DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(13), 1557-1562 (1995)

DISSOLUTION STUDY OF PROLONGED RELEASE MORPHINE TABLETS USING HYDROPHILIC MATRICES

Marín Boscá, M.T., Ismail Salem, I.,
Sánchez Morcillo, J. and Cerezo Galán, A.
Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, E-18071 Granada, Spain.

ABSTRACT

This study presents the results of "in vitro" dissolution of prolonged release morphine tablets using hydroxypropylmethylcellulose. Tablets with four different doses were elaborated and the liberation from these formulated tablets was compared with that of the only commercial pharmaceutical preparation of this type registered in the Spanish Pharmaceutical Market.

The results of the dissolution tests show that the drug was gradually released in all cases and tablets had released from 60 to 90% of its contents after 8 hours.

In the comparative study, the commercial tablets showed the fastest release. In both cases the release rate was lower when artificial intestinal fluids were used as the dissolution medium.

INTRODUCTION

The use of analgesics to treat pain in terminal patients is based on two basic concepts "time dependent" and "increased dose" administration (1,2). Of all the analgesics used the opiates are the most potent and of these morphine is the most effective.

One of the alternatives for optimizing analgesic treatment with morphine is the use of oral prolonged release dosage forms. These permit better fulfilment of the medical objectives, a decrease in the side effects and a smaller amount of the drug is needed for treatment.

During the past two decades, hydrophilic polymers, especially celluloses, have been extremely popular in controlling the release rate of soluble drugs from solid dosage forms. Their ease of compression, ability to accommodate large amounts of the drug and the minimum influence exerted by the processing variables on the release rates are the main reasons for their popularity (3-4).

We thus propose formulating and evaluating tablets of controlled release of morphine hydrochloride using hydrophilic matrices. One of the most important excipients of these

matrices is hydroxypropylmethylcellulose (HPMC) which we use to formulate tablets with 100, 60, 30 and 10 mg of active substance.

These dosages are the same as those present in the only commercial preparation of this type registered in the Spanish Pharmaceutical Market (MST^R continus) and which serves as a reference against which we can compare release kinetics.

MATERIALS

The formulations tested consisted of Morphine HCl (General Management of Pharmacy and Sanitary Products; Narcotic and Psychotropic Control, Madrid, Spain) and different grades of hydroxypropylmethylcellulose (HPMC) (Methocel K-100 and Methocel K-15 M, Dow Chemical Int.). Lactose was used to aid compression and a 8:2 mixture of talc:magnesium stearate was used as a lubricant.

Prolonged release morphine tablets of 60 mg were also used (MST^R continus, 60 mg lot 33 C 2, Asta Medica Laboratories, Madrid, Spain). These tablets (nominated formulation V) are prepared using a matrix system comprising hydrophilic and hydrophobic parts.

Table 1 shows the formula of the tablets elaborated with the four different doses. In all cases the components were blended and the powder mixtures were compressed to prepare 315 mg tablets using the direct compression technique with a tableting machine (Bonals A type MTDM, Barcelona, Spain) with a 10mm diameter punch.

The tablets had the following dimensions: 10 $\pm$ 0.1mm diameter and 4.8 $\pm$ 0.1mm thick.

The hardness level measured by the Stoke's Hardness tester was between 10 and 15kg.

METHODS

Dissolution tests

Dissolution measurements were carried out in a USP dissolution test apparatus with the paddle method, rotated at 75 rpm. In each study, six dosage forms were tested simultaneously, with one dosage form in each position of the dissolution apparatus. The dosage forms were not added until 1000 ml of the dissolution medium had reached 37° C in a water bath. Solvent used was distilled water for the dissolution tests of prepared tablets (formulations I - IV). Simulated gastric and intestinal fluids (USP XXII/NF XVII) without enzymes were used in the comparative study of formulations II and V.

The solubility of morphine HCl is 1g /24ml in distilled water (5). The maximum dose of drug evaluated was 100 mg and the 1000 ml initial volume was always kept constant that sink conditions were maintained in all studies.

Morphine HCl samples (5 ml) were taken over an 8h period and immediately replaced with an equal volume of dissolution medium. Samples were then filtered and analysed spectrophotometrically at 285 nm using a Perkin Elmer Hitachi spectrophotometer.

TABLE 1
Formulations used in the study

Ingredients	Formulations (mg)			
	I	II	III	IV
Morphine HCl	100	60	30	10
Lactose	--	40	70	90
Methocel K-100	100	100	100	100
Methocel K-15	100	100	100	100
Talc	12	12	12	12
Magnesium Stearate	3	3	3	3

Kinetic study of dissolution tests

Despite the great complexity of the process, data of the release of hydrosoluble active principles from hydrophilic matrices are normally interpreted using the Higuchi square root law (6,7), later adapted by Lapidus (8,9).

However the hydrophilic matrix system is constantly changing and the usual linear dependence of the active fraction released on the square root of time is not observed. Consequently we have fitted the release data to zero order, first order and square root kinetics.

RESULTS AND DISCUSSION

The mean experimental values of absorbance obtained in each time showed a percent confidence interval ($p = 0.1$) less than 15%, and these results were converted to amount of drug, m, released at time t.

Drug release profiles of morphine HCl from the four formulations tested in distilled water are shown in figure 1. Points marked represent the means of six separately tested dosage forms. Lactose brings about an increase in the release rate of the drug. When 0%, 12.7%, 22.2% and 28.6% of lactose were incorporated into the formulations, these corresponded to percentages of morphine HCl released of 62.7% , 80.1%, 80.6% and 91.2% respectively.

The increase of the morphine HCl release rate due to the addition of the water soluble diluent lactose to the HPMC matrix could result from the high solubility of lactose and its subsequent effect on the matrix tortuosity factor; as the lactose dissolves it diffuses outwardly and decreases the tortuosity of the diffusion path of morphine HCl. This phenomenon is seen most clearly in formulation IV which has a lactose content of around 28%, the highest of all the formulas.

Figure 2 shows the results of the dissolution tests plotted according to square root kinetic. Linearity for the Higuchi square root was studied for 15 to 80% of the drug released.

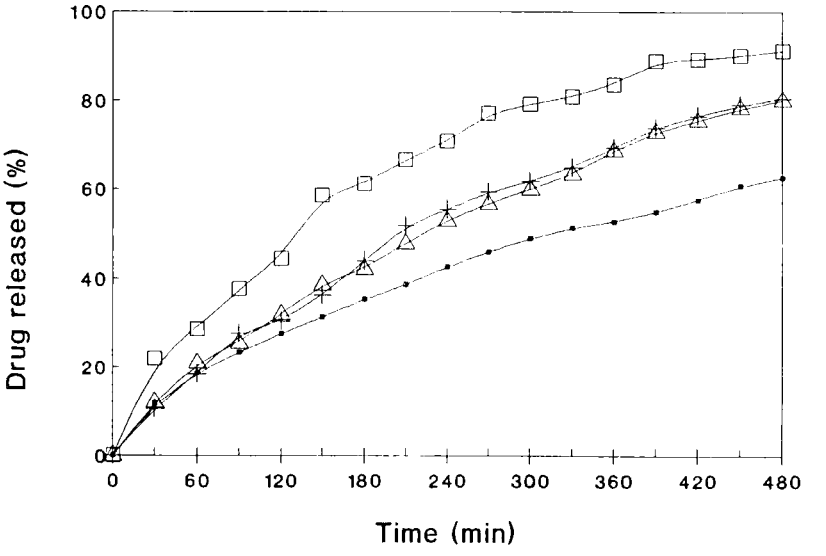

FIGURE 1

Dissolution profiles of morphine HCl from prolonged release tablets.
• : formulation I. △ : formulation II.
+ : formulation III. □ : formulation IV.

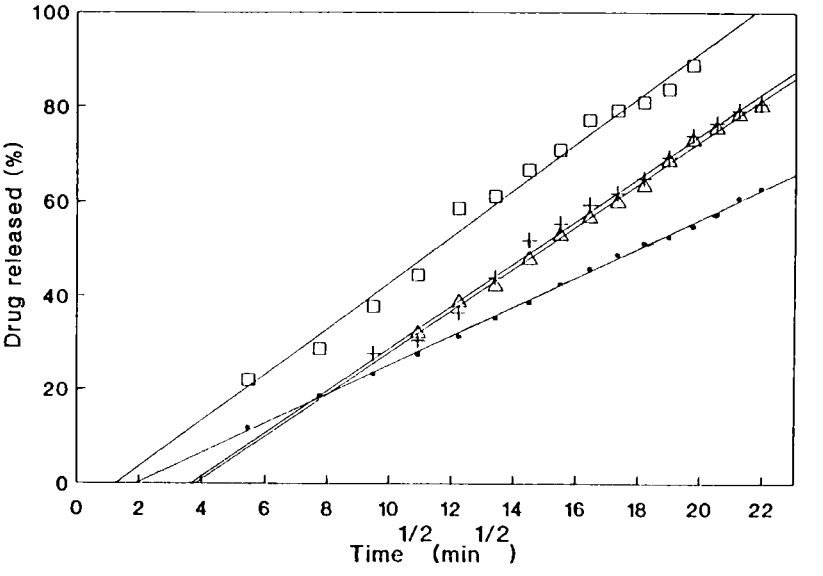

FIGURE 2

Square root plots of formulations I, II, III and IV plotted as amount released (percent) versus the square root of time ($min^{1/2}$). (Symbols as in figure 1).

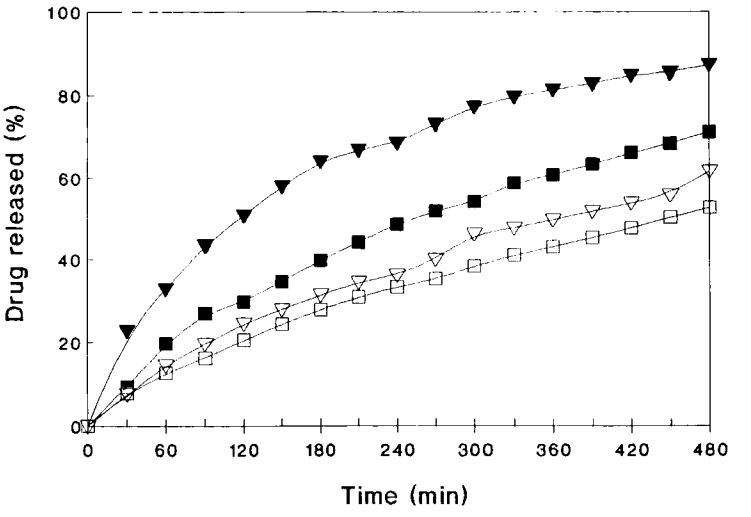

FIGURE 3

Dissolution profiles of morphine from prolonged release tablets (60 mg): influence of dissolution medium.

□ : formulation II pH 7.5; ■ : formulation II pH 1.2
▽ : formulation V pH 7.5; ▼ : formulation V pH 1.2

Lactose is shown to modify the release rate since formula I, without lactose has a different gradient than the other three formulas which contain lactose in different proportions.

The correlation coefficients (r) for the Higuchi's square root were very high (0.9940 to 0.9992) showing a better fit than the first order and zero order equations. The linearity of the relationship and the resulting high correlation suggest that the drug is released according to this kinetic equation within the specified release percentage. Release rate constants determined from slopes of the linear square root plots gave the lowest value for the formulation without lactose (n°.I). The presence of this diluent in the other three formulations, of even greater importance than its effect on increasing the release rate, is how it affects the beginning of the release process, causing a decrease in period of latency (t_0) as the percentage of lactose increases. This is probably due to changes in the matrix structure which in turn lead to modifications in the hydration and swelling of the hydrocolloid.

In the second part of this study we compare the dissolution profiles of the formulation II tablets with those of the commercial preparation , formulation V, both of which contain 60 mg of morphine. Figure 3 shows the dissolution profiles for the two types of tablets. The data in figure 3 clearly shows that release is dependent on pH, with a more rapid

release in the stomach than the intestine. Moreover, release was slower for formulation II than for the commercial preparation (formulation V). In the commercially available sustained release tablets the time for the 50% drug release was 6h at pH 7.5 and 2h at pH 1.2. Corresponding values for formulation II were 7.5 h at pH 7.5 and 4.5 h at pH 1.2.

Nevertheless, a higher release rate could be obtained in alkaline medium and this would be less affected by the changes in pH, adding an organic acid to the hydrophilic matrices and the pH of the matrix (micro-pH) would thus be maintained at a very low value (10,11).

In order to study the release mechanism , the percentage release against time profile was evaluated by the goodness of fit method.

Comparing the correlation coefficients for each formulation, Higuchi's square root equation gives a significantly better fit than either the zero order or first order equations. In both dissolution media the data fit Higuchi's equation better for the hydrophilic matrix (formulation II). This poorer fit of formulation V could be due to a combination matrix consisting of a hydrophilic granular system inserted in a hydrophobic matrix, as shows the preparatory laboratory (Asta Medica Laboratories).

CONCLUSIONS

The results of this investigation let us to state that the hydrophilic matrices are a very interesting way to formulate oral sustained release morphine tablets which fabrication process is easy and does not require special production equipment. There are slight variations between different samples of a same batch and their release kinetics are in accordance with Higuchi square root for matrix tablets.

Finally, from the comparative study with the commercially available preparation, hydrophilic matrices seems to be a good choice for formulation of oral sustained release morphine dosage forms. However, to be sure of, we are currently investigating the in vivo absorbance of these formulations.

REFERENCES

(1) OMS, Ginebra, 1987.
(2) T.D. Walsh and T.S. West, Brist Med. J., 296, 477 (1988).
(3) K.V. Ranga, D.K. Padmalatha and P. Buri, Drug Dev. Ind. Pharm., 14, 2299 (1988).
(4) M.J. Vázquez, B. Perez-Marcos, J.L. Gomez-Amoza, R. Martinez Pacheco, C. Souto and A. Concheiro, Drug Dev. Ind. Pharm., 18, 1355 (1992).
(5) British Pharmacopoeia, Vol. I. Her Majesty's Stationery Office, London, 1988.
(6) W. Higuchi, J. Pharm. Sci., 51, 802 (1962).
(7) T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
(8) H. Lapidus and N.G. Lordi, J. Pharm. Sci., 55, 840 (1966).
(9) H. Lapidus and N.G. Lordi, J. Pharm. Sci., 57, 1292 (1968).
(10) P. Buri and E. Doelker, Pharm. Acta Helv., 55, 189 (1980).
(11) P. Buri, Boll. Chim. Farm., 123, 453 (1984).