit-PEG mixture was found to be the best technique, enabling the desired release profile to be obtained through variation of the coating thickness.

INTRODUCTION

Ketoprofen [2-(3-benzoylphenyl)propionic acid], one of the most active non-steroidal antiinflammatory drugs, is employed in the long-term treatment of rheumatoid arthritis and also as an analgesic in the treatment of pain of varying origins (1). Clinical use however requires a dose schedule of 100-200 mg 3-4 times a day, the duration action of a single oral dose being only 6-8 h (2).

Development of a prolonged-action dosage form of ketoprofen will bring about several desirable therapeutic advantages: improvement of patient compliance; minimization of blood level oscillation; reduction of the total amount of drug administered; reduction of incidence of both local and systemic adverse side effects (3).

The aim of this investigation was to create a sustained release dosage form able to provide a constant blood level pattern for up to 12 hours after oral administration of ketoprofen. Three different techniques for delaying drug release from the hydrophilic matrices of hydroxypropylmethyl cellulose were evaluated.

EXPERIMENTAL

Materials - Ketoprofen (SIMS), hydroxypropylmethylcellulose E5 (HPMC, η = 2%, 5 mPa s, Dow Chemical), glyceryl monostearate (Precirol, Gattefossè), Eudragit E 30 D (Rhom Pharma), Polyethylene glycol 400 (PEG 400, Merck) and cellulose acetate phthalate (CAP, Ambrochim) were used directly without any prior purification.

Systems preparation - a) Hydrophylic matrices: hydrophylic matrices were prepared with HPMC as a matrix agent and magnesium stearate as a lubricant, according to the following formula: Ketoprofen mg 110; HPMC mg 488; Mg stearate mg 2. The powders were mixed after the sieving (300 μm) of single components, and

TABLE 1

Properties of the Tablets

Tablet	Weight (mg ± S.D.)	Drug content (mg ± S.D.)	Hardness (Kp)	Thickness (mm ± S.D.)
KET-R	603 ± 3.8	112 ± 1.5	12	6.6 ± 0.08
KET-R A	614 ± 5.7	109 ± 1.6	6	6.5 ± 0.10
KET-R B	649 ± 6.8	111 ± 1.8	9	7.1 ± 0.05
KET-R C	702 ± 7.0	109 ± 2.4	9	7.5 ± 0.02

the rheological properties of the mixture were controlled. The tablets (hereafter called KET-R tablets) were manufactured on a Korsch rotative tabletting machine. The hardness of the tablets was measured on a Schleinigher Mod.2E hardness tester.

b) Hydrophylic matrices containing Precirol: varying amounts of precirol in the following precirol/drug ratios: 1:3 (KET-R A); 1:2 (KET-R B) and 1:1 (KET-R C) were added to the previously described formulation (a). The properties of these tablets are shown in Table 1 (average of 20 measurements).

c) partially-coated tablets: the surface of KET-R cores was 2/3 coated by careful immersion in CAP acetone-saturated solution (KET-R CAP tablets).

d) coated tablets: the surface of KET-R cores was pan-spray-coated with a mixture having the following composition: Eudragit "E30 D" 50%; PEG 400 2%; talc 2%; deionized water 46%. Talc was included as an antiagglomerant agent in order to prevent stickiness during the coating process (4).Tablets with three different polymer film thicknesses (6, 10 and 15 mg of dry lake) were prepared (hereafter

called KET-R 6, 10 and 15 tablets). The hardness of all coated tablets was greater than 25 kp.

All the finished systems prepared were stored for 24 hours at 20° C before the execution of release tests.

Release experiments - The release tests were performed with the USP dissolution method (apparatus I) and utilized 1000 ml of pH 1.2 simulated gastric fluid (USP XXI) or pH 6.8 simulated intestinal fluid (USP XXI) without enzymes, equilibrated to 37° C and stirred with the basket rotating at 50 or 150 rpm. Drug concentrations were assayed by U.V. spectrophotometry at 255 nm. The experiments were continued until 100 % dissolution was achieved. The release data were analysed according to a zero order equation, by plotting the percentage released versus time and calculating the slope and intercept of the line. Each data point is the average of 6 individual determinations. In all cases the standard deviation was less than 9 %.

Core volume diminution measuremements - The diminution in volume of glassy core was measured with a penetrometer (5) calibrated at 0.01 mm with a 0.5 mm diameter pin, determining the position of the glassy/rubbery interface (swelling front) relative to the initial height and diameter of the glassy core. At fixed intervals during the dissolution test the system was withdrawn from the basket and placed under the penetrometer pin in a horizontal or vertical position; then the pin was dipped into the swollen layer until the glassy core was reached (swelling front). The reductions in height and diameter respectively were measured; then the volume diminution of glassy core was calculated, plotted versus time and fitted with a straight-line equation.

RESULTS AND DISCUSSION

The proper dose of Ketoprofen for an optimized zero-order model which obtains the desired drug level pattern to remain in the

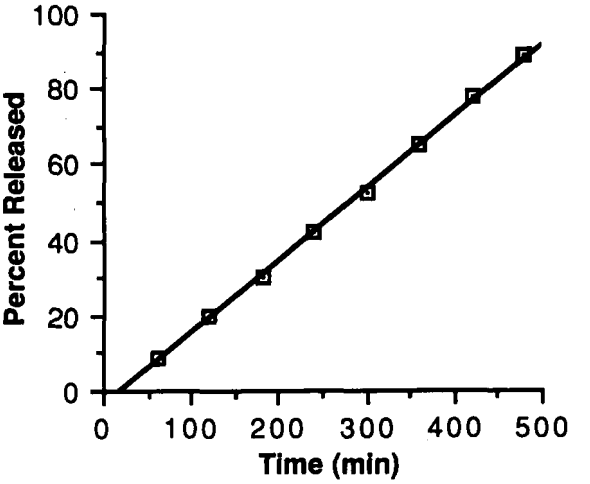

FIGURE 1
Release profile of ketoprofen from tablet KET-R; basket 50 rpm; pH 1.2.

therapeutic range for 12 hours (twice-a-day formulation) was estimated from drug pharmacokinetic parameters (6) by conventional equations (3) on the basis of a one-compartment open model and was found to be 110 mg.

The use of cellulose ethers as retardants in producing matrix-type sustained-release tablets is well documented (7). Hydrophilic matrices of ketoprofen with hydroxypropylmethylcellulose (KET-R) were manufactured by direct compression. That allowed us to optimize the reproducibility of the core substrate avoiding granulation and its related variables (constant characteristics of granulated, residual humidity, etc.)

The release curve of ketoprofen obtained from the KET-R tablet at pH 1.2 and 50 rpm is shown in Fig. 1. The release profile was zero-order linear up to 90% drug content. The equation of the straight line obtained by plotting the percentage released versus time was $y = 0.187 x - 1.997$, $r=0.99$. No burst effect or time lag was present.

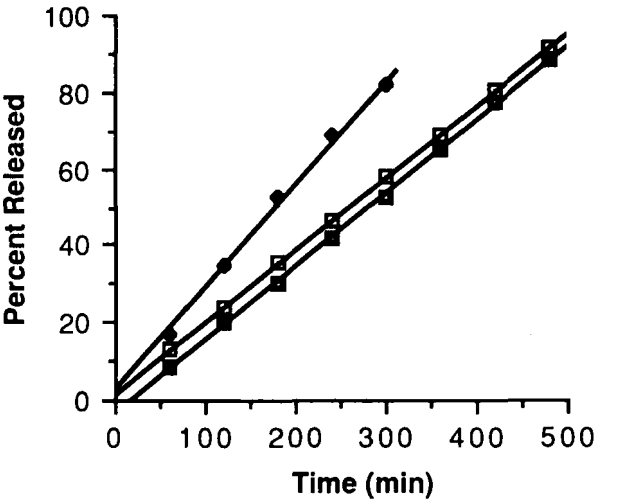

FIGURE 2
Effect of basket rotation rate and of pH on the release profile of ketoprofen from tablets KET-R. Key: ■ 50 rpm, pH 1.2; □ 50 rpm, pH 6.8; ● 150 rpm, pH 1.2.

The effect of basket rotation rate and pH variation on the release profile of ketoprofen from the KET-R tablet is presented in Fig. 2. The release rate of ketoprofen from the system increased with increasing basket rotation rate and changed from 11 % /h at 50 rpm to 16 % /h at 150 rpm, but the profile remained linear up to 80 % drug content.

Moreover the drug release profile at pH 6.8 ($y = 0.189x - 1.091$, $r = 0.99$) was very similar to that at pH 1.2 and thus the ketoprofen release from such a matrix tablet was practically independent of pH. The glassy core volume decrease was linear, as Fig. 3 shows, and the decrease rate was greater at pH 1.2 (20.363 mm^3 /min) than at pH 6.8 (12.985 mm^3 /min), even if it does not influence the drug release rate. Therefore this drug delivery system can be considered favorable to the reservoir system that follows a constant drug release. However, in spite of demonstrated positive characteristics,

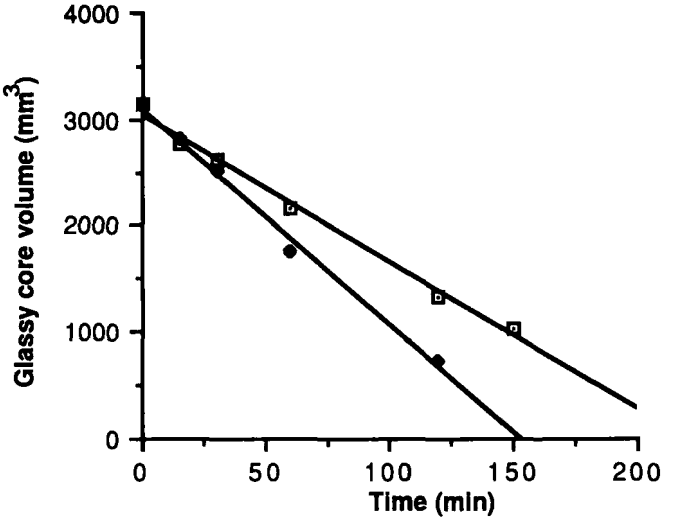

FIGURE 3
Glassy core volume decrease of tablets KET-R versus time. Key: ● pH 1.2; ◘ pH 6.8.

the drug release rate from KET-R tablets was too high for obtaining the desired twice daily formulation. Three different techniques for delaying drug release from these cores were hence evaluated:

a) incorporation of a release retardant like precirol;
b) coating of 2/3 core surface with an impermeable covering by careful immersion in cellulose acetate phthalate (CAP);
c) a new approach based on pan-spray coating with a mixture of insoluble (Eudragit E 30D) and soluble (PEG 400) polymers.

Precirol was successfully used as a retardant in matrix tablet formulations (8). The effect of precirol incorporation into the hydroxypropylmethylcellulose matrix tablets was therefore investigated. Precirol-drug ratios of 1:3, 1:2 and 1:1 were used (tablets KET-R A, B, and C). No significant differences in the volume decrease profiles of glassy cores and in ketoprofen release profiles

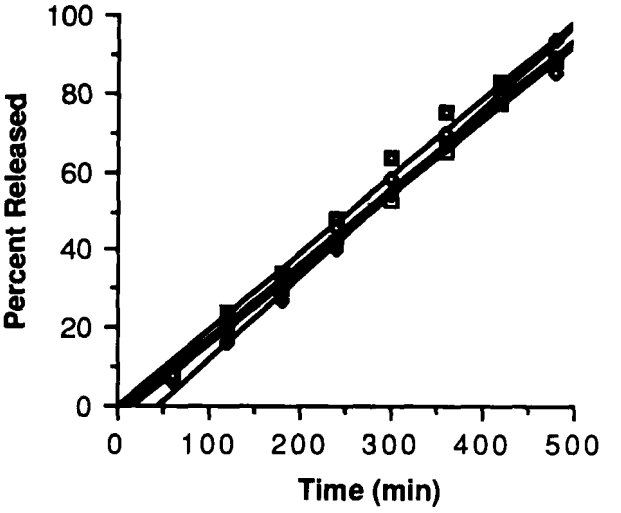

FIGURE 4
Release profile of ketoprofen from tablets containing precirol; 50 rpm; pH 1.2. Key: ▣ tablet KET-R; ◆ tablet KET-R A; ■ tablet KET-R B; ◆ tablet KET-R C.

(Fig.4) in comparison with original core were obtained , even with increased precirol.

In order further to reduce the ketoprofen release rate from matrix tablets, the partial coating of the cores with CAP was assayed. This technique was successfully applied to obtain a programmable zero order drug delivery system (5).

The release profile of ketoprofen from the 2/3 CAP coated core (KET-R CAP tablet) was of zero-order ($y = 0.037 x - 1.263$, $r = 0.99$) and the drug release rate was clearly lower than the original core, as is shown in fig.5. However, the technique of preparation of KET-R CAP tablets was somewhat complex, requiring considerable accuracy in the partial coating phase, and not easily applicable on a vast scale.

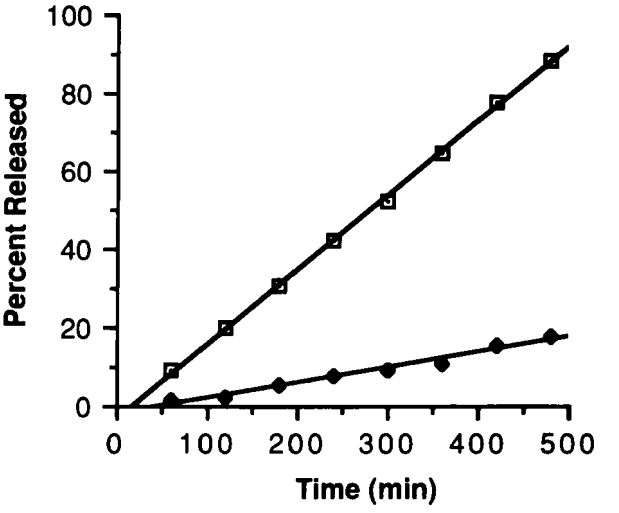

FIGURE 5
Release profile of ketoprofen from tablet 2/3 CAP coated; 50 rpm; pH 1.2. Key: ● tablet KET-R; ◘ tablet KET-R CAP.

In view of the above results a new approach based on core pan-spray coating was experimented. A mixture of Eudragit E 30D and PEG 400 was chosen as coating lake: Eudragit, completely insoluble in water, was the retardant, while hydrophilous PEG 400 , was added in order to form ionophorous pores on the lake layer, thus allowing the drug release rate to be controlled.

Tablets coated with the Eudragit-PEG 400 mixture were made with three different polymer film thicknesses, respectively 6, 10 and 15 mg of dry lake (KET-R 6, 10 and 15 tablets). For these tablets it was not possible to obtain swelling measurements because this was prevented by the lake coating.

The ketoprofen release profiles from these tablets are shown in Fig.6. The release curves were linear (r=0.99) and the release rate appeared to decrease with increasing coating amounts. On the basis of the linear inverse relation found between the drug release rate and the lake amount (Fig.7), the release rate can be varied with

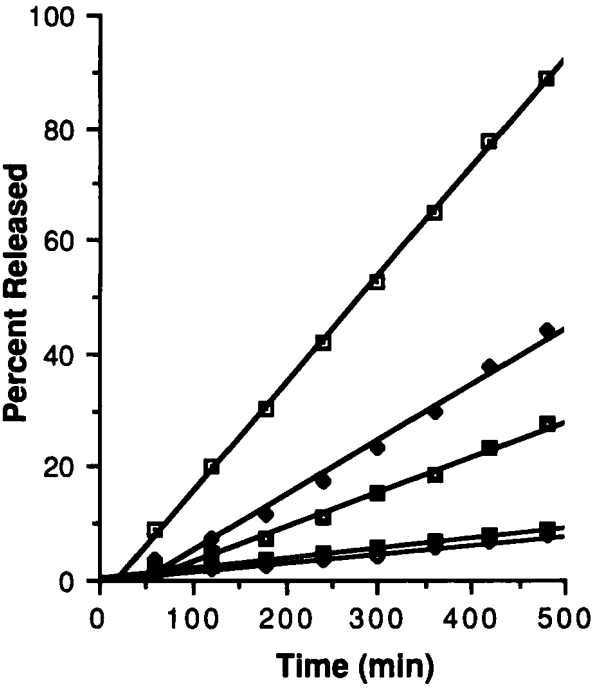

FIGURE 6
Release profile of ketoprofen from Eudragit-PEG 400 coated tablets; 50 rpm; pH 1.2. Key: ▣ tablet KET-R; ● tablet KET-R 6; ■ tablet KET-R 10; ◆ tablet KET-R15; ■ Orudis retard.

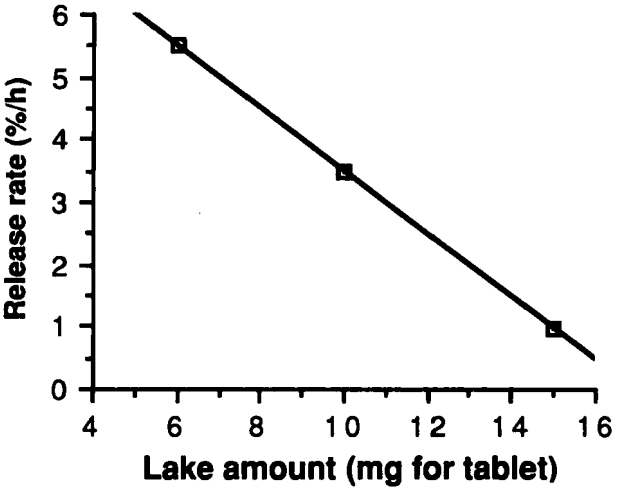

FIGURE 7
Effect of lake amount on the ketoprofen release rate.

predictable effects by varying the coating amount. In particular the KET-R 15 tablet showed a lower rate of drug release than the 2/3 CAP coated tablet (0.96%/h instead of 2.2%/h) and its release profile was similar to that of commercial sustained-release capsules of ketoprofen (Orudis Retard®, 150 mg).

CONCLUSIONS

Of the techniques examined for drug release delaying from hydrophilic matrices of HPMC, only precirol incorporation proved ineffective.

Partial coating with CAP enabled the desired decrease to be obtained, but the technique was rather complex and caused difficulties for industrial production.

Pan coating with a Eudragit-PEG 400 mixture proved the best technique. The relative ease of manufacture and the variety of release profiles attainable make pan coating with a Eudragit E30D-PEG 400 mixture a useful technique for obtaining sustained-release tablets. Further studies will be necessary to assess the Eudragit-PEG 400 ratio influence on ketoprofen release characteristics.

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