DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(15), 2409-2424 (1994)

MORPHINE POLYMERIC COPRECIPITATES FOR CONTROLLED RELEASE: ELABORATION AND CHARACTERIZATION[1]

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

Departamento de Farmacia y Tecnología Farmacéutica
***Departamento de Química Orgánica y Farmacéutica**
Facultad de Farmacia. Universidad de Sevilla. España.

ABSTRACT

Coprecipitates of morphine were prepared by using Eudragit[R] L30D as a carrier in order to obtain controlled release dosage systems. Differential Scanning Calorimetry and IR, ^{1}H- and ^{13}C-NMR spectroscopies were applied in order to explain the mechanism of this interaction. The results obtained indicated that there was an intermolecular association between the polymer and the drug consisting in two different hydrogen bonds interactions. The proposed reaction involves coprecipitates having morphine contents greater than 50 %.

---

[1] The present paper is part of a research project (nr. PM90-0151) developed with a grant from the "Dirección General de Investigación Científica y Técnica (DGICYT)" of the Ministry of Education and Science of Spain. It has been presented in part at the 1st European Congress of Pharmaceutical Sciences; Amsterdam, October 7-9, 1992.

INTRODUCTION

Controlled release oral morphine hydrochloride compressed 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 (1). The aim of this work was to prepare controlled-release coprecipitates of morphine with acrylic polymers, by introducing the drug in the polymeric structure. According to the bibliographical revision performed, no interaction process between morphine and any carrier have been found. Nevertheless, some investigations in this field have been made using drugs as amitriptiline (2), *p*-aminosalycilic acid (3) or dipiridamol (4). Interaction nature resulting from those reactions was not properly established.

The used drug is morphine, which is an organic base that shows a quick but incomplete absorption from the gastro-intestinal tract (5). However, its first-pass metabolism reduces its bioavailability (1, 6). Eudragit^R L30D is an anionic copolymer based on polymethacrylic acid and ethylacrylate (1:1). Its solubility is dependent on pH value, being Eudragit^R L30D soluble above pH 5.5 (7). It has been extensively used by us in the field of the controlled release of drugs (8 - 11).

EXPERIMENTAL

Materials

The following products have been used: Morphine hydrochloride (Alcaliber S.A., Madrid); Eudragit^R L30D (Curtex S.A., L'Hospitalet, Barcelona); sodium hydroxide (Acofarma, Tarrasa, Barcelona); hydrochloric acid (Panreac, Barcelona). All reagents conformed to the European Pharmacopeia.

Preparation of coprecipitates

Coprecipitates were prepared following a technique proposed by ORBÄN *et al.* (12 - 15) and modified by us. Commercial aqueous suspensions of Eudragit^R L30D were diluted to obtain Eudragit L6D. Aqueous solutions of NaOH at several concentrations were added with shaking to the polymer suspensions to obtain neutralized resin (Eudragit L-Na) at 30 % of neutralization, having a pH value between 6 and 7. The amount of

NaOH needed to achieve this neutralization degree was calculated as a function of the acidic index of the polymer (315 mg KOH / g Eudragit® L). After 24 hours in repose, stoichiometric amounts at different concentrations of morphine-HCl in aqueous solutions were added with shaking to the former solutions. The shaking was maintained for 30 minutes. All the process was carried out at room temperature. The formed precipitates were separated by filtration and dried in a oven (Selecta, mod. 204) at 35 - 40 °C for two days. The resulting products were pulverized and washed with purified water. The solids were separated and dried in the same conditions as described above. After crushing, the final coprecipitates of Eudragit L-morphine were sieved, selecting the powder fraction between 75 - 300 μm.

The different lots of the coprecipitates are summarized in table 1.

As it is shown, we have studied the influence of two variables over the reaction process: concentration of the morphine-HCl aqueous solutions and normality of NaOH solutions. Each lot was prepared, at least, in triplicate.

Quantification of the morphine content

A high performance liquid chromatography method is described for the quantification of morphine hydrochloride content in the coprecipitates. The HPLC system consisted of a constant-flow pump (Kontron Instruments, type 420), a rotatory valve injector (Rheodyne type 7125) equipped with a 20 μL loop, a variable wavelength detector (Kontron Instruments, type 432) and an integrator (Konik Instruments, type Data Jet 4600). The column used (Merck, LiChrospher 100 RP-18, 5 μm particle size, 12.5 cm x 4 mm ID) was packed with silica particles bonded with octadecylsilane.

A flow rate of 1 mL / min for the mobile phase (methanol : water : di-ammonium hydrogenphosphate, 70 : 30 : 0.20; pH was adjusted with HCl to 7.5) was employed and the variable wavelength detector was set at 254 nm and 0.5 AUFS. Stock solutions were prepared by dissolving 100 mg of morphine hydrochloride in 100 mL of purified water. The standard solutions were obtained by diluting the stock solution with water to the following concentrations: 600, 400, 200, 100 and 50 ppm. Separation were carried out isocratically at room temperature (22 $\pm$ 2 °C) and quantification was carried out by

TABLE 1

Conditions of the coprecipitates elaboration.

(N.D. = Neutralization Degree; MH = Morphine hydrochloride)

N.D.	NaOH MH	155 mL	160 mL	165 mL	170 mL	175 mL
30 %	4.50 g MH	Lot 1 100 mL MH 4.5 %	Lot 2 10 mL NaOH 0.5 N 100 mL MH 4.5%		Lot 3 20 mL NaOH 0.25 N 100 mL MH 4.5%	
	0.20 g NaOH	5 mL NaOH 1.01 N		Lot 4 5 mL NaOH 1.01 N 110 mL MH 4.1%		Lot 5 5 mL NaOH 1.01 N 120 mL MH 3.75%

comparison of the areas of peaks obtained from test solutions with the area of the peak obtained from standard morphine hydrochloride solutions.

Physico-chemical determination of the interaction

Thermal analysis was performed on Eudragit® L30D, morphine hydrochloride, Eudragit L-Na, Eudragit L-morphine coprecipitates and physical drug-polymer mixtures, using an automatic thermal analyzer system (Mettler FP80 HT Central Processor and FP85 TA Cell). The data processing system Mettler FP89HT was connected to the thermal analyzer. Sealed and holed aluminum pans were used for the experience for all the samples. Temperature calibrations were made using indium as a standard. An empty pan, sealed in the same way as the sample, was used as reference. All samples were run at a scanning rate of 10 °C/min, from 30 to 320 °C. This study tries to determine the influence of different processes on the glass transition temperature of the polymer (T_g), as the neutralization of the resin and the inclusion of the drug in its structure.

The IR spectra of the samples were obtained using a IR spectrophotometer (Bomen-Michelson), employing KBr disks. The NMR spectra of the samples were recorded using a Bruker 200-AC type spectrometer employing DMSO-d6 as solvent.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry

The thermograms corresponding to the different samples assayed are shown in figure 1. Morphine hydrochloride and the polymer were weighed in a 1:1 ratio (16) and then mixed by light trituration in a mortar. The physical mixture (fig. 1b) exhibits endothermic peaks corresponding to the initial substances (fig. 1d and 1e for Eudragit^R L30D and morphine hydrochloride, respectively), indicating that the drug is in its crystalline form without suffering any degradation. In the thermogram of the coprecipitate (fig. 1a) the characteristic peak of morphine hydrochloride disappears (vid. fig. 1e), indicating that the coprecipitate has different physico-chemical properties in comparison with the physical mixture of drug and polymer (fig. 1b). So, there are some interactions between the initial substances (17). The nature of these interactions can not be known by studying the resultant thermograms.

The amorphous polymers show a typical change in their structures corresponding to a temperature known as glass transition temperature (18). It represents a change in the polymer from a brittle state (glassy state) to a less brittle one (rubbery state) and is regarded as second-order transition because it reflects changes in secondary thermodynamic properties such as expansion coefficients and heat capacity. The changes in this temperature are exhibited in figure 1. As it is shown, the thermogram of the polymer neutralized (1c) and the corresponding to the coprecipitate (1a) are different from that of Eudragit^R L30D (1d). The polymer neutralized exhibits an increase in its glass transition temperature (87 °C) with regard to that found for Eudragit^R L30D (75 °C) (19), but its melting point is reduced from 215 °C to 194 °C. On the other hand, it can be appreciated that the incorporation of morphine (vid. fig. 1a) unaffects significantly the glass transition temperature of the neutralized polymer (vid. fig. 1c). The modification in T_g of a polymer is dependent on the interaction degree between this compound and the

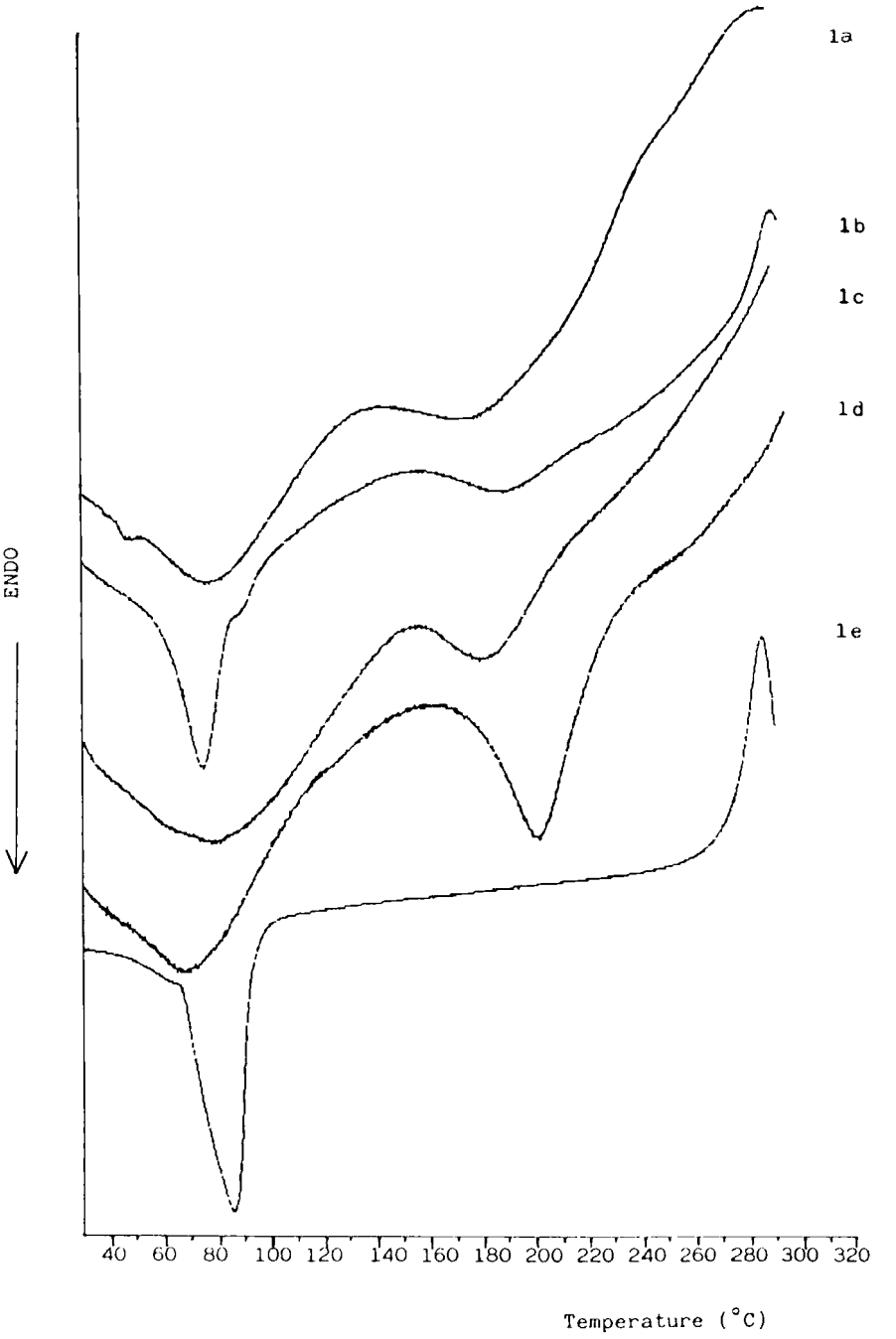

FIGURE 1
DSC thermograms corresponding to:
1a: Eudragit-morphine coprecipitate corresponding to lot 1
1b: physical mixture (1:1) of the raw substances
1c: Eudragit L-Na 30%
1d: Eudragit® L30D
1e: morphine hydrochloride

drug (20). An increase in this temperature is substantially associated with a high interaction, as this means a fall in the polymer chains mobility. On the other hand, the mere physical presence of the drug molecules between adjacent polymer chains could exert an opposite effect, and an increase in the segmental mobility and free volume of the resin is found. So, it can be appreciated a fall in T_g because of this plasticizing action. Therefore, it can be concluded that the interaction degree between morphine and Eudragit L-Na is enough to balance these two opposing phenomena, with the result that T_g remains essentially unchanged.

IR Spectroscopy

Figure 2 shows the IR spectra of the copolymer Eudragit L-Na and the coprecipitate Eudragit L-morphine. The differences between both spectra correspond to the peaks at 1650, 1630, 963 and 948 cm^{-1}, indicating the presence of double C=C bonds in the last product, because of the presence of morphine in the structure of the coprecipitate. This technique is not relevant to identify the interaction nature in the obtained coprecipitates and only shows the presence of morphine in the final product.

NMR Spectroscopy

In order to assess what kind of interaction binds morphine and Eudragit L-Na copolymer, a spectroscopic study of the coprecipitates by ^{1}H-NMR and ^{13}C-NMR was carried out. The comparative study of the NMR-spectrum of coprecipitate Eudragit L-morphine with those of each separated components suggests that morphine is present in the polymer as free base and not in the ammonium salt form, as stated by LEE *et al.* (21) and HOLGADO (22) for similar compounds of Eudragit L-Na and propranolol and carteolol, respectively.

^{1}H-NMR Spectroscopy

Figure 3 shows ^{1}H-NMR spectra taken in DMSO-d6 solution for morphine (3a), morphine hydrochloride (3b), the coprecipitate Eudragit L-morphine (3c) and the methacrylic acid copolymer Eudragit L-Na (3d). Spectra were assigned by 2D-COSY

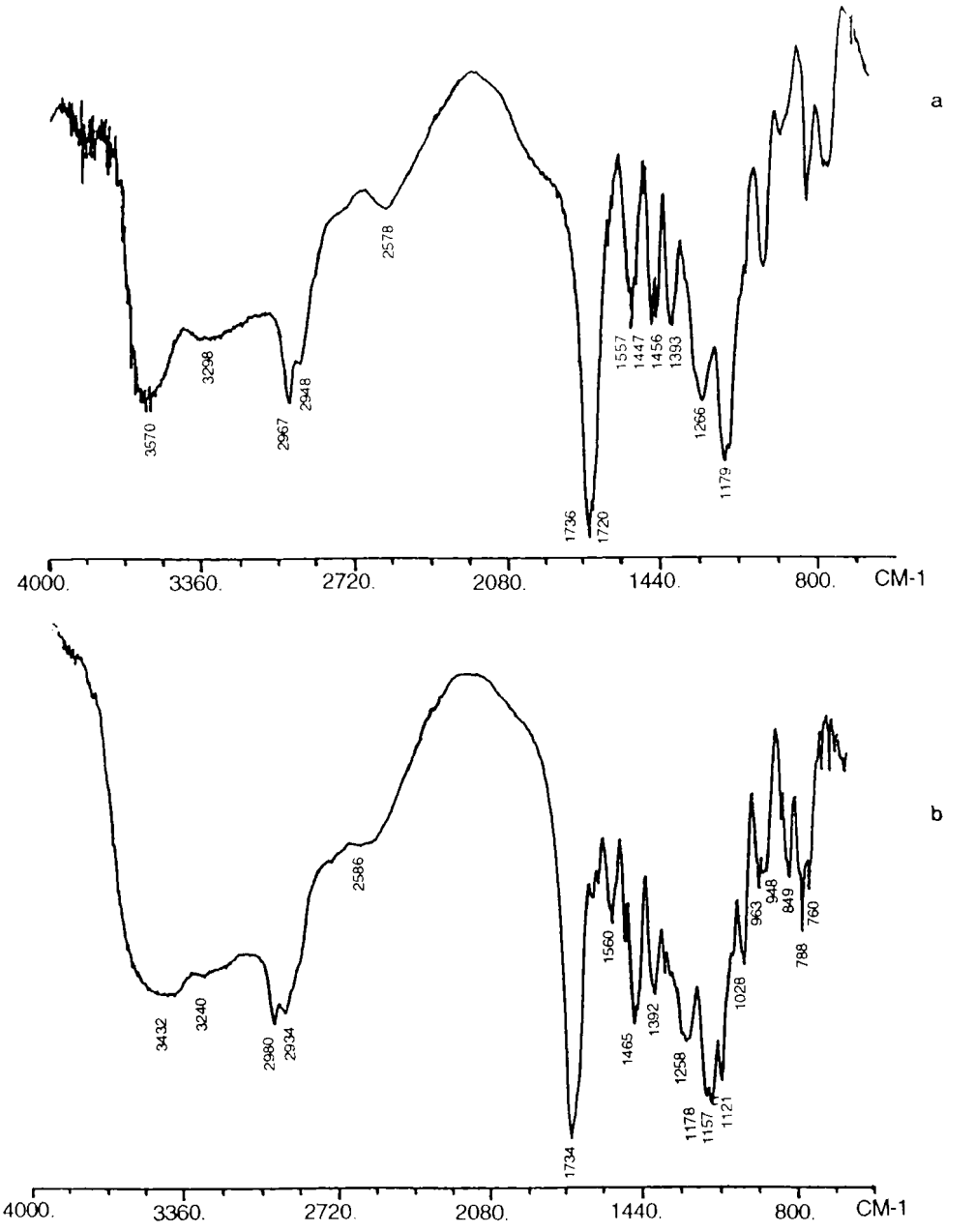

FIGURE 2
IR spectrum corresponding to:
a: acrylic copolymer Eudragit L-Na 30%
b: Eudragit L-morphine coprecipitate, corresponding to lot 1

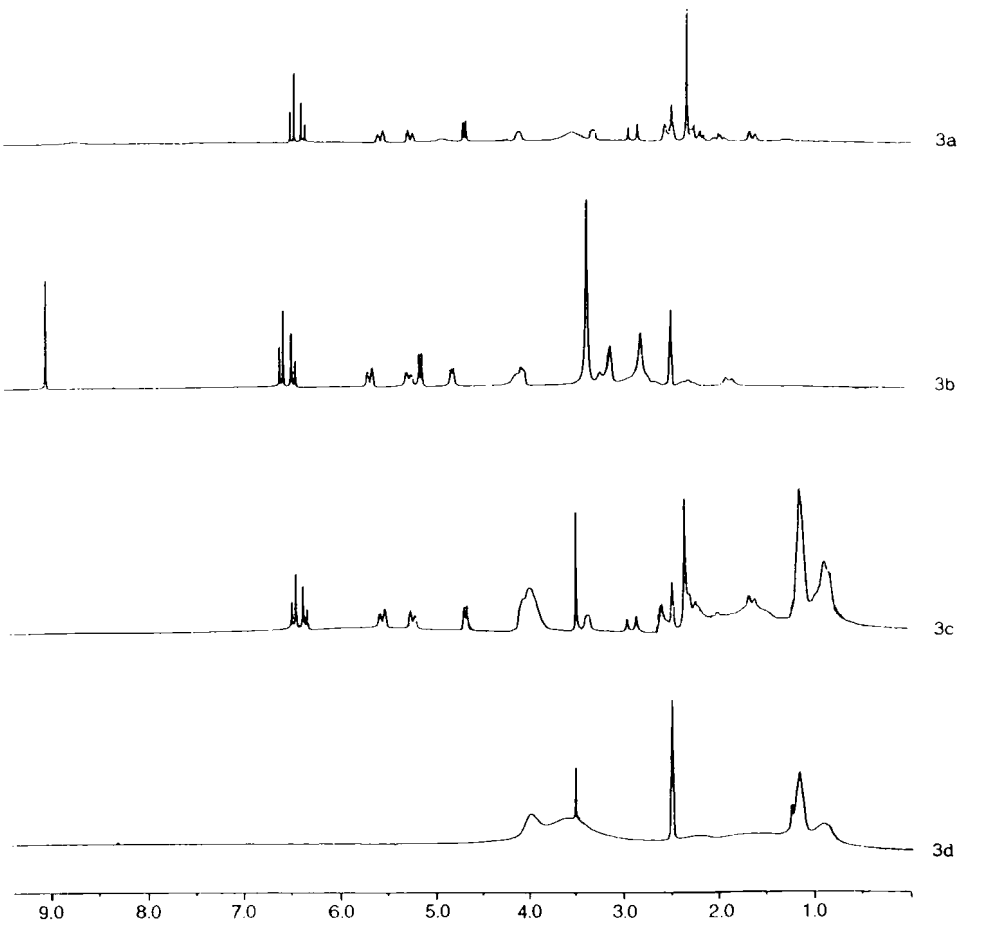

FIGURE 3
^{1}H-RMN spectra for:
3a: morphine
3b: morphine hydrochloride
3c: Eudragit L-morphine coprecipitate (lot 1)
3d: Eudragit L-Na 30 %

experiments, selective decoupling techniques and taking into account data obtained from the literature (23).

Spectrum 3d was registered for Eudragit L-Na and is the typical one of a polymer. Thus, all the resonance signals are broad and were assigned as follows. Aliphatic methyl groups and those corresponding to the esther function resonate at 0.9

and 1.2 ppm, respectively; aliphatic methylene and methine protons appear between 1.4 - 2.5 ppm, while carboxylic OH protons and methylenes from the ester function were found in the region 3.0 - 4.3 ppm. One might expect that the ^{1}H-NMR spectrum for the coprecipitate should nearly be the superposition of the spectra of the two isolated components. Figure 3 shows that this is approximately, with the exception of the signal that resonates at 9 ppm. This singlet corresponds to the $^{+}$NH group of morphine hydrochloride (vid. fig. 3 b). This circumstance indicates that morphine is present in the coprecipitate as free base. According to this, the spectrum taken for the coprecipitate (vid. fig. 3c) is almost the algebraic sum of those corresponding to morphine (fig. 3a) and methacrylic acid copolymer Eudragit L-Na (fig. 3d).

^{13}C-NMR Spectroscopy

Spectra were recorded in DMSO-d6 and assigned by using DEPT experiments, considering data in the literature (24).

Table 2 shows ^{13}C chemical shifts experimentally found for the morphine portion of the coprecipitate, including those for morphine hydrochloride and morphine base. Data were obtained in the same conditions for comparison purpose. As can be deduced from the analysis of these data, the spectroscopic behaviour of morphine carbons in the coprecipitate is very similar to that found for morphine base ($\Delta\delta_i$ = 0.0 - 0.8 ppm), being larger differences in comparison with morphine hydrochloride carbons ($\Delta\delta_i$ = 0.1 - 2.9 ppm). As in ^{1}H-NMR experiments, ^{13}C data point again to the fact that morphine is present in the coprecipitate as free base and not as ammonium salt. So, the addition of morphine hydrochloride to a solution of Eudragit L-Na seems to involve the neutralization of HCl from the amino group of the morphine-HCl by the R-COONa subunits of the partially neutralized polymer. The base released from this process interacts with the polar groups of the polymer, most probably by means of hydrogen bonds. In this sense, OKHAMAFE *et al.* (20) and JENQUIN *et al.* (25) have considered this kind of interaction as responsible for the binding of drugs with amino groups and acrylic polymers as Eudragit^{R} L30D.

There are two possible types of hydrogen bonds between morphine and the used resin. They are shown in figure 4. In both, the reactive groups of the polymer were

TABLE 2

^{13}C chemical shifts found experimentally for the morphine portion of the coprecipitate, including those for morphine·HCl and morphine base.

	Morphine hydrochloride	Eudragit L-morphine	Morphine
C_1	119.2	118.7	118.6
C_2	117.4	116.5	116.4
C_3	139.3	138.6	138.5
C_4	146.4	146.3	146.3
C_5	90.6	91.3	91.5
C_6	66.0	66.3	66.4
C_7	134.9	133.6	133.4
C_8	**125.4**	**128.0**	**128.5**
C_9	59.5	58.1	58.1
C_{10}	21.6	20.5	20.2
C_{11}	**122.1**	**125.0**	**125.5**
C_{12}	129.1	130.7	131.0
C_{13}	**40.2**	**42.2**	**43.0**
C_{14}	**37.3**	**40.2**	**40.6**
C_{15}	**32.2**	**34.8**	**35.6**
C_{16}	45.9	45.8	46.1
C_{17}	41.8	42.7	42.8

carboxylic functions; however, the morphine can interact with its hydroxyl groups and the morphinic nitrogen.

Processing complexation efficiency

Once the resultant products of the proposed reaction have been identified as Eudragit L-morphine coprecipitates with interactions type hydrogen bonds, in this section we analyze the efficiency of this reaction. So, it will be possible to standardize and optimize the complexation reaction. A HPLC technique has been used to quantify morphine in the coprecipitates. An example of the obtained chromatograms using this

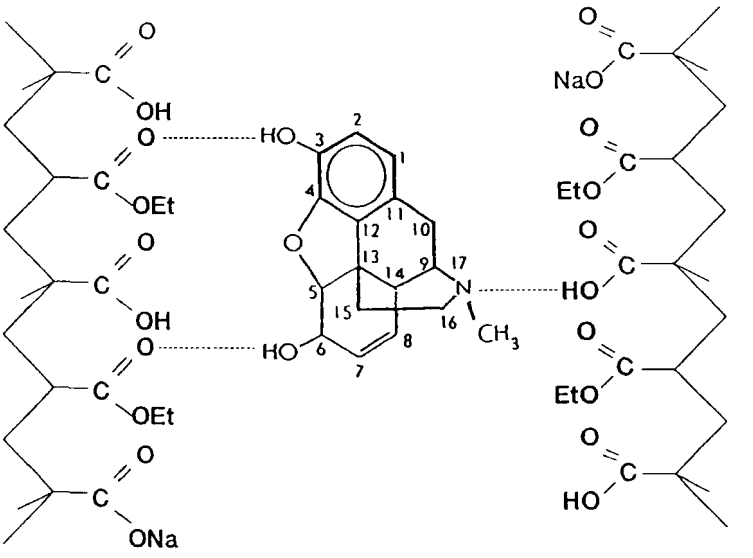

FIGURE 4
Hydrogens bonds between morphine and Eudragit^{R} L

method is shown in figure 5. In the assayed conditions the retention time for morphine was 5.08 $\pm$ 0.05 minutes. A plot of peaks areas versus concentrations was linear in the range of 50 to 1000 ppm of morphine hydrochloride. Regression analysis of the calibration curve gave the statistical parameters showed in table 3.

In order to determine the reaction efficiency, the coprecipitates mass and their content in morphine were taken into account as dependent variables. The influence of the reaction volume has been investigated. In tables 4 and 5 are shown the obtained data and the results of the ANOVA made over those dependent variables.

It has been found that both NaOH and morphine hydrochloride concentrations affect the mentioned parameters with statistical significance. These influences are greater over the percentage of coprecipitated drug than over the coprecipitates mass. This situation is due to the fact that a diminution in the reaction volume originate an increase in the probability of interaction between the drug and the polymer molecules.

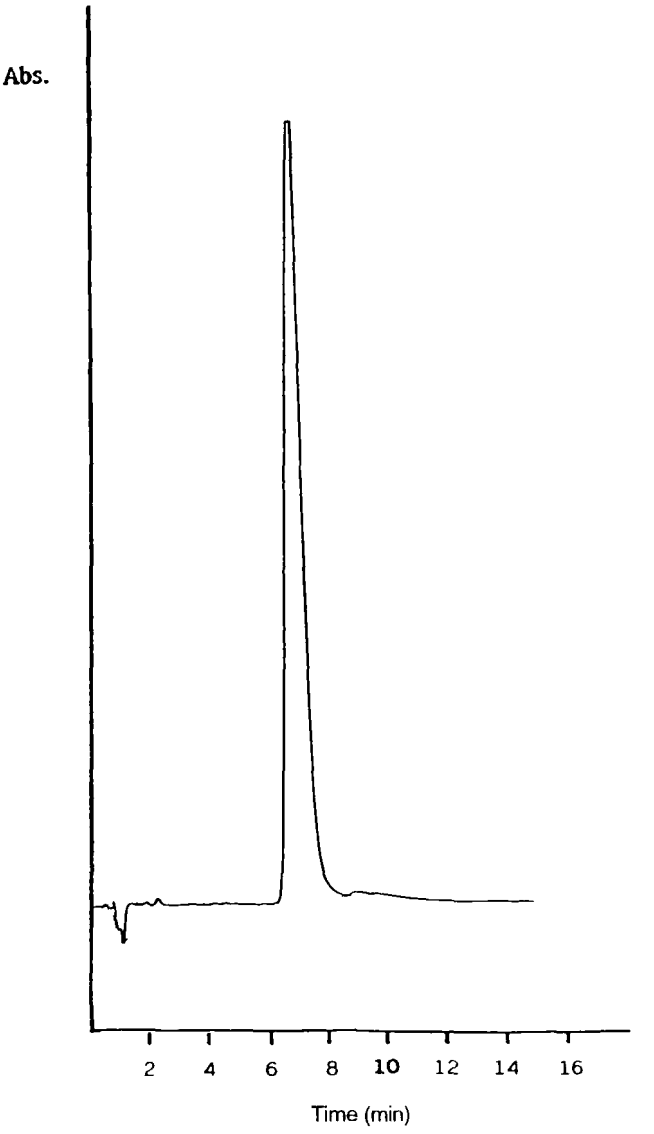

FIGURE 5
Chromatogram of morphine hydrochloride

TABLE 3

Calibration curve data of morphine hydrochloride in HPLC study

Coeff. of Determ.: 0.9988			Estimated constant term.: 0.0053		
Corr. Coeff: 0.9994			Standard Err. of Estimate: 0.0116		
Source	D. F.	Sum. of Squares	Mean of Squares	F	Prob.
Regression	1	1.82648	1.82648	13578.1	0.0000
Residuals	16	0.00215	1.345E-4		
Total	17	1.82863			
Regression Coeff.		Stand. Coeff.	Stand. Err.	T	Prob.
0.96626		0.9994	0.008292	116.525	0.0000

TABLE 4

Influence of the concentration of NaOH aqueous solution over the coprecipitation process (D.F. = 8).

(N.D. = Neutralization Degree)

N.D.	NaOH normality	Morphine content (g)	Coprecipitate mass (g)	Morphine content (%)
30%	1.01 N (lot 1)	2.273	4.200	54.12
	0.50 N (lot 2)	2.138	4.163	51.36
	0.25 N (lot 3)	2.118	4.152	51.01
		F = 304.94 p < 0.0000	F = 18.468 p = 0.0030	F = 645.67 p < 0.0000

TABLE 5

Influence of the concentration of morphine hydrochloride solution over the coprecipitation process (D.F. = 8).

(N.D. = Neutralization Degree)

N.D.	Morphine-HCl concentration	Morphine content (g)	Coprecipitate mass (g)	Morphine content (%)
30%	4.50 % (lot 1)	2.273	4.200	54.12
	4.10 % (lot 4)	2.250	3.973	56.63
	3.75 % (lot 5)	2.020	3.904	51.74
		F = 1189.98 p < 0.0000	F = 508.01 p < 0.0000	F = 4930.61 p < 0.0000

As a sort of a summary, it can be concluded that a process to obtain morphine polymeric coprecipitates has been developed. The proposed reaction has been standardized and the resultant coprecipitates have been studied to characterize the nature of the interactions. This reaction involves coprecipitates having morphine contents greater than 50 %. Spectroscopic data indicate that the reaction involves interaction type hydrogen bonds. Actually, we are studying the nature of the interaction for similar coprecipitates using other drugs. These investigations are centered in the study of the influence of the type of the binding over the thermal properties of the initial polymer and its consequential effect over the release characteristics of the resultant coprecipitates.

REFERENCES

1. G.W. Hanks, P.J. Wand, Clin. Pharmacokinet., **17**, 65 (1989).

2. P.I. Fekete, E. Orbän, I. Elekes, Brit. pat. 1.596.166 (1981).

3. A.A. Badawi, A.M. Fouli, A.A. El-Sayed, Int. J. Pharm., **6**, 55 (1980).

4. D.B. Beten, M. Gelbcke, B. Diallo, A.J. Moës, Proceedings du 6ème Congrés International de Technologie Pharmaceutique, Paris, 2 - 4 Juin 1992, vol. 5, pp. 458 - 467

5. E. Swinyard, "Analgésicos y antipiréticos" in "Remington. Farmacia", A. Gennaro (Ed.), 17ª ed., Ed. Panamericana, Buenos Aires, 1987, p. 1501

6. J.H. Jaffe, W.R. Martin, "Analgésicos y antagonistas opiáceos" in "Las bases farmacológicas de la terapéutica", A. Goodman, L.S. Goodman, T.W. Rall, F. Murad (Ed.), 7th ed., Ed. Panamericana, Buenos Aires, 1986, p. 477

7. Eudragit Information sheets, Röhm Pharma, Darmstadt

8. A.M. Rabasco, M.A. Holgado, M. Fernández-Arévalo, J.M. Ginés, Eur. J. Pharm. Biopharm., **37**, 147 (1991).

9. M. Fernández-Arévalo, M.A. Holgado, J.M. Ginés, A.M. Rabasco, Pharm. Techn. Int., **4**, 24 (1992).

10. M.A. Holgado, M. Fernández-Arévalo, J.M. Ginés, A.M. Rabasco, Drug Dev. Ind. Pharm., **18**, 911 (1992).

11. M. Fernández-Arévalo, M.A. Holgado, J.M. Ginés, A.M. Rabasco, Int. J. Pharm., (in press, 1993).

12. E. Orbän, Gyógyszerészet, **23**, 249 (1979).

13. E. Orbän, Gyógyszerészet, **23**, 293 (1979).

14. E. Orbän, Gyógyszerészet, **24**, 27 (1980).

15. E. Orbän, Gyógyszerészet, **24**, 77 (1980).

16. E. Ciranni, C. De Sena, A. Dell'utri, S. Alimonti, Drug Dev. Ind. Pharm., **14**, 1167 (1988).

17. S.A. Botha, A.P. Lötter, Drug Dev. Ind. Pharm., **16**, 1945 (1990).

18. J.L. Ford, P. Timmins, "Pharmaceutical thermal analysis", Ellis Horwood Ltd., Chichester, 1989, p. 25

19. R. Wada, S.H. Hyon, Y. Ikada, J. Pharm. Pharmacol., **43**, 605 (1991).

20. A.O. Okhamafe, P. York, J. Pharm. Pharmacol., **41**, 1 (1989).

21. H.K. Lee, J. Hajdn, P. McGoff, J. Pharm. Sci., **80**, 178 (1991).

22. M.A. Holgado, "Diseño y elaboración de dos sistemas orales de liberación controlada de clorhidrato de carteolol. Evaluación biofarmacéutica", Tesis Doctoral, Facultad de Farmacia, Sevilla 1993

23. L.M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1962

24. E. Breitmaier, W. Voelter, "Carbon-13 NMR Spectroscopy", VCH, Weinheim, 1987

25. M.R. Jenquin, S.M. Liebowitz, R.E. Sarabia, J.M. McGinity, J. Pharm. Sci., **79**, 811 (1990).