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Study of a complexation process between naltrexone and Eudragit® L as an oral controlled release system[1]

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Abstract

Polymeric complexes based on the interaction between Eudragit® L and naltrexone hydrochloride were elaborated. A preformulation study of the drug was designed to address the following points: (a) the development of two alternative methods (high performance liquid chromatography (HPLC) and UV spectrophotometry) for the analysis and quantifying of naltrexone; (b) the determination of the aqueous solubility of naltrexone hydrochloride; and (c) the characterization of naltrexone hydrochloride from the following points of view: morphological (scanning electronic microscopy, SEM), thermal (differential scanning calorimetry, DSC and hot stage-microscopy, HSM) and spectroscopical (^{1}H- and ^{13}C-nuclear magnetic resonance, NMR). Furthemore, some of these thechniques were used for the physical and chemical characterization of naltrexone polymeric complexes. An interaction by means of hydrogen bonds between the polymer and naltrexone was demonstrated using NMR spectroscopic techniques. The in vitro release of naltrexone–Eudragit® L complex using a pH gradient technique was studied. A significant reduction in the release rate of drug from the complex used as naltrexone controlled release system as well as a very high efficiency in the dissolution process have been found. © 1997 Elsevier Science B.V.

Keywords: Naltrexone hydrochloride; Eudragit® L30D; Preformulation; Controlled release complex

1. Introduction

Naltrexone is a potent narcotic antagonist, approximately 30 to 40 times as active as nalorphine and 2 to 3 times as active as naloxone. Consequently, it is used as an adjunct to the maintenance

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of the opioid-free state in detoxified, formerly opioid-dependent individuals (Blumberg and Dayton, 1974).

It is rapidly and almost completely absorbed following oral administration but it undergoes an extensive first-pass metabolism in the liver. Only 5 to 20% of an orally administered dose reaches systemic circulation unchanged. However, its principal metabolite, 6β-naltrexol, is also a pure antagonist and may contribute to the opioid receptor blockade. Mean elimination half-lives for naltrexone and 6β-naltrexol are 3.9 and 12.9, respectively (Swinyard, 1990).

On the basis of these pharmacokinetic parameters, naltrexone is a potential candidate to be incorporated in a controlled release system. For this purpose and considering its physicochemical characteristics, the drug can be introduced in a polymeric structure such Eudragit® L30D (Alvarez-Fuentes et al., 1994a,b; Holgado et al., 1995). This resin is an anionic copolymer based on polymethacrylic acid and ethylacrylate (1:1). Its solubility is pH dependent, being soluble above pH 5.5.

The complexation technique used has already succesfully assayed with other drugs such as carteolol, morphine, dextromethorphan, diphenhydramine, phenylpropanolamine, phenylephrine and pseudoephedrine (Alvarez-Fuentes et al., 1994a,b; Holgado et al., 1995).

So, the main objective of this paper is to elaborate the proposed naltrexone controlled release system and to carry out the complete characterization of naltrexone hydrocloride and naltrexone–Eudragit® L controlled release system.

2. Experimental

2.1. Materials

Naltrexone was a gift from Zambón S.A.; methanol used was HPLC grade (Panreac, Barcelona, Spain); diammonium phosphate was obtained from Merck (Darmstadt, Germany); Eudragit® L30D was obtained from Curtex S.A. (L'Hospitalet, Barcelona, Spain); sodium chloride, sodium hydroxide and hydrochloric acid from Panreac (Barcelona, Spain).

3. Methods

3.1. Analytical methods

3.1.1. High-performance liquid chromatography

A HPLC method is described for the quantifying of naltrexone hydrochloride in controlled release complexes naltrexone–Eudragit® L. The HPLC method avoids the interference between the drug and the polymer that occurs when the 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 (Merck, Aluspher 100 RP-select B, 5 μm particle size, 12.5 cm × 4 mm I.D.) 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 283 nm. Each peak area was computed automatically by the integrator. The elution was carried out in isocratic conditions at room temperature (22 ± 2°C).

Naltrexone 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 accuracy of the HPLC determination was evaluated from the recovery data for naltrexone at different concentrations. The precision of the method was studied by analyzing a solution containing 400 μg/ml in 20 replicates. Furthermore, this same solution was analyzed by quadruplicate on five different days (20 times). The intra-assay precision was determined from the coefficient of variation (CV) of the obtained values for the samples analyzed on the same day. Inter-assay data were calculated using the mean value of the four injections performed on each day.

3.1.2. UV spectrophotometry

This analytical method is able to be used as an alternative in those situations where no interference problems appear as, for example, solubility assays.

Calibration curve for naltrexone hydrochloride (Spectrophotometer Hitachi, mod. U-2000) was calculated (maximum of absorption 283 nm) using standard solutions containing 600, 400, 200, 100, 50, 25 and 12.5 μg/ml of this drug. The precision of the method was studied by analyzing a solution containing 200 μg/ml in 20 replicates, following the procedure previously described for the HPLC method.

3.2. Solubility assays

The experimental aqueous solubility of naltrexone hydrochloride was calculated. Hydrochloride salts of drugs frequently exhibit less than desirable solubility in gastric fluids because of the abundance of chloride ion in the gastric fluid (Miyazaki et al., 1981). For this reason, the solubility study as a function of ionic strength (NaCl) was carried out. In this sense, the Setschenow equation is considered to describe the effect of the chloride ion on the solubility of drug hydrochloride salts (Miyazaki et al., 1981; El Egakey and Speiser, 1982; Park et al., 1984; Florence and Attwood, 1988):

$$\log \frac{S_o}{S} = K \cdot C$$

where S_o and S are the solubilities in pure water and in the salt solution respectively, K is the salting-out constant and C is the molar concentration of the salt.

From this equation, it can be obtained the salting-out constant, parameter that measures the extent of the common ion effect (sensitivity to the chloride ion).

The study was conducted at room temperature (22 ± 2°C) and aqueous solutions with several ionic strengths varied from 0 to 1 M NaCl were used. The filtrates were appropriately diluted and analyzed by UV spectrophotometry at 283 nm.

3.3. Scanning electron microscopy

The morphological characteristics of naltrexone hydrochloride were analyzed using a scanning electron microscope (Philips XL-30). A very thin coat of carbon was applied to each sample, which was examined at different magnifications. Micrographs were taken for each sample.

3.4. Thermal analysis

Thermal analysis has rapidly gained importance as a routine instrumental method for obtaining qualitative predictions on the stability of drugs, excipients or their mixtures. The melting range of a substance is defined as those points of temperature within which the solid coalesces and is completely melted. Because of this a melting temperature range must be reported unless the melting of the compound takes place instantaneously. Differential scanning calorimetry is particularly valuable in studying the beginning of melting of a compound. Differential scanning calorimetry (DSC) and hot stage-microscopy (HSM) were used to characterize the thermal behaviour of naltrexone hydrochloride.

Thermal analysis using DSC method was performed using an automatic thermal analyzer system (Mettler FP80HT 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 all the experiences. 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 the samples were run at a rate of 10°C/min, from 40 to 320°C.

To extend the study of the thermal behaviour of naltrexone hydrochloride, a HSM assay was carried out. A microscope Olympus BH-2 fitted to a Mettler FP82 hot-stage was used to observe phase transitions of the sample.

A small amount of drug was placed on sample stage and heated from 30 to 300°C at a rate of 10°C/min which was decreased at 2°C close to the melting temperature point of drug.

In order to investigate a possible incompatibility between naltrexone hydrochloride and Eudragit® L30D, thermal analysis was performed on naltrexone hydrochloride, Eudragit® L30D and physical drug–polymer mixtures. Naltrexone hydrochloride and the polymer were weighed in a 1:1 ratio (Signoretti et al., 1988) and then mixed by light trituration in a mortar.

3.5. Spectroscopical study

A spectroscopical study of naltrexone, naltrexone hydrochloride and Eudragit® L30D by ^{1}H-NMR and ^{13}C-NMR have been carried out. The NMR spectra of the samples were recorded using a Bruker 200-AC type spectrometer employing DMSO-d6 (ICN Biomedical, UK-Cambridge) as solvent. ^{1}H-NMR spectra were assigned by using 2D-COSY experiments and selective uncoupling techniques. ^{13}C-NMR were assigned by using DEPT experiments. Both studies were carried out taking into account data obtained from the literature (Jackman, 1962; Breitmaier and Voelter, 1987).

It is known that ^{13}C chemical shifts are very sensitive to small structural changes in a molecule. ^{13}C-NMR spectra uncoupling totally allow to assign the individual signals of different carbons of naltrexone hydrochloride. The ^{1}H-NMR spectra of the original products (naltrexone, naltrexone hydrochloride and Eudragit® L30D) were compared with those corresponding to the elaborated controlled-release naltrexone complexes. This comparison allowed to suggest the type of interaction produced between naltrexone and the acrylic polymer Eudragit® L (Alvarez-Fuentes et al., 1994a; Holgado et al., 1995).

3.6. Preparation of naltrexone-Eudragit L complexes

Commercial suspensions of Eudragit® L30D were diluted and partially neutralized with an aqueous solution 1 N of NaOH. Afterwards, stoichiometric amounts of naltrexone hydrochloride in aqueous solution were added. The formed precipitates, separated by filtrating, were dried in a oven (Selecta, mod. 204). The resulting products were pulverized and washed with purified water. The solids were separated, dried and crushed and the final coprecipitates of Eudragit L–naltrexone were obtained by selecting the powder fraction between 75–300 μm.

From previously results (Fernández-Arévalo et al., 1994) it can be appreciated the great influence exerted by the neutralization degree over the coprecipitates weights and their drug contents. The experimental data suggest that an increase in the neutralization degree from 26% (minimum limit that allows the solubilization of the resin) to 39–40% implies a slight increase in the drug content and coprecipitates weights, reaching an asymptotal value. Subsequently, the complexes weights decrease abruptly from the maximum percentage of neutralization reached (40%). However, a similar decrease in the drug content, expressed in percentage, was not found.

So, in order to obtain the maximum efficiency in the complexation process the 39 and 40% neutralization degree were used.

3.7. Quantification of naltrexone content in the complexes and its characterization

In order to determine the efficiency of the complexation process the coprecipitates weights and their contents in naltrexone were considered.

A HPLC method was chosen for quantifying the content of naltrexone hydrochloride in controlled release complexes naltrexone–Eudragit® L. Using the HPLC technique previously described, Eudragit® L–naltrexone complex solutions in mobile phase at 0.1% w/v were analyzed. Each sample was assayed at least in triplicate.

On the other hand, the complex containing the maximun charge in drug was characterized from a thermal and spectroscopical point of view, using the methods indicated above.

3.8. In vitro dissolution study

The in vitro dissolution behaviours of naltrexone hydrochloride and naltrexone polymeric complex were investigated. In order to compare them, the in vitro dissolution study was carried out at 37 ± 0.5°C for 8 h, in the USP XXIII basket apparatus (Turu Grau, mod. D-6) at a speed of 50 rpm. A total of 500 ml of artificial gastric fluid without enzymes was employed as initial dissolution medium. A pH gradient technique was used. At predetermined intervals, test solutions were assayed by a HPLC technique previously developed by us.

Table 1
Recovery data for the determination of naltrexone (each value represents the average of three replicates)

HPLC method		UV spectrophotometry	
Concentration (μg/ml)	Recovery (%)	Concentration (μg/ml)	Recovery (%)
540	98.61	480	96.43
307	102.50	440	100.77
248	99.05	400	101.40
243	99.26	380	97.03
236	100.93	340	95.71
198	100.05	300	98.02
176	100.50	220	95.45
167	91.60	120	102.02
	Accuracy = −8.40		Accuracy = −4.55

4. Results and discussion

4.1. Physicochemical characterization of naltrexone hydrochloride

4.1.1. Analytical methods

4.1.1.1. High-performance liquid chromatography. In order to optimize the HPLC method, different methanol/water ratios were assayed. The selected mobile phase was methanol/purified water/diammonium phosphate 70:30:0.1 v/v/w. The retention time for naltrexone was 2.09 ± 0.1 min.

The calibration curve obtained for naltrexone hydrochloride using the HPLC method previously described ($y = 0.1222 \pm 1.80 \cdot 10^{-4}) \cdot x + 4.35 \cdot 10^{-5} \pm 2.34 \cdot 10^{-4}$) was linear from 6.25 to 1000 μg/ml giving $r = 0.9999$ as correlation coefficient ($n = 27$) and $F = 459596$ as Snedecor ratio ($P < 0.0001$).

4.1.1.1.1. Accuracy. As it can be observed in Table 1, where the recovery data are shown, the accuracy of this method (−8.4%) is adequate in the assayed concentrations.

4.1.1.1.2. Precision. The CVs for intra- and inter-assay precision were both lower than 1% (see Table 2). The results show the adequate precision of the HPLC method proposed.

4.1.1.2. UV spectrophotometry. In order to investigate the linearity of the spectrophotometrical method, the calibration curve for naltrexone hydrochloride was performed. The regression analysis of this curve ($y = (320.02 \pm 1.50) \cdot x + (0.28 \pm 0.4)$) gave $r = 0.9998$ as regression coefficient ($n = 21$) and $F = 45311.5$ as Snedecor ratio ($P < 0.0001$). These parameters showed that the detector response is linear from 12.5 to 600 μg/ml.

4.1.1.2.1. Accuracy and precision. As it can be observed in Table 1, the accuracy of this method, as measured from the recovery data, was adequate (−4.55%). Furthermore intra- and inter-day precision were lower than 1% (see Table 2).

4.1.2. Solubility assays

The experimental value of aqueous solubility of naltrexone hydrochloride was 85.43 ± 1.1 mg/ml at 22 ± 2°C; this datum shows a clear similarity with the value found in the bibliography, close to 90 mg/ml (Naltrexone Information Sheets). The results obtained from the solubility study as a function of ionic strength in purified water are shown in Fig. 1.

These data demonstrate a negative ionic strength influence due to a salting-out effect (Fig. 1). Nevertheless, even considering this diminution, the solubility values yielded never are below the required limit of solubility to design controlled release systems (0.1 mg/ml) (Park et al., 1984).

In relation with this study, Miyazaki et al. (1981) found a high correlation between the water solubility of several drugs with their salting-out constants; as the solubility in water increased, the

Table 2
Intra- and inter-assay precision for the determination of naltrexone

	Levels	Mean area	Variance	Degrees of freedom	Coefficient variation
HPLC method (400 μg/ml)	Intra-day	0.324020	1.24E-6	20	0.343195
	Inter-day	0.323419	3.48E-6	20	0.576705
UV spectrophotometry (200 μg/ml)	Intra-day	0.616143	1.25E-5	20	0.574473
	Inter-day	0.615250	6.20E-6	19	0.404624

salting-out constant decreased. Considering this inverse relationship and the experimental aqueous solubility of naltrexone hydrochloride (85.43 mg/ml), a low salting-out constant value much more minor than 3.73 (corresponding to demeclocycline, with a $S_o = 32.55$ mg/ml at 25°C, the most soluble substance studied by Miyazaki) is expected. In order to determine a theoretical salting-out constant value, the transformation of Setschenow equation has been used (Holgado, 1993).

$$\log S = \log S_o - K \cdot C$$

This equation suggests a linear relationship between log S and NaCl concentration (Fig. 2). So, from the linear regression between log S and NaCl concentration an experimental salting-out constant with sodium chloride of 0.78 was obtained, giving $r = 0.9779$ as correlation coefficient. This salting-out constant is taken as a parameter that indicates the extent of the common ion effect, i.e. the sensitivity of the naltrexone hydrochloride to the chloride ion (Fig. 2).

On the other hand, the transformed Setschenow equation allows an estimation of the aqueous solubility from the linear regression between log S and NaCl concentration (discontinuous line in Fig. 2) (Holgado, 1993): the aqueous solubility value for naltrexone hydrochloride obtained from intercept was 70.30 mg/ml. This value is not sufficiently close to the experimental aqueous solubility of the drug (85.43 mg/ml).

On the line of these results, Bogardus (1982) indicated that the empirical Setschenow equation is valid only with low concentrations of the added NaCl, as a resulting of a lost of the linearity from a determined NaCl concentration value; the lower the solubility of the drug is, the lower of this concentration value is. In this sense Bogardus proposes that the limiting slope of Setschenow plot at the lower added salt concentrations can be taken as the salting-out constant. Considering the results obtained in this paper (continuous line in Fig. 2), the result of this treatment is a K value of 1.5 ($r = 0.9989$).

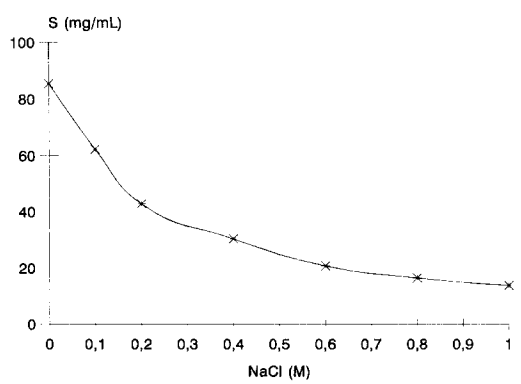

Fig. 1. Solubility values versus ionic strength.

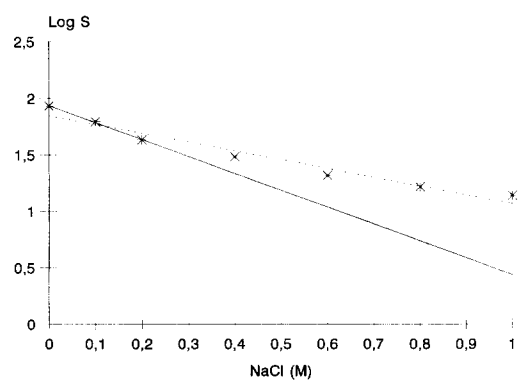

Fig. 2. Log S versus ionic strength.

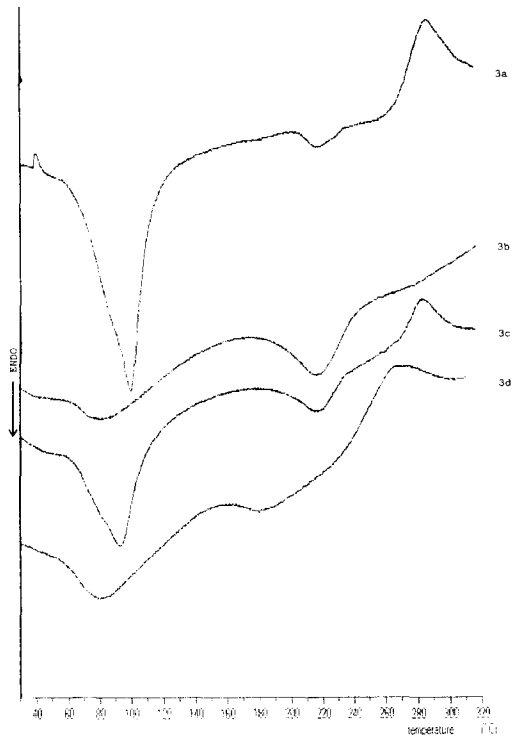

Fig. 3. DSC thermograms corresponding to: (a) naltrexone hydrochloride; (b) Eudragit® L30D; (c) physical mixture (1:1) of the raw substances; and (d) naltrexone–Eudragit L complex.

4.1.3. Thermal analysis

The DSC scan of naltrexone hydrochloride (Fig. 3b) showed a dehydration peak ($\Delta H \approx -300$ J/g) and an endothermic peak corresponding to the melting of the drug ($\Delta H \approx -13$ J/g) with temperature onsets of 67.9 and 206.0°C, and temperature peaks at 102.3 and 217.7°C, respectively. It can be also seen an exothermic decomposition peak at 285.8°C with an onset temperature of 268°C. These conclusions are consistent with the results obtained from HSM analysis (Fig. 4). Furthermore, as it is shown in the thermogram of Eudragit® L30D (Fig. 3a), this polymer exhibits a melting peak with a $\Delta H \approx 90$ J/g and temperature onset and peak of 190 and 217°C, respectively. A soft transition at 83°C, approximately, can be seen. This temperature could correspond to a typical temperature of amorphous polymers known as glass transition temperature, T_g (Ford and Timmins, 1989). It represents a change in the polymer characteristics 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

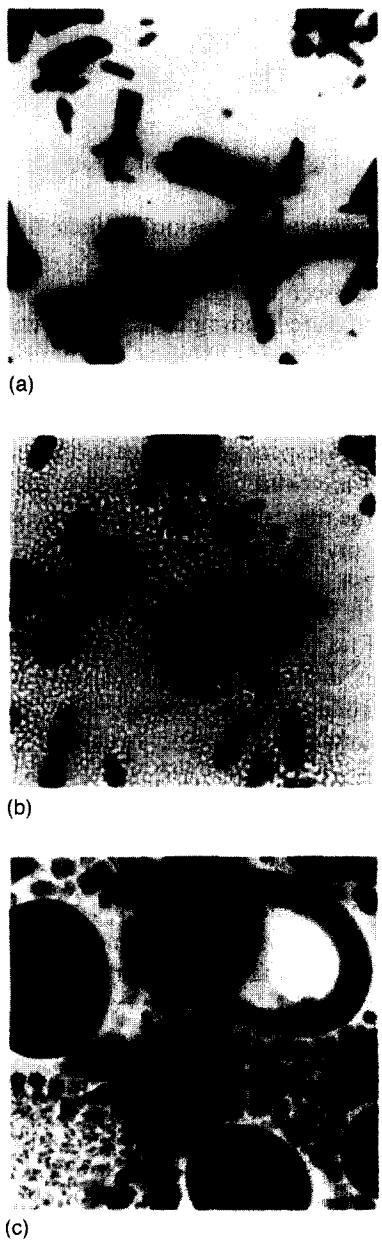

Fig. 4. HSM photographs showing naltrexone hydrochloride at: (a) room temperature; (b) 210°C; and (c) 300°C.

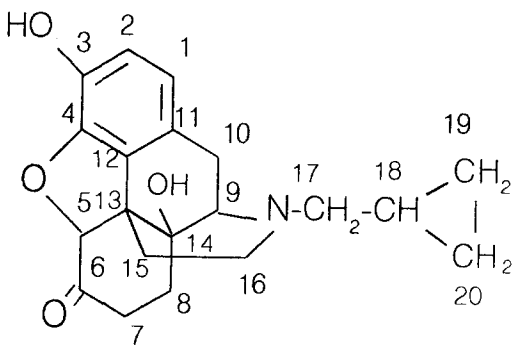

Fig. 5. Structure of naltrexone.

properties such as expansion coefficients and heat capacity.

As can be seen in Fig. 3, the thermogram of 1:1 physical mixture Eudragit® L30D/naltrexone hydrochloride (Fig. 3c) exhibits endothermic peaks corresponding to the two initial substances (Fig. 3a, b for Eudragit® L30D and naltrexone hydrochloride, respectively). Furthermore, no new transitions are found. So, all these situations indicate that the drug is in its crystalline form without suffering any chemical interaction nor degradation process.

Therefore, it can be affirmed that the acrylic polymer Eudragit® L30D, as excipient, and naltrexone, as drug, are compatible in order to prepare controlled-release complexes by introducing the drug into the polymeric structure (Fig. 5).

4.1.4. Spectroscopical study

^{1}H-NMR spectrum for Eudragit® L30D was registered. This 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 ester 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.

^{1}H-NRM spectra for naltrexone and naltrexone hydrochloride allow to assign the different hydrogens as is shown in Table 3.

In a following phase, from the comparative study of the ^{1}H-NMR spectra of the complex naltrexone–Eudragit L with those of each separated components (naltrexone hydrochloride and Eudragit® L) the nature of the interaction between them can be deduced.

4.1.5. Scanning electron microscopy

Fig. 6 shows scanning electron microscopy (SEM) photographs of commercial naltrexone hydrochloride. The particles present a smooth and no porous surface, showing a heterogeneous particle size. The form of particles is also very heterogeneous, observing elongated particles and others less elongated. The smallest particles seem to be formed by fracturing of the acicular ones.

4.2. Physicochemical characterization of naltrexone–Eudragit L complexes

4.2.1. Quantification of the drug content in naltrexone–Eudragit L complexes

The quantification of naltrexone polymeric complexes is carried out by the HPLC method indicated above. Table 4 shows the obtained results. From statistical analysis of the data of drug content, a significative diference was found between the different complexes obtained from the three neutralization degree indicated ($F = 17.95$, $p = 0.0012$, $df = 13$). So, the in vitro dissolution assay was realized using both products.

4.2.2. Thermal analysis

This study was firstly carried out for determining a possible interaction between naltrexone hydrochloride and Eudragit® L. The DSC scan of the naltrexone–Eudragit L complex (Fig. 3d) shows the disappearance of the characteristic peaks of naltrexone hydrochloride (see Fig. 3b). This DSC scan exhibits a soft transition a 83.9°C that could be related to the glass transition temperature of the polymeric structure, T_g. Furthermore, no melting peaks at temperature range of 217–218°C are showed and a new endothermic peak appears at approximately 182.6°C, indicating that the complex has different physico-chemical properties in comparison with the physical mixture of drug and polymer (Fig. 3c); so, it can be deduced that there is some kind of interaction between the initial substances (Botha and Lötter, 1990).

Table 3
Assignments of ^{1}H-NMR spectra for naltrexone hydrochloride

Naltrexone			Naltrexone hydrochloride		
Position (ppm)	Assignment	Integral	Position (ppm)	Assignment	Integral
0.15–0.56	H_{19}, H_{20}, $H_{19'}$, $H_{20'}$	2H+2H	0.3–0.7	H_{19}, H_{20}, $H_{19'}$, $H_{20'}$	2H+2H
0.88	H_{18}	1H	1.05	H_{18}	1H
1.58	$H_{15'}$	1H	1.45	$H_{8'}$, $H_{15'}$	2H
1.66	$H_{8'}$	1H	2.05	H_8, $H_{7'}$	1H
1.90	$H_{7'}$	1H	2.45	$H_{16'}$	1H
2.18	H_8	1H	2.70	H_{15}	1H
2.33	H_7	1H	3.00	H_7, $H_{10'}$, H_{16}, $H_{17'}$	4H
2.43	H_{15}, H_{17}, $H_{17'}$	3H	3.30	H_{10}, H_{17}	2H
2.57	$H_{10'}$	1H	3.55	H_2O crystallization	4H
2.70	$H_{16'}$	1H	4.05	H_9	1H
3.06	H_{10}, H_{16}	2H	5.05	H_5	1H
3.20	H_9	1H	6.55	H_1	1H
4.73	H_5	1H	6.70	H_2	1H
5.31	H_3 (OH phenolic), H_{14} (OH)	2H	7.05	H_{14}(OH)	1H
6.59	H_1	1H	9.00	H($^+$NH)	1H
6.73	H_2	1H	9.55	H_3(OH phenolic)	1H

The nature of these interactions can not be known by studying the resultant thermograms and, therefore, a spectroscopical study is needed.

4.2.3. Spectroscopical study

Respect to the interaction between amino groups of drugs as naltrexone hydrochloride and acrylic polymers as Eudragit® L30D, Okhamafe and York (1989) and Jenquin et al. (1990) have considered the hydrogen bonds as the principal and responsible bond originated in that type of reaction.

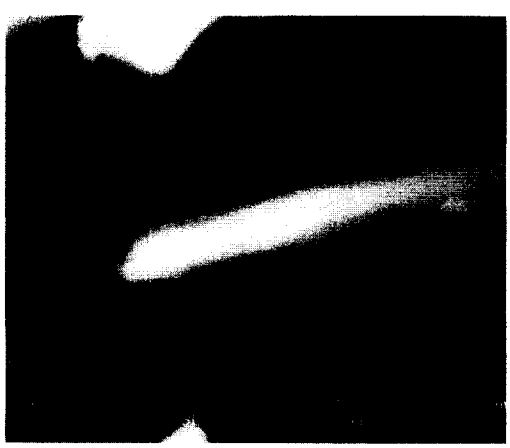

Fig. 6. SEM photographs of naltrexone hydrochloride crystals (× 1236).

The comparative study of the ^{1}H-NMR spectra of the complex naltrexone–Eudragit L with those of each separated components suggests that naltrexone is present in the polymer as free base and not in its ammonium salt form. The ^{1}H-NMR spectrum for the complex should be the superposition of the spectra of the two isolated components; however, this assumption can be considered approximate, with the exception of a signal that resonates at 9 ppm. This singlet corresponds to the $^+$NH group of naltrexone hydrochloride indicating that naltrexone is present in the complex as free base. According to this, the spectrum ob-

Table 4
Complex weight and drug content for the different lots of naltrexone complexes

	Neutralization degree	
	39%	40%
Complex weight (g)	2.612	3.096
Drug content (%)	34.56	32.11

Table 5
^{13}C chemical shifts experimentally found for the naltrexone hydrochloride, naltrexone portion of complex and naltrexone base

	Naltrexone hydrochloride	$\Delta\delta_i$ ↔	Eudragit L–naltrexone complex	$\Delta\delta_i$ ↔	Naltrexone base		Naltrexone hydrochloride	$\Delta\delta_i$ ↔	Eudragit L–naltrexone complex	$\Delta\delta_i$ ↔	Naltrexone base
C_1	119.9	0.8	119.1	0.8	119.9	C_{11}	120.6	2.7	123.3	0.2	123.5
C_2	118.2	0.9	117.3	0.8	118.1	C_{12}	127.9	1.5	129.4	0.7	128.7
C_3	140.2	0.7	139.5	0.1	139.4	C_{13}	48.7	1.5	50.2	0.7	50.9
C_4	143.6	0.1	143.5	0.1	143.4	C_{14}	69.9	0.1	69.8	0.4	70.2
C_5	88.7	0.7	89.4	1.0	90.4	C_{15}	27.2	2.9	30.1	0.5	30.6
C_6	208.0	0.0	208.8	1.7	210.5	C_{16}	46.1	2.6	43.5	0.0	43.5
C_7	35.2	0.7	35.9	0.2	36.1	C_{17}	56.8	1.6	58.4	0.7	59.1
C_8	30.7	0.5	31.2	0.1	31.3	C_{18}	5.6	3.5	9.1	0.2	9.3
C_9	60.9	0.5	61.4	0.6	62.0	C_{19}	5.3[a]	1.4	3.9[a]	0.0	3.9[a]
C_{10}	23.0	0.8	22.2	0.3	22.5	C_{20}	2.8[a]	0.8	3.6[a]	0.1	3.7[a]

[a]This signals can be changed.

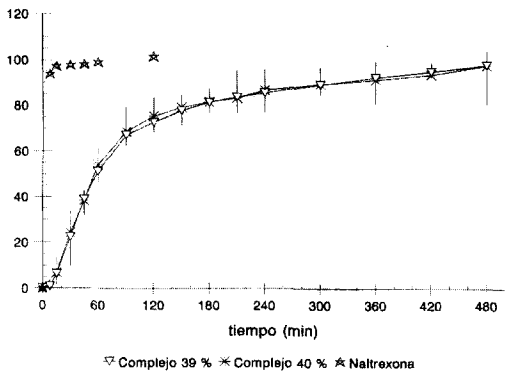

Fig. 7. In vitro dissolution profiles.

served for the complex naltrexone–Eudragit L is almost the algebraic sum of those corresponding to naltrexone in its base form (Fig. 7a) and methacrylic acid copolymer Eudragit® L-Na.

Table 5 shows ^{13}C chemical shifts experimentally found for the naltrexone hydrochloride, naltrexone base and those corresponding to the naltrexone included in the naltrexone–Eudragit L complex. Data were obtained in the same conditions for comparison purpose.

From the analysis of these data the type of interaction between naltrexone and Eudragit® L can be deduced: the spectroscopical behaviour of naltrexone carbons in the complex is closer to naltrexone base ($\Delta\delta_i = 0-1.7$ ppm) than to naltrexone hydrochloride ($\Delta\delta_i = 0-3.5$ ppm); it can be deduced that the drug is present in the complex as free base and not as ammonium salt. So, the obtained results indicated that naltrexone interacts with the polar groups of the polymer by means of hydrogen bonds. In this sense, various authors have considered this kind of interaction as the principal and responsible bond for binding of drugs with amino groups and acrylic polymers as Eudragit® L (Okhamafe and York, 1989; Jenquin et al., 1990). In previous papers (Alvarez-Fuentes et al., 1994a,b; Holgado et al., 1995), the nature of the interaction for similar coprecipitates using other drugs was studied. In this way, the same interaction type (hydrogen bonds) was found in morphine polymeric complexes. On the other hand, different interaction behaviour has been found in complexes containing carteolol hydrochloride. This drug contains a secondary amine group instead of a more stable tertiary amine group giving rise to a saline bond interaction. So, these differences in structure may directly affect either the interaction type or the strength of the bonds between several drugs and Eudragit® L.

4.2.4. *In vitro dissolution*

The obtained results indicate a significant reduction in the release rate of drug from the studied naltrexone controlled release systems in comparison with naltrexone hydrochloride, as well as a very high efficiency in the dissolution process (Fig. 7). The final release percentage are very similar in the two complexes investigated, without any significative diferences. In these release profiles, it can be seen an initial zero order period from the start of the assay to 60 or 90 min (Table 6). In these time periods, a release percentage of 50–60% is reached. This result is very interesting as the release of the half of drug charge in the first hour is assured. The rest of the charge is gradually released in the following 6 h: from the second hour to the end of the assay. This release profile is very adequate according to our objectives, that is, to obtain an immediate and effective antagonism action of opioid substances and to mantain this action during a long period of time.

In order to study this behaviour, a preclinical assay using mice is being evaluated in order to determine the in vivo efficacy of these naltrexone complexes. The preliminary results indicate that after the oral administration of these products at

Table 6
Coefficient correlations for zero-order kinetic naltrexone at different time periods

	Naltrexone complex (39%)	Naltrexone complex (40%)
0–60 min	$r = 0.9986$	$r = 0.9973$
	$P < 0.001$	$P < 0.005$
	$F = 1064.71$	$F = 0.9973$
0–90 min	$r = 0.9894$	$r = 0.9905$
	$P < 0.001$	$P < 0.005$
	$F = 164.915$	$F = 149.935$

least 2 h before the beginning of the experimental test, an effective antagonism of the analgesic action corresponding to a subcutaneous administration of morphine is yielded. These in vivo results are in according to the in vitro release profiles of the naltrexone structure assayed. Further studies are needed in order to deep into the in vivo behaviour of naltrexone complexes.

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