

NEW CONTROLLED INERT MATRIX TABLETS OF MORPHINE.

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Introduction

As a continuing part of a FEDER research project (1), in this paper an oral tablet formulation for controlled release of morphine (total dose 60 mg) has been developed.

This new tablet formulation is based on a morphine polymeric complex (2). The complexation process between Eudragit L and morphine hydrochloride has been previously optimized (3). Moreover, a more detailed study over the technological and dissolution behaviour of the selected complex was realized (4).

The objective of the present paper was to develop an oral controlled release morphine tablet based on polymeric complex providing two-step dissolution behaviour. During the first step, an immediate release of 1/3 of the total morphine should be achieved during the first 60 minutes, by means of a diffusional Higuchi kinetic. In the second step, a controlled release kinetic of the remaining dose should be achieved during the following 8 hours.

Material and Methods

The following materials have been used: morphine hydrochloride (Alcaliber, Madrid, Spain); Eudragit® L 30D and Eudragit® RS-PM (Degussa, Barcelona, Spain); sodium hydroxide and lactose (Acofarma, Tarrasa, Spain); sodium chloride, methanol (high performance liquid chromatography [HPLC] grade), and diammonium hydrogen phosphate (Merck, Barcelona, Spain).

The complexation process used has been previously described in a patent (2).

Tablets of 150 mg weight have been obtained using an eccentric machine (*Bonals A-300*, Barcelona, Spain) by direct compression flat-faced punches of 9.0 mm diameter. The components of tablets were homogeneously mixed (5). The compositions of the elaborated formulations are indicated in table 1.

Table 1. Composition of different tablets lots

Lot	% complex	% free M ^(a)	% L ^(b)	% total M ^(a)
A	---	100	---	100
B	100	---	---	40
C	85	---	15	34
D	95	5	---	43
E	90	10	---	46
F	85	15	---	49
G	80	20	---	52
H	70	30	---	58

(a) M: morphine; (b) L: lactose

Quantification of the Morphine

An HPLC method was chosen for quantifying morphine: Hitachi HPLC system manager (Frankfurt, Germany), pump L-7100, manual injector 77251, diode array detector L-7455, interphase D-7000, column Merck Aluspher 100 RP-select B, 5 µm particle size, 12.5 cm × 4 mm inner diameter (ID). A flow rate of 1 mL/min was employed, and the variable wavelength detector was set at 273 nm. The selected mobile phase was methanol / purified water / diammonium phosphate 50:50:0.01 vol/vol/wt. The validation of the chromatographic method, in terms of linearity, precision, and accuracy was described in a previous paper (3).

In Vitro Dissolution Study

The in vitro dissolution study was performed at 37°C ± 0.5°C in the *United States Pharmacopeia (USP)* 26 basket apparatus (model D-6, Turu Grau, Tarrasa, Spain) at a speed of 50 rpm over 8 hours. A pH gradient method has been used. Simulated gastric fluid without enzymes (pH=1.2) was employed as initial dissolution medium (500 mL). After the first hour, a predetermined volume of 1N sodium hydroxide solution was added to the dissolution medium. This operation was repeated from the second hour onwards to achieve the following pH values:

t (h)	0-1	1-2	2-3	3-4	> 4
pH	1.2	1.9	5.8	6.5	7.4

3 mL samples were withdrawn at various time intervals and analyzed using a HPLC method previously described. All the experiences were assayed in triplicate.

The dissolution experimental data of the first 60 min were fitted to Korsmeyer equation (6):

$$Q_t/Q_\infty = K_K \cdot t^n$$

where, Q_t/Q_∞ is the drug-released ratio at different times; K_K , is the Korsmeyer constant; and n , is a parameter that defines the release mechanism. Furthermore, the amodelistic parameter Q_{60} was calculated.

The second step of the profile (60-480 min) was fitted to a linear regression.

Results and Discussion

One of the most important problems presenting the extended-release oral morphine systems is that they do not provide an enough morphine plasma concentration since the first moment of the administration. The ideal delivery system should provide an immediate release of morphine until therapeutic plasma concentrations are reached. After that, the delivery system should maintain a controlled release of drug during a longer time period. Furthermore, a delivery system correctly designed should maintain a fairly consistent level of pain relief, preventing abrupt peaks and valleys of pain (7).

This desired *in vitro* dissolution profile corresponding to the oral morphine system is shown in figure 1. As it was indicated above, the objective of the present research was to reach an immediate release of 1/3 of total morphine in 60 minutes and, after, a controlled release of the remaining dose, showing controlled release kinetic.

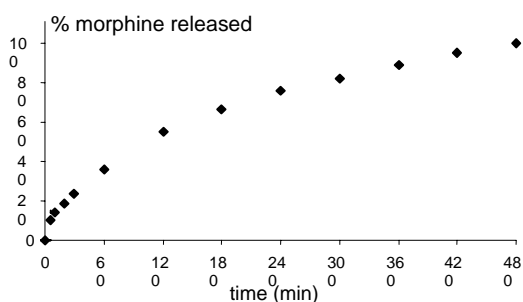


Figure 1. *In vitro* dissolution profile of the proposed morphine system

In a first step, two concrete lots of tablets were elaborated: lots A and B. Their release profiles are shown in figure 2. As it can be seen, none of them is useful: lot A releases drug too fast and the profile of lot B shows an excessive decrease in the dissolution rate; moreover, this formulation does not allow a complete release of the total dose. So, in order to improve the dissolution profile of lot B, 15% of a hydrophilic substance, lactose, is introduced in the formulation. The release profiles of lots B and C are shown in figure 3.

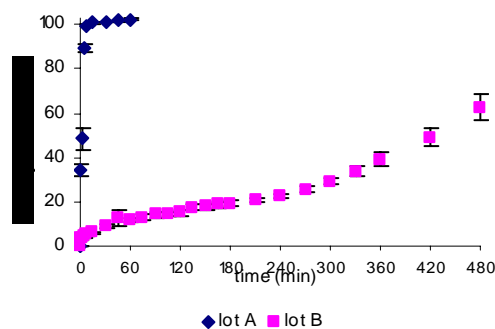


Figure 2. *In vitro* dissolution profiles of lots A and B

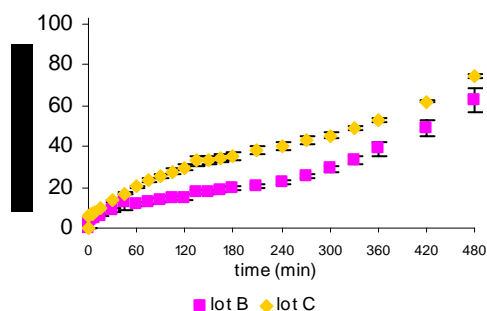


Figure 3. *In vitro* dissolution profiles of lots B and C

The dissolution behaviour of lot C does not offer a release profile similar to the reference system (figure 1). So, binary mixtures of complex and free morphine were produced (see table 1, formulations D-H). The *in vitro* release profiles corresponding to these formulations are shown in figure 4.

A kinetic study was realized in order to characterize the dissolution behaviour of each lot.

Table 2 shows the results corresponding to this kinetic study: the first step (0-60 min) has been studied by means of Korsmeyer equation; the second step (60-480 min) has been fitted to a linear regression.

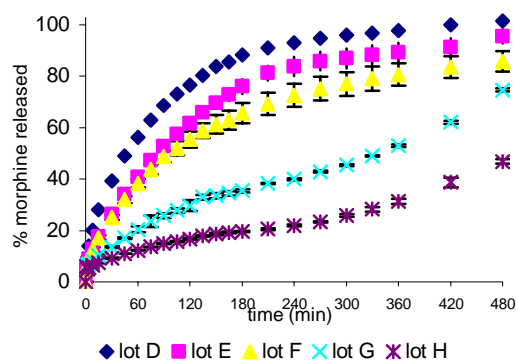


Figure 4. In vitro dissolution profiles of lots D-H

Table 2. Data corresponding to the kinetic study of the indicated tablets lots

Lot	0 – 60 min			60 – 480 min		
	Q ₆₀ (%)	n	r ²	r ²	F	P
D	11.4	0.24	0.950	0.942	226.99	0.5E-09
E	21.7	0.49	0.982	0.955	297.97	0.8E-10
F	37.5	0.53	0.998	0.910	142.30	0.1E-07
G	40.0	0.56	0.997	0.844	75.72	0.5E-06
H	56.3	0.51	0.999	0.815	61.69	0.2E-05

Among the several tested formulations, lot F (15 % of free morphine) present the better release behaviour: both a suitable Q₆₀ as well as an appropriate kinetic fitting in the two phases of the profile.

So, this formulation has been chosen to continue the optimization of the oral controlled release morphine tablet.

The weight of all the tablets elaborated was 150 mg in order to obviate the possible influence of this variable. In these conditions, the proportion of free morphine has ranged from 5 to 30%, so, the total dose of morphine in the several formulations has also ranged (see table 1).

So, in order to finish the design of the controlled release morphine tablet (150 mg), the total dose of morphine was fitted to 60 mg (a therapeutic commercial dose), keeping the proportion of free morphine in 15%. This new formulation is named lot I. Both release profile of this lot I and release profile of the reference system are shown in figure 5.

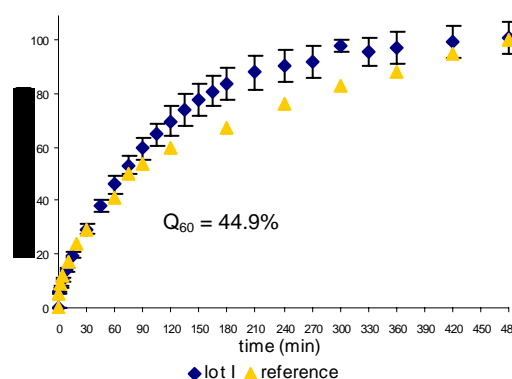


Figure 5. In vitro dissolution profile of lot I and the proposed morphine system (reference)

As it can be seen, both release profiles are similar. However, lot I shows a faster morphine release, considering the total process. So, in order to achieve a more controlled release, the formulation has been reformulated, setting the tablet weight (150 mg), morphine total dose (60 mg) and proportion of free morphine (15%).

To achieve this objective, the proportion of complex in the tablet has been decreased until 62.5%, adding Eudragit® RS-PM to complete the weight of the tablet (150 mg). This new formulation is named lot J. Both release profile of this lot and release profile of the reference system are shown in figure 6. As it can be seen both release profiles are almost superimposed, reaching an immediate release of 1/3 of total morphine (Q₆₀ = 37.7%).

Table 3 shows the data corresponding to the kinetic study of this lot.

Table 3. Data corresponding to the kinetic study of the lot J

Q ₆₀ (%)	0 – 60 min			60 – 480 min		
	n	r ²	r ²	F	P	
37.7	0.54	0.989	0.884	106.4	0.6E-07	

Therefore, on the basis of these results, the objective proposed in this research, to reach an immediate release of 1/3 of total morphine in 60 minutes and, after, a controlled release of the remaining dose, has been achieved with this formulation.

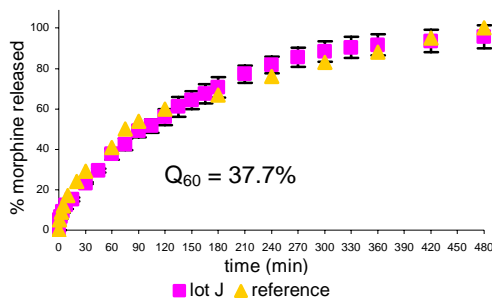


Figure 6. In vitro dissolution profile of lot J and the proposed morphine system (reference)

In order to complete this research, a comparative study between release profiles of lot J and MST[®]continus 60 mg has been realised. Figure 7 shows both release profiles of above indicated systems.

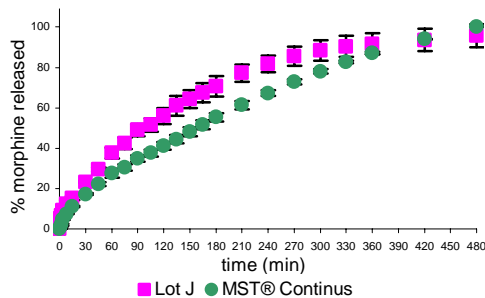


Figure 7. In vitro dissolution profile of lot J and MST[®]continus

Both release profiles are similar. Nevertheless, there is a difference between the values of Q_{60} of the two formulations: of $Q_{60} = 27.6\%$ for MST[®]continus 60, and $Q_{60} = 37.7\%$ for Lot J (60 mg of total morphine).

As a conclusion, the proposed objective has been achieved by means of the assayed formulation. This seems to allow an in vitro release profile similar to MST[®]continus 60 with

an initial faster release during the first 60 minutes.

References

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