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Research paper

Development and in vitro evaluation of a controlled release formulation to produce wide dose interval morphine tablets

M.A. Holgado *, A. Iruin, J. Alvarez-Fuentes, M. Fernández-Arévalo

Departamento de Farmacia y Tecnología Farmacéutica, Universidad de Sevilla, Sevilla, Spain

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ABSTRACT

In this paper, a new pharmaceutical formulation for the administration of morphine has been developed. This system is based on a polymeric complex previously characterized. After the studies performed, it has been selected the following formulation: 62.5% of morphine complex, 15% of free morphine and 22.5% of Eudragit® RS. The morphine formulation proposed has been characterized by means of the study of the influence of several parameters such as pH, ionic strength, mean particle diameter of the components and total morphine dose by means of the tablet dimensions.

This assayed formulation is able to provide a specific in vitro release profile that will be no influenced by possible variations in the GIT conditions. Moreover, this formulation can reproduce the same biopharmaceutical behaviour in an independent manner of the mean diameter particle of the components and the dimension of the tablet produced with several doses inside a wide interval of doses.

1. Introduction

The controlled-release dosage forms often are administered to assure uniform blood concentrations that provides the optimum clinical efficacy and minimises the occurrence of adverse reactions. Controlled-release oral morphine systems offer the clinical advantage of less frequent dosing with an increase in quality of life for patients with chronic pain requiring repeated-dose opioid analgesia. These formulations may also ensure uninterrupted sleep and allows patients to realize their daily activities. This facilitates the adherence and optimizes the pharmacological therapy [1]. Moreover, oral morphine in either immediate release or sustained release form remains the analgesic of choice for moderate or severe cancer pain [2].

One of the first controlled release systems for the oral administration of morphine in the pharmaceutical market was MST Continus®, which is a combination matrix consisting of a hydrophilic granular system inserted in a hydrophobic matrix. Other system named Avinza® contains both immediate release and extended release beads of morphine for once daily oral administration. An important characteristic of this system is that the drug release is independent of the pH of the surrounding GI environment. [1,3].

In previous papers, Eudragit® L30D was used as a carrier to prepare morphine polymeric complexes in order to obtain controlled release systems by a reaction between the drug and the polymer, yielding a chemical drug–polymer interaction. The complexation technique used was patented by University of Seville [4]. In this technique, the acrylic resin is partially diluted and neutralized. The polymer in its sodium salt form reacts with the added drug to obtain a precipitate, the morphine complex. Several preliminary studies were realized over this initial complex. A hydrogen bond interaction was reported between morphine and Eudragit [5]. The in vitro dissolution behaviour was studied. The obtained results indicated that pH was not the only factor influencing the dissolution profiles. Ionic strength was pointed out to be an important influence over the dissolution process [6,7]. Finally, a preclinical study was performed in rats. The results indicated that this complex had a marked analgesic effect from 30 min to 8 h [8].

In further studies, several modifications on the initial preparation technique were performed in order to optimize the elaboration process of complexes [9]. So, critical factors affecting the development of the proposed reaction were established, and parameters such as morphine content (percentage w/w of morphine-HCl in the complex), morphine entrapment (percentage w/w of morphine-HCl incorporated into the complex, with respect to the total amount of drug added to the reaction medium), and weight efficiency (percentage of the total weight of the substances employed [drug plus excipients] that is transformed in complex) were evaluated. These parameters have been described previously [9]. Considering the experimental conditions assayed, the best efficiency complexation was yielded by using Eudragit L 12D 40% neutralized and adding morphine necessary to react with the 54% carboxylic acid/carboxylate groups of the polymer (35% drug

* Corresponding author. Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González no. 2, 41012 Sevilla, Spain. Tel.: +34 954 551624; fax: +34 954 556726.
E-mail address: holgado@us.es (M.A. Holgado).

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excess with respect to the stoichiometric drug amount corresponding to the 40% neutralized groups). This complex was further selected to realize a more detailed study over its rheological and dissolution behaviour [10]. The obtained results indicated that no technological problems in the elaboration of further solid dosage forms will be expected. Moreover, the factor "ionic strength" exerted a great influence over dissolution behaviour of the complex when its values are below physiological conditions.

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 and then, to maintain a controlled release of drug during a determined time period. Furthermore, a delivery system correctly designed would provide a fairly consistent level of pain relief, preventing abrupt peaks and valleys of pain [11]. In this point, only the Avinza® system is able to achieve plateau morphine concentrations within 30 min and to maintain these plasma concentrations throughout 24 h.

So, the first objective of this paper was to develop an oral controlled release morphine tablet based on a polymeric complex able to provide an immediate in vitro release of almost 40% of the total dose, followed by a controlled in vitro release of the remainder dose during at least 8 h. Considering the width range of morphine dose corresponding to the several modified release products in the pharmaceutical market [1], the second objective of this paper was to determine the capability of the designed system and to provide the same in vitro release profile, using the same formulation containing several doses of morphine.

Further in vivo studies will be realized in order to determine the in vivo behaviour of the system in order to characterize plasma levels.

2. Materials and methods

2.1. Materials

The following materials were used: morphine hydrochloride (Alcaliber, Madrid, Spain); Eudragit® L30D and Eudragit® RS-PM (Degussa, Barcelona, Spain); sodium hydroxide and lactose (Acofarma, Tarrasa, Spain); sodium chloride, methanol (high performance liquid chromatography grade) and diammonium hydrogen phosphate (Merck, Barcelona, Spain).

2.2. Preparation of morphine complex

The morphine-Eudragit L complex was elaborated in aqueous medium from morphine hydrochloride saturated solution and Eudragit® L30D (30% w/v). According to previous results [9], the polymer was diluted to 12% w/v and partially neutralized (40%). The amount of morphine hydrochloride added was calculated to react with the 54% carboxylic/carboxylate groups of the polymer (35% drug excess with respect to the stoichiometric drug amount corresponding to the 40% neutralized groups). A white solid was obtained and separated by filtration and dried in an oven (mod. 204, Selecta, Barcelona, Spain). After crushing during 40 s (cutting method, Moulinex, Madrid, Spain), the product was opportunely sieved (Retsch, mod. Vibro, Haan, Germany), selecting 100–250 μm granulometrical fraction to elaborate the morphine tablets.

Table 1
Composition of different tablets batches

Batch	% complex	% free M[a]	% Lactose	% Eudragit RS	% total M[a]	mg total M[a]
A	–	100	–	–	100	150
B	100	–	–	–	40	60
C	85	–	15	–	34	51
D	70	–	30	–	28	42
E	95	5	–	–	43	64.5
F	90	10	–	–	46	69
G	85	15	–	–	49	73.5
H	80	20	–	–	52	78
I	70	30	–	–	58	87
J	85	15	–	–	49	60
K	62.5	15	–	22.5	40	60

[a] M, morphine.

2.3. Preparation of tablets based on the morphine complex

Direct compression tablets of 150 mg weight were obtained using an eccentric machine (*Bonals A-300*, Barcelona, Spain) and flat-faced punches of 9.0 mm diameter [12]. The compositions of the elaborated formulations are indicated in Table 1.

2.4. Technological parameters of tablets

The weight variation was evaluated over 10 tablets using an electronic balance (Mettler, type AE-50, Greifensee, Switzerland). Thickness and diameter were determined using a precision micrometer (Export-Pel, Madrid, Spain) on 10 tablets. Hardness was measured on 10 tablets using a Schleuniger durometer (Mod. 2E/205, Greifensee, Switzerland). Friability was determined on 20 tablets in a friabilometer (Erweka type TAD, Heusenstamm, Germany).

2.5. Quantification of 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 v/v/w. The validation of the chromatographic method, in terms of linearity, precision, and accuracy was described in a previous study [9].

2.6. In vitro dissolution study

The in vitro dissolution study was performed at 37 °C ± 0.5 °C in the United States Pharmacopeia (USP) 29 basket apparatus (model D-6, Turu Grau, Tarrasa, Spain) at a speed of 50 rpm over 8 h. A pH gradient method was used. Simulated gastric fluid without enzymes (pH 1.2) was employed as initial dissolution medium (500 mL). After first hour, a predetermined volume of 1 N sodium hydroxide solution was added to the dissolution medium. This operation was repeated from the second hour onwards to achieve the following pH values: 1.9; 5.8; 6.5 and 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. This methodology was used to select the concrete formulation (named batch K).

In relation to this selected formulation, factors such as pH and ionic strength values of dissolution medium were also evaluated. The influence of these factors on the in vitro dissolution behaviour of the final selected formulation was carried out at three different pH values: 2.2, 6.0 and 8.0, with a constant value of ionic strength (0.005 M). This value is clearly lower than the physiological ionic strength range (0.11–0.14 M) [13]. In relation to ionic strength factor, different values were also evaluated: 0.001, 0.01, 0.1 and 0.5 M.

The influence of the mean diameter particle of morphine complex and Eudragit® RS-PM (Table 2, batches K1-K4) on the in vitro dissolution profiles was also evaluated. The study was carried out in distilled water at an ionic strength value of 0.1 M.

In order to compare and to evaluate the dissolution data of tablets, a mathematical model independent of the dissolution process was used. This model establishes two comparison factors: the difference factor (f_1) and the similarity factor (f_2). These factors are easily calculated and provide a simple measure of similarity between pairs of dissolution profiles but do not provide information on individual batches.

The difference factor (f_1) is the percentage difference between 2 dissolution profiles at each time interval:

$$f_1 = [\Sigma(|\, R_t - T_t\,|)/\Sigma R_t)] \times 100 \quad (1)$$

where R_t indicates the amount of drug released from the reference formulation; and T_t, the amount of drug released from the tested formulation. If the dissolution profiles are superimposed, f_1 reaches a value of 0, whereas the factor value increases when the differences between dissolution profiles also increase.

The similarity factor (f_2) can be calculated using the following expression:

$$f_2 = 50 \times \log\{[1/(1 + (\Sigma(R_t - T_t)2)/n]1/2 \times 100\} \quad (2)$$

where n indicates the number of experimental data.

From a practical point of view, values of f_1 between 0 and 15 and f_2 between 50 and 100 can be considered as superimposed dissolution profiles.

On the other hand, the dissolution experimental data were fitted to Korsmeyer equation [14]:

$$M_t/M_\infty = k_k \cdot t^n \quad (3)$$

where, M_t/M_∞ is the drug released ratio at different times; k_k is the Korsmeyer constant and n is a parameter that defines the release mechanism. Q_{60} was calculated as a amodelistic parameter of dissolution process.

2.7. Study of the versatility of the selected formulation

The purpose of this study is to prove the versatility of the selected formulation for producing tablets with different weights and doses of total morphine able to provide the same dissolution profiles. Tablets were elaborated with the same proportion in components of the selected formulation (see Table 1, batch K). The new tablets containing 60 mg (batch K, 150 mg weight), 120 mg (batch K_5, 300 mg weight) and 200 mg (batch K_6, 500 mg weight) of total morphine, were elaborated using an eccentric machine (*Bonals A-300*, Barcelona, Spain) by direct compression and flat-faced punches of 9.0 mm diameter for batches containing 60 and 120 mg of total morphine and punches of 12 mm for batch containing 200 mg of total morphine. The dissolution study of these batches was carried out in NaCl aqueous solution (0.1 M).

Table 2
Composition of different formulations corresponding to batch K as a function of mean diameter particle

	Complex mean diameter particle (μm)	Eudragit® RS-PM mean diameter particle (μm)
K_1	< 100	< 100
K_2	< 100	100–250
K_3	100–250	< 100
K_4	100–250	100–250

3. Results and discussion

As it was indicated in the introduction section, the objective of the paper was to develop a formulation able to provide an immediate in vitro release of almost 40% of the total dose, followed by a controlled in vitro release of the remainder dose during at least 8 h. This behaviour implies to obtain a theoretical in vitro release profile similar to the one drawn in Fig. 1.

In the first step, it is necessary to characterize two dissolution behaviours of tablets considering as point of reference: batch A containing free morphine and batch B containing polymeric complex. Their release profiles are shown in Fig. 2. As it can be seen and expected, none of them is useful: batch A releases morphine too fast and the profile of batch B shows an excessive decrease in the dissolution rate; moreover, this last formulation does not allow a complete release of the total dose.

So, in order to reach the proposed release profile, it is necessary to add other component to the formulation in order to develop a binary system. In this point, it is convenient to incorporate an aqueous soluble substance that acts as channelling agent to accelerate the dissolution of the polymeric complex. A double strategy can be considered: (I) to add lactose, as economic and accessible diluent, and (II) to incorporate free hydrochloride morphine to assure an immediate release of drug.

In relation of the first strategy, lactose was introduced in formulation B at several proportions: 15 and 30% (batches C and D). Greater amounts of lactose does not allow to obtain tablets with suitable technological parameters. The release profiles of batches C and D are shown in Fig. 3. As it can be seen, the dissolution

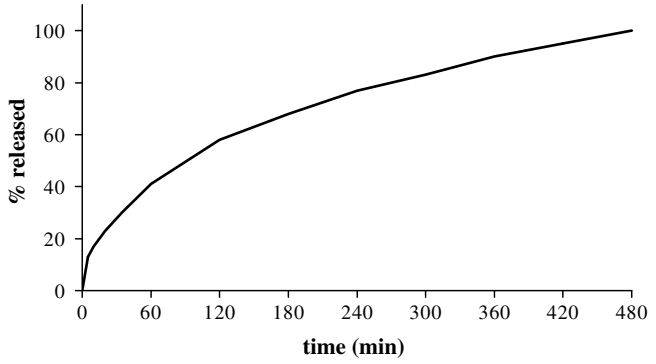

Fig. 1. In vitro dissolution profile corresponding to the proposed oral morphine system (theoretical profile).

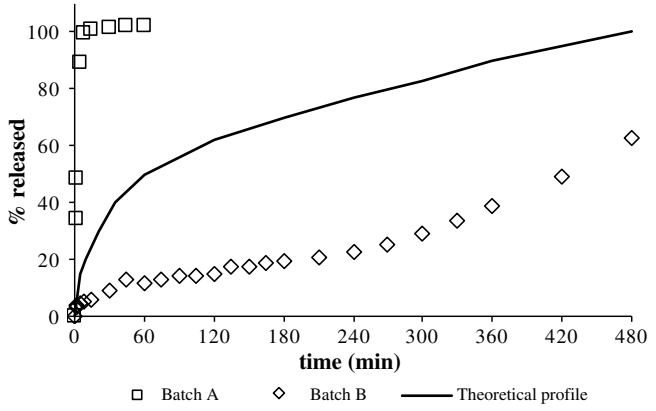

Fig. 2. In vitro dissolution profiles corresponding to batches A, B and the theoretical profile.

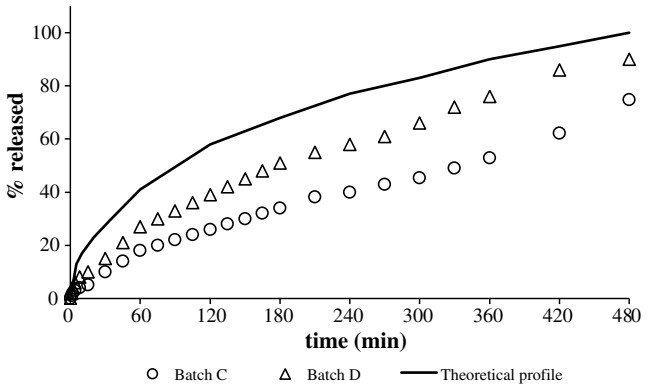

Fig. 3. In vitro dissolution profiles corresponding to batches C, D and the theoretical profile.

behaviour of both batches does not offer release profiles similar to the theoretical profile.

In relation to the second strategy, binary mixtures of complex and free morphine were produced (see Table 1, batches E–I). The in vitro release profiles corresponding to these formulations are shown in Fig. 4. As it can be expected, an increase in the dissolution rate is achieved by increasing the percentage of free morphine. Table 3 shows the obtained results corresponding to the comparison between each batch, from E to I, with the theoretical profile. As a function of f_1 and f_2 obtained values, batches G, H and I are selected to continue with the characterization of the dissolution behaviour of tablets, realizing a more detailed study of their kinetic behaviour. Table 4 shows the results corresponding to the kinetic study of these release profiles.

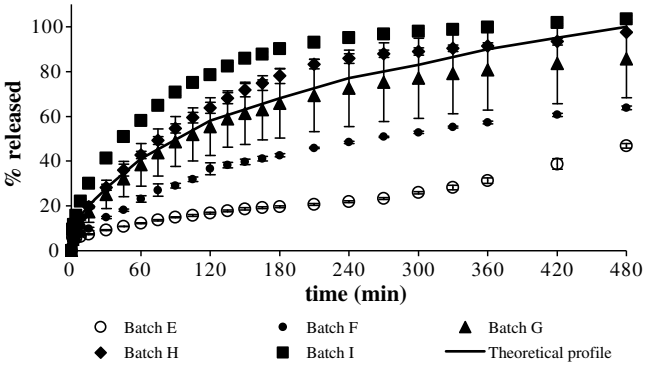

Fig. 4. In vitro dissolution profiles corresponding to batches E, F, G, H, I and the theoretical profile.

Table 3
f_1 and f_2 data corresponding to the indicated batches

	f_1	f_2
Batch E	69.07	18.26
Batch F	42.00	29.51
Batch G	10.16	59.93
Batch H	13.06	53.28
Batch I	19.27	45.30

Table 4
Data corresponding to the kinetic study of the indicated tablets batches

	Q_{60}	n	R^2
Batch G	39.37	0.4925	0.9945
Batch H	41.70	0.4831	0.9921
Batch I	58.13	0.4547	0.9980

As it can be appreciated, batch G exhibits the most adjusted behaviour according to the theoretical profile: almost a 40% of the dose is released during the first hour and its release profile shows the best fitting to a diffusional kinetic.

Nevertheless, this batch G containing 15% of free morphine presents the highest variability in the release profile (see Fig. 4). This circumstance can be due to the fact that in this binary system, the proportion of free morphine is close to the percolation cluster of drug [15]. This means that around this morphine proportion appears an infinite cluster that is able to percolate the tablet, explaining the variability observed in the dissolution profile of this formulation [16,17]. So, the inclusion of a third component in the tablet formulation, changing the binary system to a tertiary system, can obviate the influence of this variability.

On the other hand, the weight of all the tablets elaborated (batches A–I, see Table 1) was 150 mg in order to obviate the possible influence of this variable. In these conditions, the proportion of free morphine was different, so the total dose of morphine in the several formulations was also different (see Table 1). So, in order to finish the design of the controlled release morphine tablet, the total dose of morphine was fitted to 60 mg (a common therapeutic commercial dose) [18], keeping constant the proportion of free morphine in 15% and obtaining tablets with a weight of 122.45 mg. This new formulation is named batch J. Release profiles corresponding to this batch and the theoretical profile are shown in Fig. 5. As it can be seen, both release profiles are similar but the new batch shows a faster morphine release, considering the total process. This is a logical circumstance considering the reduction in weight of these tablets (122.45 mg vs. 150 mg). So, in order to optimize the system release, the formulation has been reformulated, setting the tablet weight (150 mg), the morphine total dose (60 mg) and the proportion of free morphine (15%).

So, to achieve this objective, the proportion of polymeric complex in the tablet has been decreased until 62.5%, adding a new component, Eudragit® RS, to complete the weight of the tablet (150 mg). This new formulation is named batch K (see Table 1). The addition of this component allows to achieve three goals: to decrease the global release rate of morphine, to obtain the initial weight and dimensions of the tablet and to change a binary system in a tertiary system. This last circumstance, as it has been indicated above, would obviate the variability observed in the dissolution behaviour of the system containing a morphine proportion close to the percolation cluster of drug. Fig. 6 shows the release profile of the batch K and the theoretical profile (f_1 and f_2 values and fitting kinetic parameters are also included).

On the basis of the obtained results, batch K is selected as optimized oral morphine formulation because is suitable to achieve the

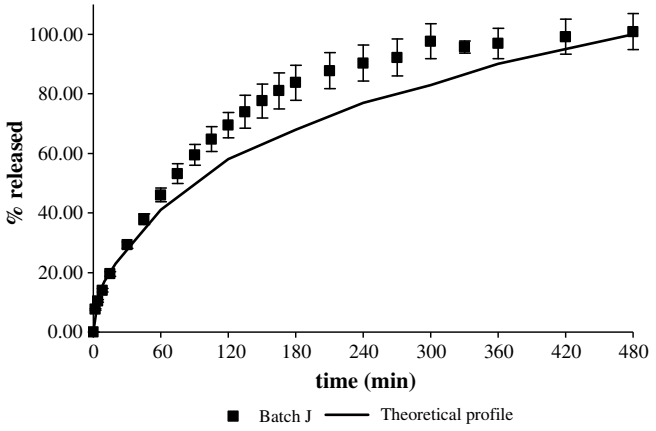

Fig. 5. In vitro dissolution profiles corresponding to batch J and the theoretical profile.

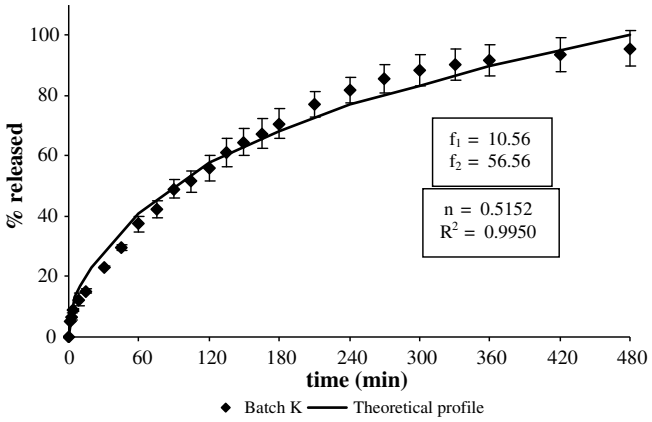

Fig. 6. In vitro dissolution profiles corresponding to batch K and the theoretical profile.

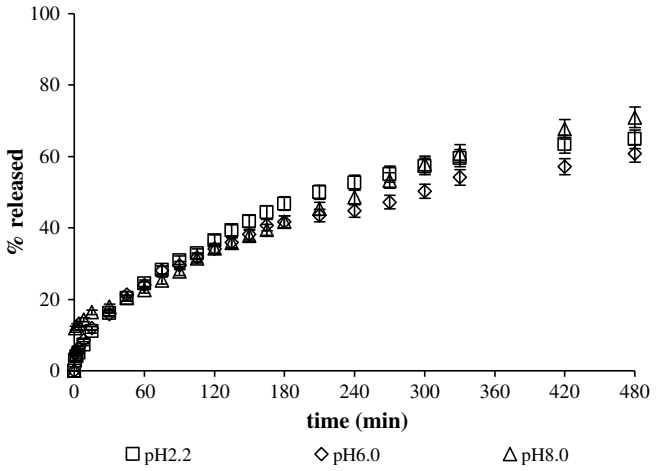

Fig. 7. In vitro dissolution profiles corresponding to batch K at different pH values (ionic strength value of 0.005 M).

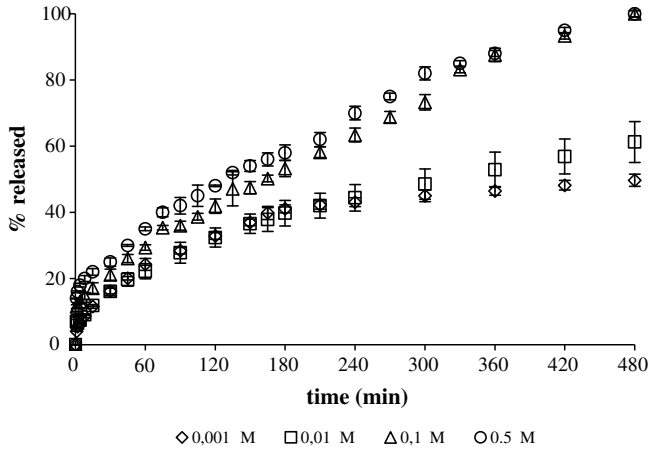

Fig. 8. In vitro dissolution profiles corresponding to batch K at different ionic strength values (pH value of 5).

desired dissolution behaviour. So, a further characterization has been realized in order to know its technological parameters and to evaluate the influence of factors as pH and ionic strength of dissolution medium over its dissolution behaviour.

3.1. Technological parameters of the selected formulation (batch K)

Tablets show a light yellow color, with a smooth and brilliant surface. Technological parameters are summarized as following: weight (mg) 151.38 ± 4.5, height (mm) 2.01 ± 0.003, diameter (mm) 9.07 ± 0.02, hardness (N) 6.92 ± 0.29 and friability (%) 0.7%.

3.2. In vitro dissolution study of the selected formulation (batch K)

3.2.1. Influence of pH dissolution medium

In a previous paper [10], the influence of pH and ionic strength of dissolution medium over the dissolution behaviour of morphine complexes was studied. It was concluded that only ionic strength values clearly lower than physiological range (0.11–0.14 M) can exert an important influence on the dissolution behaviour of complexes. Values higher than this physiological range would produce faster release rates from morphine complexes, without any difference between them. So, to study this influence, an ionic strength value of 0.005 M was selected, in order to appreciate the possible influence of pH. Three values of pH were assayed: 2.2, 6.0 and 8.0 (Fig. 7).

As it can be seen, as the ionic strength is very low, a lower initial release rate is achieved in comparison with the GIT conditions, as well as there is a no complete release process. Moreover, no influence of pH over the dissolution behaviour of tablets has been detected.

3.2.2. Influence of ionic strength dissolution medium

To show the influence of the ionic strength values of dissolution medium, a pH value of 5 was chosen in order to prevent the dissolution of the polymer (Eudragit® L). Four values of ionic strength were assayed: 0.001, 0.01, 0.11 and 0.5 M. The obtained dissolution profiles are shown in Fig. 8.

As it can be seen, the influence of ionic strength is only appreciable at values lower than physiological range (0.11–0.14 M). As pH has been fixed at 5, it has been detected a lower release rate than the one obtained in GIT conditions.

On the basis of the obtained results it can be concluded that the dissolution behaviour of this morphine formulation tablets is solid and independent of the physiological conditions of GIT. So, no changes in the biopharmaceutical behaviour of these tablets are expected by means of possible changes in the GIT conditions.

3.2.3. Influence of mean diameter particle

In order to study this influence, pH and ionic strength values have been fixed. So, as a function of the above-obtained results, pH has been established at 5.0 and ionic strength has been established at 0.0005 M.

Fig. 9 shows the dissolution profiles of the selected formulation as a function of the mean particle diameter of morphine complex and Eudragit® RS-PM (Table 2). As it can be appreciated, all the dissolution profiles are practically coincident. There is a doubt in profile corresponding to batch 4. The statistical study between this batch and batch 3 indicates that there is no difference between them (f_1 = 10.38 and f_2 = 57.05). So, the production process of the tablets can be simplified.

3.3. Study of the versatility of the selected formulation

In order to determine the ability of this selected formulation to achieve the desired biopharmaceutical behaviour in an independent manner of the dose of morphine, several tablets containing different doses (60 (batch K), 120 (batch K_5), 200 (batch K_6) mg of total morphine) have been produced using the selected formulation. This means that tablets with the same proportion of the three components but with very different weights and dimensions have been produced and tested.

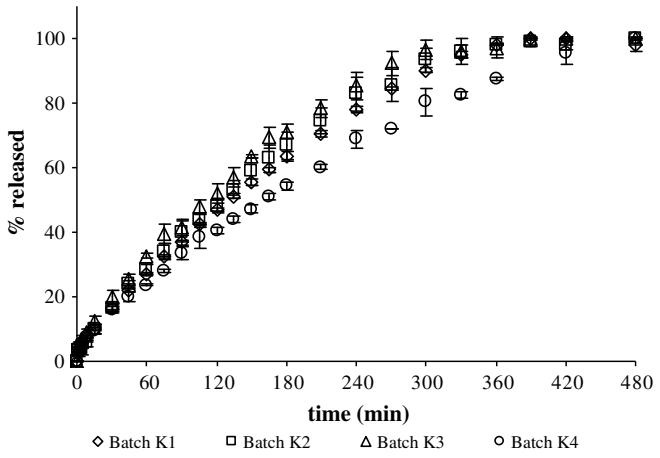

Fig. 9. In vitro dissolution profiles corresponding to batch K as a function of mean particle diameter of morphine complex and Eudragit® RS-PM.

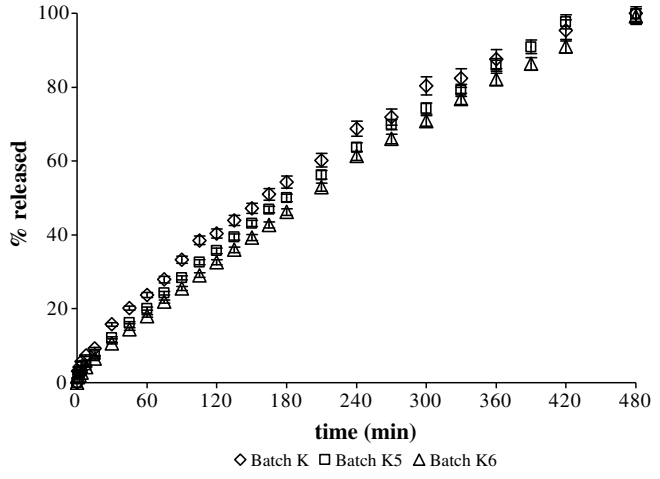

Fig. 10. In vitro dissolution profiles corresponding to batch K (60 mg total morphine), batch K_5 (120 mg total morphine) and batch K_6 (200 mg total morphine).

Following the same criteria of this paper, the conditions of the dissolution profile have been established at pH = 5.0 and ionic strength 0.005 M.

Fig. 10 shows the release profiles obtained. There is no differences between tablets containing 60, 120 and 200 mg of total drug, although the proportions of all the components of the formulation was the same in all the cases.

This is an important conclusion because the proposed formulation (62.5% of morphine complex, 15% of free morphine and 22.5% of Eudragit® RS-PM) allows to obtain tablets with the same dissolution behaviour independently of the system dimensions. This fact would allow to simplify the production process inside the morphine range assayed.

So, considering the in vitro studies realized, it can be assumed that the morphine delivery system developed is able to provide an specific release profile not influenced by possible variations in the GIT conditions. Moreover, this formulation can reproduce the same biopharmaceutical behaviour in an independent manner of the mean diameter particle of the components and the dimension of the tablet produced with several doses inside a wide interval of doses. So, the technological process for the production of this new drug delivery system can be simplified.

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