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RESEARCH PAPER

Influence of the pH Value of the Dissolution Medium on the Release Profiles of a Morphine Polymeric Complex*

J. Alvarez-Fuentes, M. A. Holgado, I. Caraballo, M. Fernández-Arévalo, and A. M. Rabasco

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González s/n, 41012 Seville, Spain

ABSTRACT

The release process from a controlled-release oral system of morphine, prepared using Eudragit® L30D as a carrier, is considered as the result of the combination of two different processes, the final release mechanism being a pH-dependent process. The release mechanism and the influence of the pH value on the dissolution behavior of this morphine complex were studied. An immediate morphine release, without any lag time, is produced in the three dissolution media employed. Considering an initial step of 120 min, the maximum release rate is reached in the assay carried out at pH = 1; above 120 min, the maximum amount of drug released was reached at pH = 7.02.

INTRODUCTION

Controlled-release oral morphine hydrochloride tablets 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. Furthermore, morphine given regularly by mouth is recommended throughout the world for the management of severe pain in cancer when less effective drugs are no longer adequate (1).

In previous works (2–6), several complexes based on Eudragit® L and morphine were elaborated. The maximum efficiency of the reaction was reached with a neutralization degree of 40%; an interaction by means of hydrogen bonds between the polymer and morphine was demonstrated (3–5) using the nuclear magnetic resonance

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(NMR) spectroscopic technique. The in vitro release of morphine–Eudragit L complex using a pH gradient technique was studied, giving a biphasic release process due to the pH-dependent solubility of Eudragit L30 (6,7).

The main objective of the present work was to investigate the influence of the dissolution medium on the dissolution behavior of this controlled-release complex. For this purpose, dissolution media having three different pH values were assayed in order to realize a more exhaustive study about the release mechanism of the morphine–Eudragit L complex.

MATERIALS

The following matrials were used: morphine hydrochloride (Alcaliber S.A., Madrid); Eudragit L30D (Curtex S. A., L'Hospitalet, Barcelona); hydrochloric acid (Panreac, Barcelona); diammonium phosphate (Merck, Darmstadt); sodium hydroxide (Acofarma, Tarrasa, Barcelona); methanol, high-performance liquid chromatography (HPLC) grade (Merck, Darmstadt); buffer solutions of pH = 1 and pH = 7.02 (Panreac, Barcelona), and distilled water (pH = 6.0). All reagents conformed to the European Pharmacopeia.

METHODS

Elaboration and Quantification of Drug in Morphine–Eudragit L Complex

Commercial aqueous suspensions of Eudragit L30D were diluted to obtain 6% w/v. The diluted aqueous suspensions of the polymer were partially neutralized with a 1 M NaOH solution to obtain a neutralization degree of 40%. The amount of NaOH needed to achieve this neutralization degree was calculated as a function of the acidic index of the polymer. A stoichiometric amount of morphine hydrochloride in aqueous solution was then added to the neutralized polymer solution, forming a white solid that was separated by filtration and dried in an oven (Selecta, Mod. 204). After crushing, the final coprecipitate of morphine–Eudragit L was sieved, selecting the powder fraction between 75 and 300 μm. A HPLC procedure was performed to quantify drug content in the morphine–Eudragit L complexes. The HPLC method avoids the interference between the drug and the polymer that occurs when ultraviolet (UV) spectrophotometry is employed. The HPLC system consisted of a constant-flow pump (Kontron Instruments, Type 420), a Rheodyne Type 7125 injector equipped with a 20-μl loop, a variable wavelength detector (Kontron Instruments, Type 432), and an integrator (Konik Instruments, Type DataJet 4600). The column used (E. Merck, Aluspher 100 RP-select B, 5-μm particle size, 12.5 × 4 mm ID) was packed with alumina particles bonded with polybutadiene.

A flow rate of 1 ml/min was employed and the variable wavelength detector was set at 254 nm. Each peak area was computed automatically by the integrator. The elution was carried out in isocratic conditions at room temperature (22° ± 2°C). Morphine hydrochloride standard solutions containing 1000, 800, 400, 200, 100, 50, 25, 12.5, and 6.25 μg/ml were used for calculating the calibration curve. The solutions were analyzed in triplicate.

In Vitro Dissolution Study

The in vitro dissolution behavior of 6 samples of 100 mg of morphine polymeric complex was investigated. The in vitro dissolution study was carried out at 37° ± 0.5°C in the USP XXIII basket apparatus (Turu Grau, Mod. D-6) at a speed of 50 rpm during 8 hr. Three different dissolution media, 700 ml, were employed: pH = 1, pH = 7.02, and distilled water. At predetermined time intervals, samples were assayed by HPLC.

The calibration curves for morphine hydrochloride in these three different media were calculated. The HPLC assay was carried out in the same conditions indicated above.

RESULTS AND DISCUSSION

In previous works (2–6), diverse complexes based on Eudragit L and morphine hydrochloride was elaborated. The polymer is partially neutralized with a 1 M NaOH solution at different neutralization degrees (30–42%). An aqueous morphine solution is then added and a white solid forms that it is separated by filtration. The maximum efficiency of the reaction was reached with a neutralization degree of 40%. The solid thus formed is then characterized by differential scanning calorimetry (DSC) and ^{1}H-NMR, ^{13}C-NMR, and infrared (IR) spectroscopies. Using these analytical techniques, an interaction by means of hydrogen bonds between the polymer and morphine was demonstrated (3–5). So, the morphine interacts with the polar groups of the polymer, giving two possible types of hydrogen bonds (Fig. 1). In both, the reactive groups of the polymer are their carboxylic functions; however, the morphine can interact both with

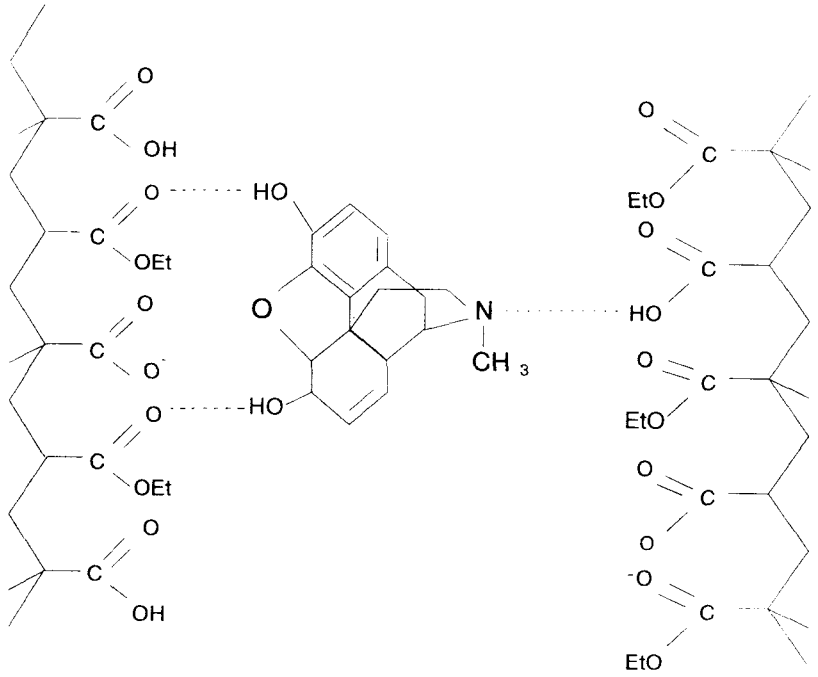

Figure 1. Hydrogen bonds between morphine and Eudragit L.

the hydroxyl groups and with the morphinic nitrogen (4,5).

The dissolution characteristics of the complex were investigated using a pH gradient technique (3,6). A biphasic release process was obtained due to the pH-dependent solubility of Eudragit L (soluble at pH values above 5.5). In the first step of the release process, from 0 to 120 min, the acrylic polymer integrity acts as a control element. The kinetic model that provides the best fit in this phase is the Higuchi model. In the second step, from 120 min to the end of the assay, the polymer, which acts as the physical barrier that controls morphine diffusion, gradually disappears. So, the release of drug is considered to be the result of the combination of two different kinetic processes, giving rise to a multiple release mechanism.

On the other hand, the initial in vivo studies realized using the tail flick test have pointed out that the tested morphine polymeric complex has a pronounced analgesic effect in rats (7). This effect is very clear between 30 min and 8 hr. At 12 hr the effect remains clear but with a lower level of statistical significance. Furthermore, there are no significant differences between the different doses tested. So, by using this test in rats and with this experimental protocol, it can be concluded that the analgesia elicited by the tested morphine polymeric complex seems to be effective from 30 min and for more than 12 hr.

Quantification of Morphine Content in Morphine–Eudragit L Complexes

In order to develop the HPLC method that allows adequate quantification of drug in the complexes, different methanol/water ratios were assayed. The selected mobile phase was methanol:water:diammonium phosphate 50:50:0.1 v/v/w. The statistical parameters of the calibration curve obtained for morphine hydrochloride dissolved in the mobile phase using the HPLC method previously described are shown in Table 1. The detector response is linear from 800 to 6.25 μg/ml. Six samples of the same batch of production were analyzed in triplicate to quantify the morphine content of the complex. The results obtained are given in Table 2. As can be appreciated, the mean morphine content obtained was 40.87% w/w.

In Vitro Dissolution Study

Calibration curves were carried out in the three different dissolution media used for the in vitro studies (pH

Table 1

Calibration Curve: Morphine Hydrochloride in Mobile Phase

	Coeff. of determ.: 0.9998		Estimated constant term.: −1.33E−4		
	Multiple corr. coeff.: 0.9999		Standard err. of estimate.: 5.37E−4		
Source of Variance	*df*	Sum of Squares	Variance	*F*	Prob.
Regression	1	0.033167	0.033167	115045	<0.0001
Residuals	25	7.21E−6	2.88E−7		
Total	26	0.033174			
	Regression coeff.: 5.78E−8		*T*: 339.183		
	Standardized coeff.: 0.9999				
	Standard error: 1.70E−10				
			Prob.: <0.0001		

Table 2

Morphine Content (% w/w) in Morphine–Eudragit L Complex: Statistical Parameters

Morphine Content (% w/w) (n = 3)		Statistical Parameters
Lot 1	43.72	Mean = 40.87%
Lot 2	39.58	
Lot 3	39.63	Standard dev. = 1.7252
Lot 4	39.72	Variance = 2.9764
Lot 5	41.58	Std. error = 0.4454
Lot 6	39.68	Coeff. variation = 4.2212

= 1, pH = 7.02, and distilled water at pH = 6.0). The corresponding parameters are indicated in Tables 3–5. The linearity of the method was investigated between 200 and 6.25 ppm in the three dissolution media. As Tables 3–5 show, adequate results were found.

The release profiles of the morphine–Eudragit L complex in the three different dissolution media employed are shown in Fig. 2. The dissolution profile of morphine hydrochloride is indicated for comparison. As can be seen in this figure, an immediate release of

Table 3

Calibration Curve: Morphine Hydrochloride at pH = 1

	Coeff. of determ.: 0.9998		Estimated constant term.: −3.89E−5		
	Multiple corr. coeff.: 0.9999		Standard err. of estimate.: 4.46E−5		
Source of Variance	*df*	Sum of Squares	Variance	*F*	Prob.
Regression	1	1.16E−4	1.16E−4	58309.3	<0.0001
Residuals	8	1.59E−8	1.99E−9		
Total	9	1.16E−4			
	Regression coeff.: 5.92E−8		*T*: 241.473		
	Standardized coeff.: 0.9999				
	Standard error: 2.45E−10				
			Prob.: <0.0001		

Table 4

Calibration Curve: Morphine Hydrochloride in Distilled Water at pH = 6

Coeff. of determ.: 0.9961 Estimated constant term.: -5.51E-4
Multiple corr. coeff.: 0.9980 Standard err. of estimate.: 9.09E-4

Source of Variance	*df*	Sum of Squares	Variance	*F*	Prob.
Regression	1	0.00468	0.00468	5662.53	<0.0001
Residuals	22	1.82E-5	8.26E-7		
Total	23	0.00470			

Regression coeff.: 5.24E-8 *T*: 75.249
Standardized coeff.: 0.9980
Standard error: 6.96E-10
Prob.: <0.0001

Table 5

Calibration Curve: Morphine Hydrochloride at pH = 7.02

Coeff. of determ.: 0.9977 Estimated constant term.: -0.0014
Multiple corr. coeff.: 0.9989 Standard err. of estimate.: 8.93E-4

Source of Variance	*df*	Sum of Squares	Variance	*F*	Prob.
Regression	1	0.00104	0.00104	1315.22	<0.0001
Residuals	3	2.39E-6	7.97E-7		
Totals	4	0.00105			

Regression coeff.: 6.03E-8 *T*: 36.266
Standardized coeff.: 0.9989
Standard error: 1.66E-9
Prob.: <0.0001

morphine is produced in the three dissolution media employed, without any lag time.

Considering an initial step between 0 and 120 min, the maximum release rate is reached in the assay carried out at pH = 1. The release mechanism in these conditions is probably conditioned by the nature of the interaction between morphine and Eudragit L. As has been indicated previously, this interaction is by means of hydrogen bonds. The high concentration of H^+ ions in these pH conditions would imply the immediate drug release from the surface of the solid in contact with this dissolution medium. Once the external surface of the complex has been exhausted of morphine, the remaining drug is not accessible for the dissolution medium because the polymer is soluble only at pH values above 5.5. For this reason, the release behavior of the morphine–Eudragit L complex tends to acquire a slower release rate from 120 min to the end of the assay. The in vitro release behavior of the complex at pH = 1 indicates that the product allows a fast initial release of morphine in the acidic conditions of the stomach. On the other hand, in the second stage (i.e., from 120 min to the end of the assay), the maximum amount released in the process is reached in the pH = 7.02 dissolution medium. This situation is due to the pH-dependent solubility of polymer: the more basic the conditions of the medium, the higher is the solubility of Eudragit L.

In relation to the release profiles obtained using distilled water as dissolution medium at pH = 6, a slower release rate was obtained. This situation can be related to the influence of the ionic strength. Both the pH = 1 and pH = 7.02 dissolution media have a high content of ions. These ions produce a quite elevated ionic strength. Considering this fact and the release profile obtained for the complex in distilled water, it can be pointed out that the ionic strength of the dissolution

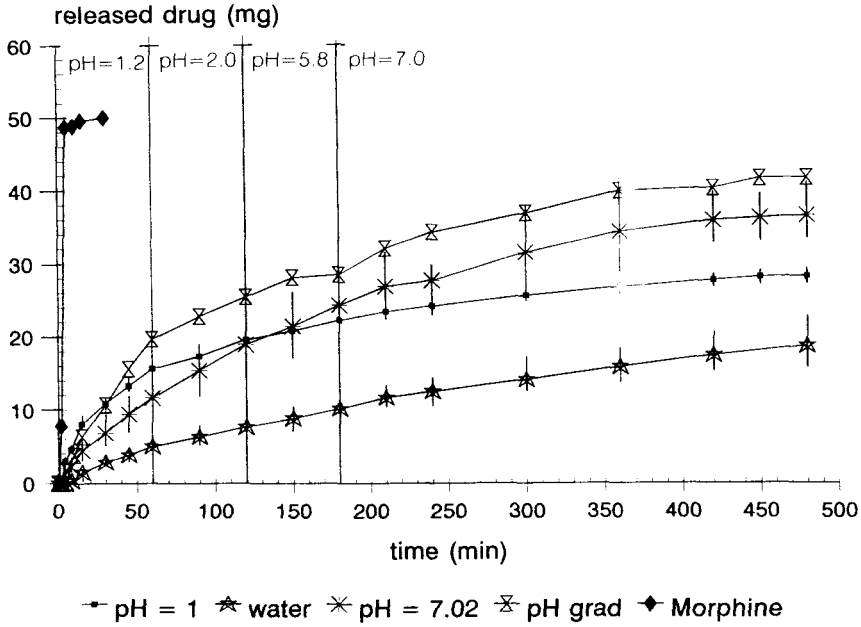

Figure 2. Release profiles of morphine–Eudragit L complex in three different pH dissolution media and by using the pH gradient technique.

medium exerts an important influence on the dissolution behaviors of the morphine complex. This point will be studied in further assays.

If these release profiles obtained at different pH constant values are compared with that obtained using a pH gradient technique, different steps can be observed. In a first stage, from 0 to 120 min (at this last time, a change in the pH from 1.9 to 5.8 is produced), the in vitro behaviors of the complex in both the pH = 1 dissolution medium and artificial gastric medium are rather similar. Nevertheless, there are some differences between the two profiles that can be attributed to the different ionic strength of these media (buffer solution at pH = 1 and artificial gastric medium at pH = 1.2). In the second stage, from 120 min to the end of the dissolution assay, the released morphine amounts increase when the pH value and the ionic strength of the dissolution media are also increased.

So, studying the in vitro profiles of the complex and considering the fact that at pH = 1 the final percentage of morphine released is relatively elevated (≈ 50%), it could be indicated that the polymer does not act as a real protective barrier for the release of morphine.

As a summary, it can be concluded that the polymer Eudragit L used as a support of the complex would act as a modulation agent, allowing a high dissolution efficiency at the end of the dissolution assay but exerting a clear control of the dissolution process and assuring the total release of the morphine in a 8-hr time period.

REFERENCES

1. World Health Organization, *Cancer Pain Relief*, WHO, Geneva, 1986, p.5.
2. J. Alvarez-Fuentes, Estandarización de una técnica de elaboración de complejos de morfina para su liberación controlada: Diseño y evaluación, Tesis de licenciatura, Universidad de Sevilla (1992).
3. I. Caraballo, J. Alvarez-Fuentes, M. A. Holgado, M. Fernández-Arévalo, and A. M. Rabasco, Studies on the formation and kinetic release of morphine polymeric complexes, *Abstracts Book*, I European Congress of Pharmaceutical Sciences, Amsterdam, 1992, p. 71.
4. M. Fernández-Arévalo, M. A. Holgado, J. Alvarez-Fuentes, I. Caraballo, M. T. Vela, and A. M. Rabasco, Water-insoluble complexes of morphine and carteolol-Eudragit® L: A comparative study of the complexation

process, in *Proceedings of the 13th Pharmaceutical Technology Conference*, Strasbourg, 1994, Vol. 3, p. 158.
5. J. Alvarez-Fuentes, M. Fernández-Arévalo, M. A. Holgado, I. Caraballo, J. M. Llera, and A. M. Rabasco, Drug Dev. Ind. Pharm., 20, 2409 (1994).
6. J. Alvarez-Fuentes, M. Fernández-Arévalo, M. A. Holgado, I. Caraballo, J. M. Llera, and A. M. Rabasco, Pharmazie, 49, 834 (1994).
7. J. Alvarez-Fuentes, M. Fernández-Arévalo, M. A. Holgado, I. Caraballo, A. M. Rabasco, J. A. Micó, O. Rojas, and A. Ortega-Alvaro, Biopharmaceutical and preclinical evaluation of a morphine-Eudragit® L complex for controlled release, in *Fourteenth Pharmaceutical Technology Conference*, Barcelona, 1995, Vol. 1a, p. 447.