

In Vitro Evaluation of a Morphine Polymeric Complex: Flowability Behavior and Dissolution Study

Submitted: February 11, 2004; Accepted: June 4, 2004.

Mercedes Fernández-Arévalo,¹ Josefa Alvarez-Fuentes,¹ Ana Iruin,¹ and Maria Angeles Holgado¹

¹Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla.

ABSTRACT

The purpose of this research was to perform a granulometrical and flow properties study of a morphine polymeric complex and determine the influence of 3 variables—particle size of complex, pH value, and ionic strength of the dissolution medium—on the dissolution behavior. The morphine-Eudragit L complex was produced in aqueous medium from morphine hydrochloride saturated solution and Eudragit L 30D diluted until 12% wt/vol and partially neutralized (40%). To determine the rheological behavior of the complex, several rheological tests were developed: bulk and tapped densities, Hausner ratio, angle of repose, and flow rate. The results corresponding to the technological study suggest that the 100- to 250- μm fraction can be considered as free flowing powder. In relation to the dissolution behavior of the complex, the results indicate that the ionic strength has been detected as the most influencing factor when values below physiological conditions are used. In conclusion, no technological problems for the production of further solid dosage forms are expected. Furthermore, no changes in the dissolution profiles of the complex have been detected when ionic strength values are inside the physiological range.

KEYWORDS: morphine-Eudragit complex, rheology, dissolution medium, dissolution medium, pH.

INTRODUCTION

Morphine given regularly by mouth is recommended throughout the world for the management of severe pain in cancer patients when less-effective drugs are no longer adequate. Moreover, 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.¹

Eudragit L 30D 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,

Corresponding Author: Maria Angeles Holgado, Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/ Profesor García González nº 2, 41012 Sevilla, Spain. Tel: 0034 95 551624. Fax: 0034 95 556726. Email: holgado@us.es.

yielding a chemical drug-polymer interaction. The complexation technique used has been patented by University of Seville.² 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.³ The in vitro dissolution behavior was studied.^{4,5} The obtained results^{4,5} indicated that there should be another factor, as well as pH, influencing the dissolution profiles. Finally, a preclinical study was performed in rats. The results indicated that this complex had a marked analgesic effect from 30 minutes to 8 hours.⁶

In further studies, several modifications on the initial preparation technique were performed in order to optimize the elaboration process of complexes.⁷ So, critical factors affecting the development of the proposed reaction were established, and parameters such as morphine content (percentage wt/wt of morphine-HCl in the complex), morphine entrapment (percentage wt/wt 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.⁷ 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 excess with respect to the stoichiometric drug amount corresponding to the 40% neutralized groups). So, this complex has been selected to continue further studies. Considering the previously reported results, in the present work a more detailed study has been performed over this selected complex.

The aim of the present study is as follows: (1) to carry out a granulometrical and flow properties study of the previously indicated complex, and (2) to determine the influence of 3 variables over the dissolution behavior: particle size of complex, pH value, and ionic strength of the dissolution medium. These 2 last factors are particularly important considering that the complex is based on the interaction between Eudragit and morphine by means of hydrogen bonds³ so it can be potentially sensitive to pH and ionic strength variations.

MATERIALS AND METHODS

Materials

The following materials were used: morphine hydrochloride (Alcaliber, Madrid, Spain); Eudragit L 30D (Degussa, Barcelona, Spain); sodium hydroxide (Acofarma, Tarrasa, Spain); McIlvaine's citric acid-phosphate (to obtain several pH values: 2.2, 4.0, 6.0, and 8.0) (Panreac Química, Barcelona, Spain); sodium chloride, methanol (high performance liquid chromatography [HPLC] grade), and diammonium hydrogen phosphate (Merck, Barcelona, Spain).

Preparation of Morphine Complexes

The morphine-Eudragit L complex was elaborated in aqueous medium from morphine hydrochloride saturated solution and Eudragit L 30D (30% wt/vol). According to previous results,⁷ the polymer was diluted to 12% wt/vol 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). The obtained white solid was then separated by filtration and dried in an oven (model 204, Selecta, Barcelona, Spain). After crushing (cutting method, Moulinex, Madrid, Spain), the product was opportunely sieved (model Vibro, Retsch, Haan, Germany).

Particle Size Distribution

In order to determine the size particle distribution of the complex and to select the optimum crushing time, a granulometrical study was developed after several times of pulverization (40, 60, 120, and 180 seconds). A sieve method (Retsch) was used to obtain different powder fractions.

To characterize the size particle distribution of different powders obtained, probit units were calculated as follows:

$$\text{Probit} = \frac{X - \mu}{SD} + 5 \quad (1)$$

where X indicates size particle and μ , mean particle size.

Particle Properties and Bulk Flow

To determine the rheological behavior of the complex, several rheological tests were developed⁸:

- Bulk density (ρ_0): 25 g of powder complex was poured into a glass measuring cylinder (SBS-model Vol-1), measuring the initial volume occupied (V_0).
- Tapped density (ρ_{1250}): the same cylinder with the powder was then automatically tapped 1250 times

(constant volume), measuring the final volume occupied.

- Hausner ratio (HR) and percentage of compressibility (%C): used as dimensionless parameters; these parameters were calculated according to the relation between tapped and bulk densities. The equations used were the following:

$$HR = \frac{\rho_{1250}}{\rho_0} \quad (2)$$

$$\% C = \frac{\rho_{1250} - \rho_0}{\rho_{1250}} \times 100 \quad (3)$$

- Angle of repose ($^\circ$): it has been used as indirect method of quantifying powder flowability; this measurement was performed using 10 g of the powder in study and a funnel described in Real Farmacopea Española.⁸
- Flow rate (g/s): the simplest method of determining powder flowability directly is to measure the rate at which the powder discharges from a funnel; 50 g of the powder in study was added to the funnel described above. The time period for the material to flow through this funnel was determined. Dividing the discharged powder mass by this time yields a flow rate that can be used for quantitative comparison of different powders.

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 μ m particle size, 12.5 cm \times 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 study.⁷

In Vitro Dissolution Study

The in vitro dissolution study was performed at $37^\circ\text{C} \pm 0.5^\circ\text{C}$ in the *United States Pharmacopeia (USP)* 26 basket apparatus (model D-6, Turu Grau, Tarrasa, Spain) at a speed of 50 rpm over 4 hours. Samples of 200 mg of morphine polymeric complex, placed by hand in colorless lock-cap gelatin capsules, were assayed in triplicate, using 700 mL of dissolution medium. At predetermined time intervals, samples were assayed by HPLC.

Table 1. Particle Size Characterization of the Complex After 40 Seconds Crushing*

Size Particle (µm)	% wt/wt	% Accumulated	Probit
< 50	16.6	16.6	4.006
50 - 150	57.9	74.5	5.643
150 - 250	21.8	96.3	6.751
250 - 350	2.6	98.9	7.326
350 - 450	0.8	99.7	
> 450	0.3	100	

* $\mu = 55.12 \mu\text{m}$; $\text{SD} = 61.35 \mu\text{m}$; $r^2 = 0.9950$.

Table 3. Particle Size Characterization of the Complex after 2 minutes of Crushing*

Size Particle (µm)	% wt/wt	% Accumulated	Probit
< 50	23.2	23.2	4.261
50 - 150	60.1	83.3	5.954
150 - 250	12.3	95.6	6.751
250 - 350	1.9	97.5	6.881
350 - 450	1.3	98.2	7.326
> 450	1.2	100	

* $\mu = 30.68 \mu\text{m}$; $\text{SD} = 36.15 \mu\text{m}$; $r^2 = 0.9934$.

Table 2. Particle Size Characterization of the Complex After 1 Minute of Crushing*

Size Particle (µm)	% wt/wt	% Accumulated	Probit
< 50	41.6	41.6	4.798
50 - 150	56.2	97.8	7.054
150 - 250	1.7	99.5	7.326
250 - 350	0.3	99.7	
350 - 450	0.2	99.9	
> 450	0.1	100	

* $\mu = 45.99 \mu\text{m}$; $\text{SD} = 69.35 \mu\text{m}$; $r^2 = 0.9886$.

Table 4. Particle Size Characterization of the Complex after 3 Minutes of Crushing*

Size Particle (µm)	% wt/wt	% Accumulated	Probit
< 50	38.2	38.2	4.695
50 - 150	57.0	95.3	6.645
150 - 250	3.9	99.2	7.326
250 - 350	0.5	99.6	
350 - 450	0.2	99.8	
> 450	0.2	100	

* $\mu = 26.61 \mu\text{m}$; $\text{SD} = 31.70 \mu\text{m}$; $r^2 = 0.9456$.

- 120 seconds: $\mu = 30.68 \mu\text{m}$ ($\text{SD} = 36.15 \mu\text{m}$)
- 180 seconds: $\mu = 28.30 \mu\text{m}$ ($\text{SD} = 24.03 \mu\text{m}$)

To characterize the dissolution behavior of the complex, the influence of 3 variables over the dissolution characteristics (particle size of complexes, pH value, and ionic strength of the dissolution medium) was determined.

Statistical Analyses

Statistical analyses were performed on area under the curve (AUC) values obtained from different dissolution profiles. The differences between groups were analyzed using a Student-Newman-Keuls test following significant main effects of treatment by analysis of variance (ANOVA). Statistical significance was accepted at the 5% level ($P < .05$).

RESULTS AND DISCUSSION

Size Particle Distribution

Tables 1, 2, 3, and 4 show data obtained in relation to size particle distribution for each crushing time. A logarithmic normal distribution was found. The good fitting obtained indicates that this model provides an adequate characterization of the size particle distribution of the complex.

On the other hand, Figure 1 shows the size particle distribution as a function of several crushing times. As can be observed, the quantitative data corresponding to the mean particle size for each crushing time are as follows:

- 40 seconds: $\mu = 54.90 \mu\text{m}$ ($\text{SD} = 71.05 \mu\text{m}$)
- 60 seconds: $\mu = 46.54 \mu\text{m}$ ($\text{SD} = 70.90 \mu\text{m}$)

Powder particle size is a critical factor to take into account when solid dosage forms are elaborated. In this case, the control of this parameter is crucial as the obtained morphine complex will be processed to obtain oral controlled release forms. So, the particle sizes of the powder product may be defined during preformulation studies to avoid problems during production.

Figure 1 shows that after either 40 or 60 seconds of crushing time, the obtained particulate size distribution is similar, being 50 to 150 µm the majority fraction. Over 120 seconds of crushing, the <50 µm fraction increases significantly. This important decrement in the particle size can produce important effects over the technological and biopharmaceutical properties of the product.

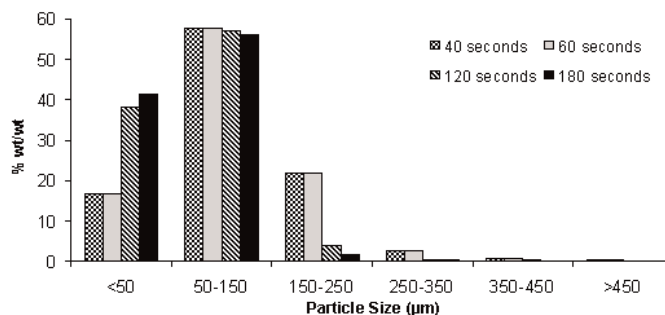


Figure 1. Particle size distribution after several crushing times.

Table 5. Bulk and Tapped Densities (g/mL) for Each Granulometrical Fraction Indicated*

Size Particle	ρ_0 (g/mL)	SD	CV (%)	ρ_{1250} (g/mL)	SD	CV (%)
< 250 μm	0.630	0.003	0.725	0.842	0.005	0.968
100 - 250 μm	0.614	0.007	1.170	0.744	0.009	1.220
< 100 μm	0.583	0.006	1.096	0.782	0.006	0.769

*CV indicates the coefficient of variation.

Table 6. Hausner Ratio, Percentage of Compressibility, Angle of Repose, and Flow Rate (g/s) Corresponding to the Particle Sizes Indicated*

	< 250 μm				100 - 250 μm				< 100 μm			
	%C	HR	$^\circ$	g/s	%C	HR	$^\circ$	g/s	%C	HR	$^\circ$	g/s
Mean	25.17	1.34	21.46	17.61	17.41	1.21	22.17	34.02	25.46	1.34	22.84	14.38
SD	1.12	0.02	4.096	4.44	0.95	0.01	1.26	2.42	0.83	0.02	3.35	0.22
CV (%)	4.46	1.50	19.09	25.18	5.47	1.14	5.70	7.12	3.24	1.12	14.64	4.96

%C indicates percentage of compressibility; HR, Hausner ratio; ($^\circ$), angle of repose; and CV indicates coefficient of variation.

For further studies, 2 granulometrical fractions (<100 μm and 100-250 μm) will be used to produce tablets based on morphine complex, in order to study the influence of mean particle size of the complex over the biopharmaceutical behavior of the tablets.⁹ Figure 2 shows the percentage (wt/wt) of these fractions in the complex powder as a function of crushing time. On the basis of the obtained results, 40 seconds of crushing time was selected because this time provides the highest proportions of these 2 granulometrical fractions. Moreover, this short time allows for (1) reducing the energy consumption during the milling process, and (2) decreasing the exposure of the complex solid to damage situations during the operation (eg, heat, vibration).

Particle Properties and Bulk Flow

The rheological study was performed using the complex powder obtained after 40 seconds of crushing time. The following granulometrical fractions were used: 0 to 250, 0 to 100, and 100 to 250 μm . Table 5 shows bulk and tapped densities data obtained for each granulometrical fraction. The higher differences observed between values of both densities are found in the <100 μm and <250 μm fractions, indicating the presence of bigger interparticular spaces in comparison with the 100 to 250 μm fraction.

HR and %C, angle of repose, and flow rate data obtained are shown in Table 6. According to HR and %C, the better flowability corresponds to 100 to 250 μm fraction. Its %C < 18% (Carr's index) indicates good flow (free flowing powders) and its HR \approx 1.2 shows that this powder has low interparticular frictions.

According to these results, it can be concluded that both granulometrical fractions (<100 μm and 100-250 μm) exhibit adequate rheological properties.

As a function of these results, it can be concluded that for further studies, no rheological problems in the elaboration of the morphine oral delivery systems are expected.

Dissolution Study of the Complex

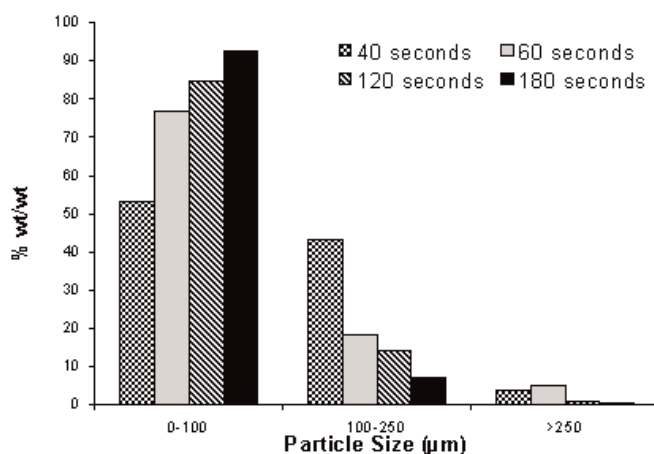
Influence of the Particle Size of the Complex Over the Dissolution Behavior

Purified water as dissolution medium was used. The dissolution profiles obtained as a function of particle size of complexes are showed in Figure 3. In order to compare and to evaluate these dissolution data, a mathematical model independent of the dissolution process was used.¹⁰ This model establishes 2 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:

$$f_1 = [\sum (|R_t - T_t|) / \sum R_t] \times 100 \quad (4)$$

where R_t indicates the released amount of drug of reference formulation; and T_t , the released amount of drug of test formulation.

**Figure 2.** Particle size distribution after several crushing times.

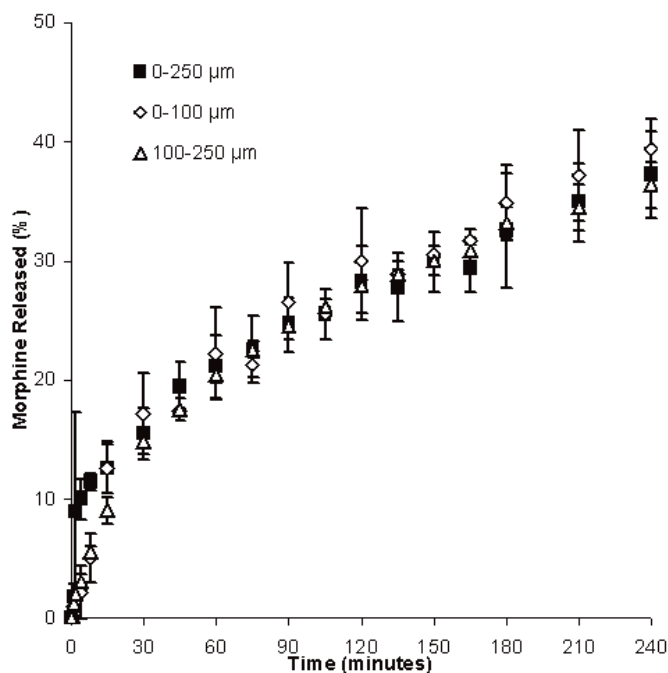


Figure 3. Release profiles of morphine complex as a function of particle size.

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 can be calculated using the following expression:

$$f_2 = 50 \times \log \left\{ \left[1 / \left(1 + \left(\sum (R_i - T_i)^2 \right) / n \right) \right]^{1/2} \times 100 \right\} \quad (5)$$

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.

Table 7 shows the obtained results corresponding to the comparison between the fractions (<250 μm , <100 μm , and <250 μm , 100-250 μm). It can be observed that there are not any differences among the obtained dissolution profiles. So, the dissolution curves can be considered as superimposed. In this sense, the factor “particle size” can be obviated for the following sections.

Influence of the Ionic Strength of the Dissolution Medium

This study was performed with the fraction <250 μm of the complex. A McIlvaine’s citric acid-phosphate buffer solution was used as dissolution medium to fit a pH value of 5.0, so as to obviate any possible interference due to the dissolution of polymer (soluble above pH 5.5). Appropriate dilutions or several amounts of NaCl were added in order to obtain dif-

Table 7. Comparative Study of f_1 and f_2 Values Corresponding to the Particle Sizes Indicated*

Particle Size Fractions	f_1	f_2
<250 μm / <100 μm	11.00	73.61
<250 μm / 100-250 μm	8.28	76.15

*The difference factor is f_1 and the similarity factor is f_2 .

ferent values of ionic strength: 0.001, 0.005, 0.01, 0.05, and 0.2 M. NaCl was used because sodium is reported as the most common ion in the upper gastrointestinal tract (GIT).¹¹

In a previous study,⁵ several in vitro dissolution studies of morphine complex at pH constant values were developed. In that study, the dissolution rate of the complex at pH 1.2 was surprisingly high considering the pH-dependent solubility of Eudragit L. These results would indicate the presence of another factor, different from pH, influencing the dissolution behavior of the complex. Taking into account that the interaction between morphine and Eudragit is by means of hydrogen bonds,³ the ionic strength of the dissolution medium should be considered as an important influencing factor on the dissolution behavior of the morphine complex.

The experimental data were fitted to Korsmeyer Equation¹²:

$$Q_t / Q_\infty = K_K \cdot t^n \quad (6)$$

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.

Figure 4 shows the dissolution profiles obtained as a function of ionic strength of dissolution medium. Table 8 shows the kinetic study data of the same curves. In all cases, a significant and positive effect of ionic strength can be observed. As a function of K_K values obtained, the higher the medium ionic strength is, the higher the drug dissolution rate is. It is

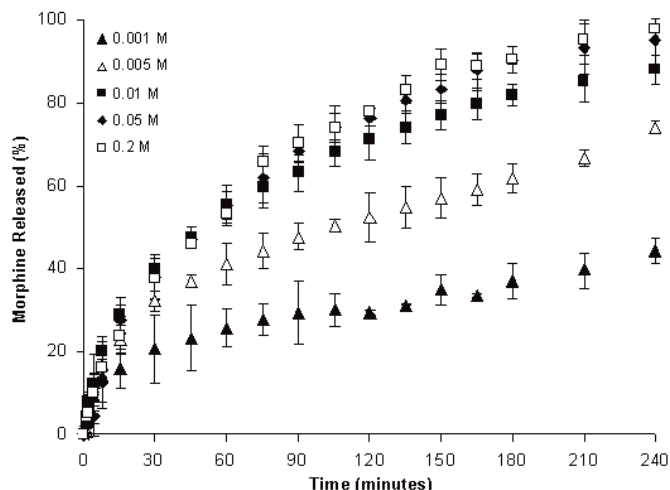


Figure 4. Release profiles of morphine complex as a function of ionic strength.

Table 8. Kinetic Study Data Using the Korsmeyer Equation as a Function of Ionic Strength*

Ionic Strength (M)	<i>n</i>	K_k	r^2
0.001	0.343	0.090	0.998
0.005	0.410	0.108	0.999
0.01	0.412	0.140	0.998
0.05	0.410	0.155	0.993
0.2	0.477	0.112	0.997

*pH = 5.0.

concluded that the factor “ionic strength” exerts a great influence over the dissolution behavior of the complex.

As shown in Figure 4, ionic strength values greater than 0.01 resulted in no significant changes in drug release ($P > .05$). This finding implies that there must be a critical value of ionic strength over which this factor exerts no further effect on morphine release from the complex. Nevertheless, from a biopharmaceutical point of view, it can be concluded that changes of ionic strength within physiological range of GIT (ionic strength range, 0.11-0.14) will not affect the in vivo performance of the morphine complex.^{13,14} Therefore, ionic strength may not be considered as a contributing factor to any indirect food effects, and the polymeric complex can be basically regarded as a system independent of ionic strength under normal physiological conditions.

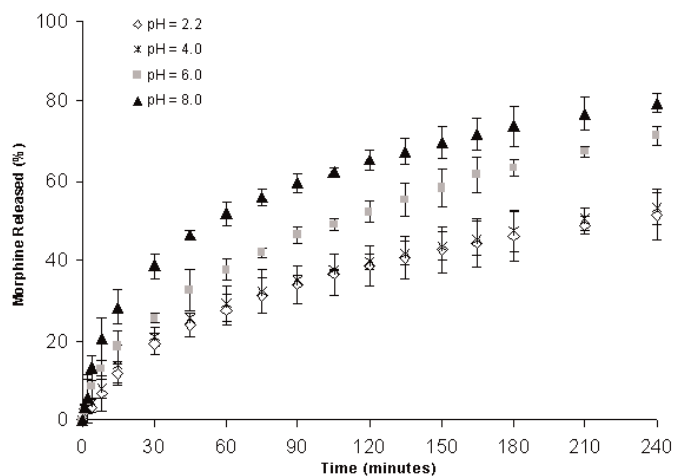
The release exponent *n* at different levels of ionic strength was almost unchanged, which clarified that the ionic strength does not significantly modify the release mechanism of the complex.

Influence of the pH Value of the Dissolution Medium

Several McIlvaine's citric acid-phosphate buffer solutions were used to obtain different pH values (2.2, 4.0, 6.0, and 8.0). In a first step of this study and to obviate the influence of ionic strength, all the dissolution media were fitted to an ionic strength value of 0.005. A fraction of <250 μ m of the complex was used for this study.

Figure 5 shows the dissolution profiles obtained as a function of pH value, and Table 9 shows the kinetic study data of the same curves. As a function of K_k values, over pH > 4, the higher the medium pH value is, the higher the drug dissolution rate is. Significant differences ($P < .05$) were obtained. The post hoc analysis indicated that these profiles belong to 3 homogeneous subsets (pH values 6, 8, and 2.2-4). This situation is caused by the pH-dependent solubility of the polymer (the solubility of Eudragit L 30D begins at pH > 5.5). So, under these ionic strength conditions, below physiological values, there is a clear influence of pH dissolution medium over the release profiles of the complex.

Nevertheless, a complete release of morphine is not reached, even with the highest pH value (pH = 8). This circumstance

**Figure 5.** Release profiles of morphine complex as a function of pH (ionic strength value of 0.005).**Table 9.** Kinetic Study Data Using the Korsmeyer Equation as a Function of pH*

pH	<i>n</i>	K_k	r^2
2.2	0.4727	0.0575	0.9994
4.0	0.4678	0.0607	0.9993
6.0	0.4997	0.0695	0.9980
8.0	0.3890	0.1460	0.9998

*Ionic strength value of 0.005 M.

can be due to the fact that, although Eudragit is a pH-dependent polymer, the concentration of ions (0.005) is far away from the physiological range.¹³ It can be deduced that there must be a minimum ionic strength value to achieve a complete release of morphine from this polymeric complex. Therefore, and taking into account the nature of drug-polymer interaction (based on hydrogen bonds), it should be concluded that the impact of ionic strength on the release behavior of the complex is more important than the pH of the dissolution medium.

In order to realize the study under physiological conditions, in a second step of this study, the same experiments were performed using an ionic strength value of 0.1. Figure 6 and Table 10 show the obtained kinetic study data. As can be seen, a complete release of morphine is reached at the end of the assay, even with the lowest pH value (pH = 2.2). Significant differences ($P < .05$) were obtained. The post hoc analysis indicated that these differences correspond to pH = 8. This circumstance is related to the fact that under physiological ionic strength conditions, the influence of pH appears only at values allowing a high dissolution rate of the polymer. This circumstance indicates again the marked influence of the ionic strength over the release process of this complex, in comparison with the former study.

Under physiological conditions of ionic strength, there is a direct relation between the pH value of the dissolution medium and the release rate of the process.

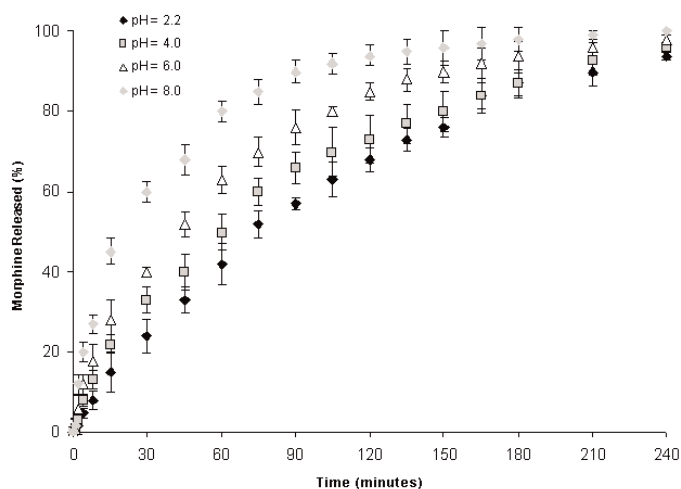


Figure 6. Release profiles of morphine complex as a function of pH (ionic strength value of 0.1).

Table 10. Kinetic Study Data Using the Korsmeyer Equation as a Function of pH*

pH	<i>n</i>	<i>K_k</i>	<i>r</i> ²
2.2	0.4831	0.1092	0.9993
4.0	0.4772	0.1380	0.9987
6.0	0.4881	0.1602	0.9994
8.0	0.4567	0.1924	0.9996

*Ionic strength value of 0.1 M.

CONCLUSION

Therefore, considering the experimental studied conditions, the ionic strength has been identified as the most influencing factor. Moreover, it can be concluded that (1) a complete release of morphine from the complex is achieved under physiological conditions of ionic strength, independent of the pH values, and (2) considering physiological conditions, changes of ionic strength do not imply any modifications of the release profile of drug from the polymeric system.

In conclusion, 40 seconds has been determined to be suitable crushing time in order to obtain 2 concrete granulometrical fractions (<100 μm and 100-250 μm). The fraction 100-250 μm can be considered as free flowing powder. Thus, it can be concluded that no technological problems in the elaboration of further solid dosage forms are expected. In relation to the study of the dissolution behavior of the complex, it has been found that the factor “ionic strength” exerts a great influence over the dissolution behavior of the complex when its values are below physiological conditions.

ACKNOWLEDGEMENTS

The present study is part of a European research project (reference number 1FD97-0624-C04). The polymer Eudragit L 30D is a gift from Degussa (Barcelona, Spain).

REFERENCES

- World Health Organization. *Cancer Pain Relief*. Geneva, Switzerland: WHO; 1986.
- Rabasco AM, Fernández-Arévalo M, Alvarez-Fuentes J, Holgado MA, Caraballo I, inventors. Sistema de liberación controlada de morfina y otros fármacos solubles en agua por complejación con sustancias poliméricas. Spanish patent P9401748. August 1, 1994.
- Alvarez-Fuentes J, Fernández-Arévalo M, Holgado MA, Caraballo I, Llera JM, Rabasco AM. Morphine polymeric coprecipitates for controlled release: elaboration and characterization. *Drug Dev Ind Pharm*. 1994;20:2409-2424.
- Alvarez-Fuentes J, Fernández-Arévalo M, Holgado MA, Caraballo I, Llera JM, Rabasco AM. Characterization of morphine polymeric coprecipitates: a biopharmaceutical study. *Pharmazie*. 1994;49:834-839.
- Alvarez-Fuentes J, Holgado MA, Caraballo I, Fernández-Arévalo M, Rabasco AM. Influence of the pH value of the dissolution medium on the release profiles of a morphine polymeric complex. *Drug Dev Ind Pharm*. 1997;23:553-559.
- Alvarez-Fuentes J, Fernández-Arévalo M, Holgado MA, et al. Preclinical study of a controlled release oral morphine system in rats. *Int J Pharm*. 1996;139:237-241.
- Fernández-Arévalo M, Caraballo I, Millán M, et al. Optimisation of a complexation process as a new method for obtaining a controlled morphine delivery system. *STP Pharma Sci*. 2002;12:334-336.
- Real Farmacopea Española. 2nd ed. Ministerio de Sanidad y Consumo: Madrid, Spain; 2002.
- Iruin A, Alvarez Fuentes J, Holgado MA, Fernández Arévalo M. Influence of particle size of morphine polymeric complex over the release behavior of tablets. Paper presented at: European Conference on Drug Delivery and Pharmaceutical Technology; May 10-12, 2004; Sevilla, Spain.
- Lin Ju H, Liaw SJ. On the assessment of similarity of drug dissolution profiles: a simulation study. *Drug Inf J*. 1997;31:1273-1289.
- Lindhal A, Ungell AL, Knutson L, Lennernas H. Characterization of fluids from the stomach and proximal jejunum in men and women. *Pharm Res*. 1997;14:497-502.
- Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983;15:25-35.
- Bonferoni MC, Rossi S, Ferrari F, Stavik E, Peña-Romero A, Caramella C. Factorial analysis of the influence of dissolution medium on drug release from carrageenan-diltiazem complexes. *AAPS PharmSciTech*. 2000;1(2):E15.
- Mu X, Tobby MJ, Staniforth JN. Influence of physiological variables on the in vitro drug release behavior of a polysaccharide matrix controlled-release system. *Drug Dev Ind Pharm*. 2003;29:19-29.