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Physical characterization of carteolol: Eudragit® L binding interaction

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Abstract

Eudragit® L 30D was used as a carrier to prepare carteolol polymeric complexes in order to obtain controlled release dosage forms. The polyanionic form of the polymer, neutralized at different degrees, reacts readily with carteolol hydrochloride to give water-insoluble complexes. Carteolol complexes were characterized by differential scanning calorimetry, IR, ^{1}H- and ^{13}C-NMR spectroscopy. In fact, results indicated that there were intermolecular associations between the polymer and the drug consisting in ammonium salt interactions. Maximum carteolol content was found to be 22% in the complexes.

Keywords: Carteolol hydrochloride; Eudragit® L 30D; Complexation process; Glass transition temperature; Saline bond interaction; Hydrogen bond interaction

1. Introduction

Sustained release dosage forms have been developed in order to avoid the problems associated with plasma level fluctuations and to increase the intervals between dosage regimens, with an increase in quality of life for patients with chronic diseases requiring repeated doses. Such systems have been formulated using various resins, plastics and polymers and applying different techniques.

The drug employed in the present paper, carteolol hydrochloride, has a potent β-adrenergic blocking action (Luther et al., 1986a,b). In a previous paper (Holgado et al., 1993), we carried out a preformulation program to generate the fundamental physicochemical parameters of the drug in order to provide a basis for design and development of appropriate controlled-release dosage forms. In this sense, we have previously investigated the release profiles of carteolol from inert matrix systems (Rabasco et al., 1991; Hol-

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gado et al., 1992; Fernández-Arévalo et al., 1993), including the study of different formulation and composition variables.

In the present paper we wish to propose another system as an alternative to obtain carteolol controlled-release dosage forms based on the complexation process between the drug and Eudragit® L. In contrast to the matrix systems, the drug interacts with the polymeric material of the support.

The polymer used is Eudragit® L 30D, which is anionic in character, based on methacrylic acid and methacrylic acid methyl ester. The mean molecular weight is 135 000. The ratio of the free carboxyl groups to the ester group is approx. 1:1 in the polymer. Its solubility is dependent on the pH value, Eudragit® L 30D being soluble above pH 5.5 (Liddiard, 1990).

According to our search of the bibliography, no complexation process between this drug and any carrier has been found. Nevertheless, some investigations in this field have been developed using drugs such as amitriptyline (Fekete et al., 1981), salycilic acid (Jenquin et al., 1990), propranolol (Lee et al., 1991) or dipyridamole (Beten et al., 1992). The nature of the interaction resulting from those complexation processes was not properly established. For this reason, the mechanism of interaction between carteolol and Eudragit® L was investigated taking into account that there exists very contradictory information about interactions between similar products. Therefore, the purpose of this paper is two-fold: the nature of the interaction between the drug and polymer will be established, furthermore taking into account the possible biopharmaceutical repercussion of this interaction. On the other hand, the complexation process between carteolol and Eudragit® L as a potential mechanism for prolonged carteolol release will be evaluated.

2. Materials and methods

2.1. Materials

Carteolol hydrochloride was obtained as a gift from Lab. Miquel S.A., Barcelona (subsidiary of Otsuka Pharmaceutical Co., Ltd). Similarly, Eudragit® L 30D was a gift from Curtex, Industrias Sintéticas S.A., L'Hospitalet, Barcelona. The remaining materials, sodium hydroxide (Acofarma, Tarrasa, Barcelona), hydrochloric acid (Panreac, Barcelona), methanol for liquid chromatography (Panreac, Barcelona) and diammonium hydrogen phosphate (Merck, Darmstadt) were of analytical grade.

2.2. Preparation of complexes

The complexes were prepared following a technique proposed by Orbän (1979a,b, 1980a,b). Commercial aqueous suspensions of Eudragit® L 30D were diluted to obtain Eudragit L 6D. Aqueous solutions of 1 N NaOH were added with shaking to the polymer suspensions to obtain neutralized resin (Eudragit L-Na) at 30–40% 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 standing for 24 h, an excess of a carteolol hydrochloride aqueous solution was added with shaking to each of the former solutions. The shaking was maintained for 30 min. All the process was carried out at room temperature. The resulting precipitates were separated by filtration and dried in an oven (Selecta, model 204) at 35–40°C for 2 days. The resulting products were ground and washed with purified water. The solids were separated and dried under the same conditions as described above. After milling, the final complexes of Eudragit L-carteolol were sieved (C.I.S.A., Barcelona), selecting the powder fraction between 100 and 400 μm. Each lot was prepared, at least, in triplicate.

2.3. Quantification of carteolol content

An HPLC method was used for the quantification of carteolol hydrochloride content in complexes. UV spectrophotometry was used to determine the drug content in filtered liquids and washing waters. Both methods have been previously described (Holgado et al., 1993).

2.4. Physico-chemical determination of the interaction

Thermal analysis using a differential scanning calorimetry (DSC) method was performed on Eudragit® L 30D, carteolol hydrochloride, Eudragit L-Na, Eudragit L-carteolol complexes and physical drug-polymer mixtures, employing 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 experiments on all the samples. Temperature calibrations were carried out 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 attempts to determine the influence of different processes on the glass transition temperature of the polymer, as the neutralization of the resin and the inclusion of the drug in its structure.

The IR spectra of the samples were obtained using an IR spectrophotometer (Bomen-Michelson), employing KBr (Merck, Darmstadt) disks.

The NMR spectra of the samples were recorded using a Bruker 200-AC type spectrometer employing DMSO-d_6 (ICN Biomedical Inc., Cambridge) as solvent.

3. Results and discussion

3.1. DSC

As an example, thermograms corresponding to the samples at 30% of neutralization are shown in Fig. 1. Carteolol hydrochloride and the polymer were weighed in a 1 : 1 ratio (Signoretti et al., 1988) and then mixed by light trituration in a mortar. The physical mixture (Fig. 1b) exhibits endothermic peaks corresponding to the initial substances (Fig. 1a and d for Eudragit® L-Na and carteolol hydrochloride, respectively), indicating that the drug is in its crystalline form without undergoing any degradation process. Nevertheless, the characteristic peak of carteolol

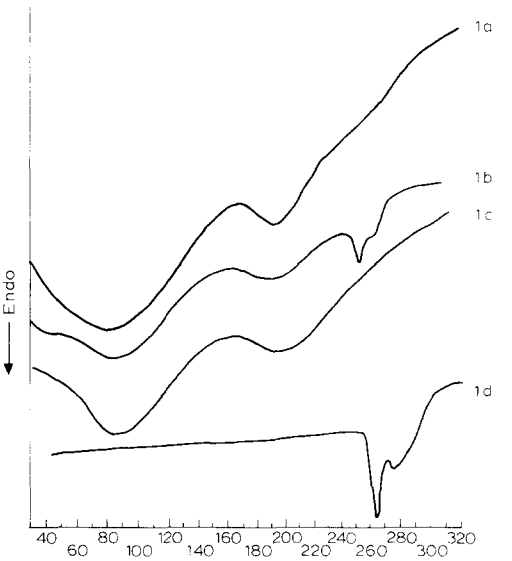


Fig. 1. Thermograms corresponding to: (a) Eudragit L-Na 30%, (b) physical mixture Eudragit L-Na: carteolol (1 : 1), (c) Eudragit L-carteolol complex, (d) carteolol hydrochloride. Abscissa: temperature (°C).

hydrochloride cannot be found (see Fig. 1d) in the thermogram of the complex (Fig. 1c), indicating that this product is different in physico-chemical properties from the physical mixture of drug and polymer (Fig. 1b). Therefore, some interactions between the initial substances can be deduced (Botha and Lötter, 1990). The nature of these interactions cannot be established only by study of the resultant thermograms.

The amorphous polymers show a typical change in their structures at a temperature known as the glass transition temperature (T_g) (Ford and Timmins, 1989). It represents a change in the polymer from a brittle state (glassy state) to a less brittle one (rubbery state) and is regarded as a second-order transition, since it reflects changes in the secondary thermodynamic properties such as expansion coefficients and heat capacity.

Fig. 2 shows the thermograms corresponding to Eudragit® L 30D (Fig. 2a) and its sodium salts at 30, 35 and 40% of neutralization (Fig. 2b, c and d, respectively). From DSC scans, the T_g value of the non-neutralized polymer (75°C) was found to increase with conversion to the salt, until approx. 30°C corresponding to the highest degree of neutralization. Similar results were ob-

tained by Alvarez-Fuentes (1992) and Wada et al. (1991). On the other hand, the contrasting effect was observed in relation to the melting point (T_m). The T_m values of the neutralized polymers were found to be 20°C below the T_m of the Eudragit® L 30D (215°C), showing no differences in relation to the neutralization degree.

Furthermore, the modification in the T_g of a polymer is dependent on the interaction degree between this compound and the drug (Okhamafe and York, 1984–85, 1989). An increase in this temperature is substantially associated with a strong interaction, as this means a fall in the polymer chain 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. Hence, a fall in T_g can be observed because of this plasticizing action.

In order to study this phenomenon three different drugs have been assayed: carteolol, morphine and ephedrine. Fig. 3 shows the thermograms corresponding to the complexes obtained with these drugs, all of them at 30% degree of neutralization of the polymer. As can be appreciated, the degree of interaction between morphine and Eudragit L-Na (Fig. 3b) is sufficient to balance the two opposing phenomena previously described (high interaction and plasticizing action), resulting in an essentially unchanged T_g value (86°C).

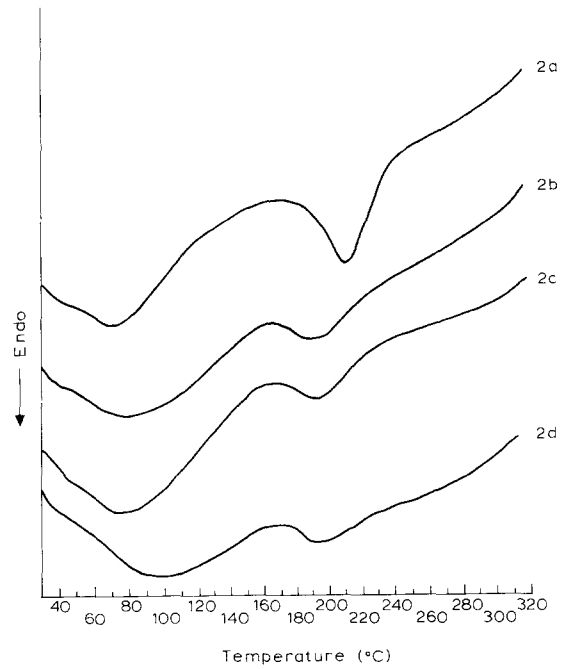


Fig. 2. Thermograms corresponding to: (a) Eudragit® L 30D, (b) Eudragit L-Na 30%, (c) Eudragit L-Na 35%, (d) Eudragit L-Na 40%.

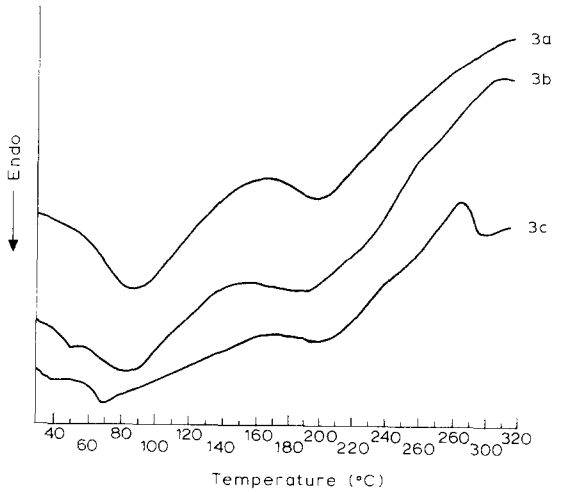


Fig. 3. Thermograms corresponding to: (a) Eudragit L-carteolol complex, (b) Eudragit L-morphine complex, (c) Eudragit L-ephedrine complex.

In contrast, ephedrine complex (Fig. 3c) presents a fall in the polymer T_g value (71°C) due to the plasticizing action of this drug. Usually, inclusion of relatively small molecules in the structures of the polymers should bring about plasticization of the latter as a result of an increase in its segmental mobility and free volume (Okhamafe and York, 1989).

The increase in the T_g value observed for carteolol complex (89°C) indicates a stiffening of Eudragit® that can be described as an 'anti-plasticizing' action of this drug. The results should therefore indicate a strong and extensive interaction between polymer and drug.

Therefore, it seems that the intensity of the ephedrine interaction is weak, this drug acting as a simple additive that induces a fall in the T_g value and hence, a rise in the polymer chain mobility. However, the behaviour of carteolol

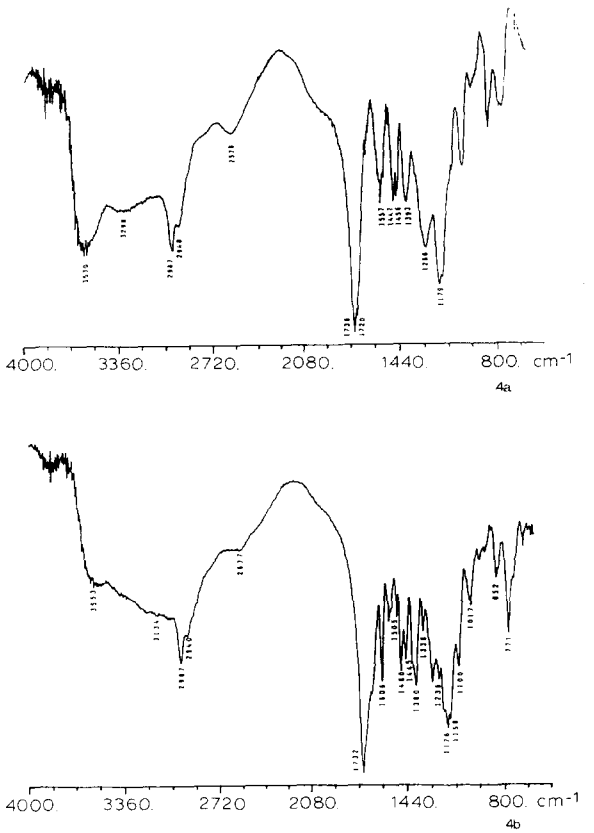


Fig. 4. IR spectra corresponding to: (a) Eudragit L-Na 30%, (b) Eudragit L-carteolol complex.

would indicate that the chemical groups of this drug are susceptible to undergoing a strong interaction with the polymer.

So, it can be concluded that the different thermal behaviours observed in the morphine and carteolol complexes can be due to the different nature and degree of drug-polymer interaction. As a consequence, both types of complexes would show differences in drug release behaviour, that may be due to structural changes in the polymer caused by the incorporation of drug.

3.2. IR spectroscopy

Fig. 4 shows the IR spectra of the copolymer Eudragit L-Na (Fig. 4a) and the complex Eudragit L-carteolol (Fig. 4b). The differences between both spectra correspond to the peaks at 1606 and 1480 cm^{-1} (ν_{C-C} aromatic), 1336 cm^{-1} (ν_{C-N} lactam) and 771 cm^{-1} (δ_{oop} benzene trisubstituted) indicating the presence of carteolol in the complex structure. The strong band corresponding to the secondary amine group of carteolol in its salt form at 2786 cm^{-1} appears to be overlapped and it cannot be identified.

However, this technique is not relevant to identify the interaction nature in the obtained complexes. Therefore, other studies have been carried out in order to establish the type of interaction between carteolol and polymer.

3.3. NMR spectroscopy

In order to assess what kind of interaction binds carteolol and Eudragit L-Na copolymer, a spectroscopic study of the complexes by ^{1}H-NMR and ^{13}C-NMR was carried out. The comparative study of the NMR spectrum of the Eudragit L-carteolol complex with those of each of the separated components suggests that carteolol is present in the structure of the complex in its ammonium salt form, as stated by Lee et al. (1991) for similar compounds of propranolol and Eudragit L-Na.

3.4. ^{1}H-NMR spectroscopy

Fig. 5 demonstrates ^{1}H-NMR spectra taken in DMSO-d_6 solution for carteolol hydrochloride (Fig. 5a), the complex Eudragit L-carteolol (Fig. 5b) and Eudragit L-Na neutralized at 30% (Fig. 5c). Spectra were assigned by 2D-COSY experiments, selective decoupling techniques and taking into account data obtained from the literature (Jackman, 1962).

The spectrum in Fig. 5c was registered for Eudragit L-Na and is typical for 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 and 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 complex should be the result of the superposition of the spectra of the two isolated components. The permanence of the signal that resonates at 10 ppm, corresponding to the amine group of carteolol hydrochloride (R-$^{+}NH_2$), indicates that the drug is present in its salt form. According to this, the spectrum taken for the complex (Fig. 5b) is almost the algebraic sum of those corresponding to carteolol hydrochloride (Fig. 5a) and Eudragit L-Na (Fig. 5c).

In a similar study previously carried out (Alvarez-Fuentes, 1994a,b), the morphine complexes showed different results. The ^{1}H-NMR spectrum of the complex did not show the signal corresponding to the morphine amine group resonating at 9 ppm. This was indicative of the different behaviour of this drug and its presence in the complex structure as a free base, not as an ammonium salt.

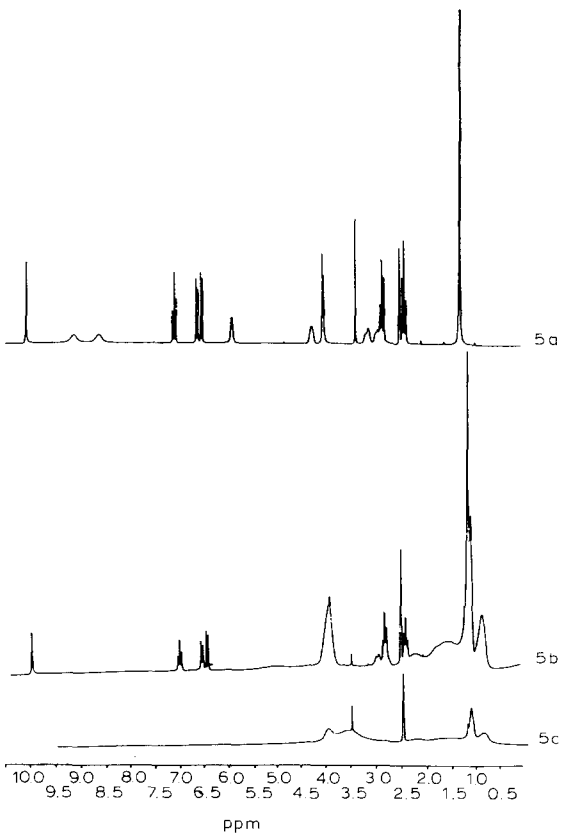
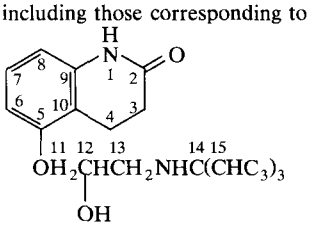


Fig. 5. ^{1}H-NMR spectra corresponding to: (a) carteolol hydrochloride, (b) Eudragit L-carteolol complex, (c) Eudragit L-Na 30%.

Table 1
^{13}C chemical shifts found for carteolol portion in the complex including those corresponding to carteolol hydrochloride



	Carteolol hydrochloride	Eudragit®-carteolol
C_2	170.1	170.1
C_3	29.2	29.8
C_4	18.3	18.2
C_5	155.4	155.6
C_6	106.0	105.9
C_7	127.7	127.7
C_8	108.4	108.2
C_9	111.3	111.2
C_{10}	139.4	139.3
C_{11}	70.0	70.5
C_{12}	65.6	66.2
C_{13}	44.4	44.3
C_{14}	56.4	53.9
C_{15}	25.0	26.0

3.5. ^{13}C-NMR spectroscopy

^{13}C-NMR spectra were recorded in DMSO-d_6 and assigned by using DEPT experiments, considering data in the literature (Breitmaier and Voelter, 1987).

Table 1 lists ^{13}C chemical shifts experimentally found for the carteolol portion in the complex, as well as those corresponding to carteolol hydrochloride. Data were obtained under the same conditions for comparison purposes. As can be deduced from the analysis of these data, the spectroscopic behaviour of carteolol carbons in the complex is very similar to that found for carteolol in its salt form, except carbons situated in positions 12, 14 and 15. The carbon in position 14 appears electrostatically shielded, showing a lower chemical shift due to the replacement of the hydrochloride anion by the resin carboxylate anion. On the other hand, the opposite effect is

observed for the carbons in positions 12 and 15. As in the ^{1}H-NMR experiments, the ^{13}C data are again indicative of the fact that carteolol is present in the complex as an ammonium salt.

Hence, the addition of carteolol hydrochloride aqueous solution to a Eudragit L-Na aqueous solution involves the neutralization of HCl from the amine group of the carteolol-HCl by the R-COONa subunits of the partially neutralized polymer. The secondary amine group of carteolol ($R\text{-}^{+}NH_2$) can then interact with these polar groups resulting in the formation of a saline bond.

With the use of morphine the same neutralization process is found, but 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 and York (1989) and Jenquin et al. (1990) have considered this kind of interaction as responsible for the binding of drugs with amine groups and acrylic polymers as Eudragit® L 30D.

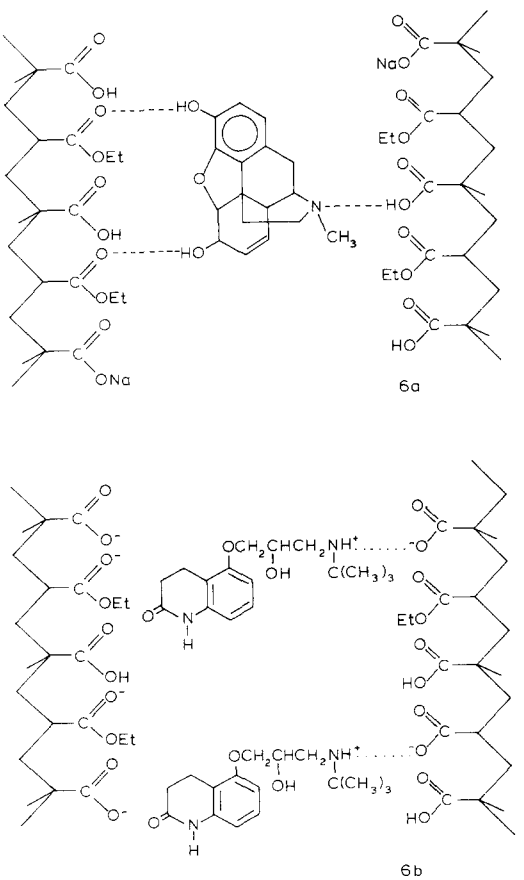


Fig. 6. Type of bonds between the drugs and Eudragit L: (a) hydrogen bonds corresponding to morphine, (b) saline bond corresponding to carteolol.

There are two possible types of hydrogen bonds between morphine and the resin used. In both, the reactive groups of the polymer were their carboxylic functions; however, the morphine can interact both with their hydroxyl groups and with its morphinic nitrogen. Fig. 6 illustrates the different type of bonds between the drugs and the polymer: hydrogen bonds corresponding to morphine (Fig. 6a) and saline bond corresponding to carteolol (Fig. 6b).

Table 2
Complex weights (g), drug incorporated (g) and content (%) as a function of neutralization degree (N.D., neutralization degree)

N.D. (%)	Drug incorporated (g)	Complex weight (g)	Content (%)
30	0.712	4.4180	16.12
32	0.885	4.5534	19.43
35	0.925	4.6211	20.02
36	0.969	4.7515	20.40
37	1.057	5.1200	20.64
38	0.974	4.7102	20.67
39	0.616	2.9788	20.69
40	0.428	1.9709	21.72

3.6. Processing complexation efficiency

Once the resultant products of the proposed reaction have been identified as Eudragit L-carteolol complexes with interactions of the saline bond type, the efficiency of this reaction can be determined. Therefore, it will be possible to standardize and optimize the complexation reaction.

In order to determine this efficiency, the weights and carteolol contents of the complexes were taken into account as dependent variables. Table 2 shows the data obtained. The considerable influence exerted by the degree of neutralization is clearly evident from the results.

In preceding investigations (Alvarez-Fuentes, 1994a,b), it was found that both the concentrations of NaOH and drug solutions affect the aforementioned parameters with statistical significance. These influences are stronger with respect to the percentage of drug incorporated into the complexes than to the weights of the complexes. This situation is due to the fact that a diminution in the reaction volume leads to an increase in the probability of interaction between the drug and the polymer molecules. So, we have used the maximum allowable concentrations of NaOH and drug solutions in order to achieve the maximum reaction efficiency.

In the drug-polymer reaction process, the addition of the carteolol hydrochloride solution to partially neutralized Eudragit L-Na results in the rapid formation of a white precipitate. As the reaction begins and progresses from 30 to 37% of neutralization, the neutralized carboxylate groups of the resin can freely interact with the drug molecules, resulting in the formation of a complex between the reactants. This situation produces a reduction in the effective charge of each of the components, thereby decreasing their water solubility. At the same time, a large and hydrophobic molecule is produced, which would also tend to have a minimal water solubility. As shown by the data in Table 2, the higher the degree of neutralization, the greater are the complex weight and the drug incorporated into complexes. Such a situation is due to the fact that an increase in the neutralization degree of the polymer results in the existence of more polar groups which are able to react with carteolol molecules.

Nevertheless, at 37% neutralization, this tendency changes suddenly: the excess of negative charges of the polymer cannot react with the drug molecules due to the occurrence of steric hindrance. With an excess of polymer partially neutralized, the surplus negative charge keeps this material partially suspended in water and the complexes' weight is found to be drastically reduced as indicated in Table 2. Therefore, the highest reaction efficiency corresponds to 37% of neutralization.

In relation to the carteolol content of complexes, the reaction involves complexes having a highest carteolol content close to 22%. Over the maximum reaction efficiency (37% of neutralization), the drug content reaches an asymptotic value due to the emergence of steric hindrance. Although the number of reactive groups of the polymer increases as the neutralization degree rises, the drug molecules cannot interact with the carboxylate groups of the polymer and the drug incorporated into complexes reaches a constant value. Similar results were obtained for morphine complexes (Alvarez-Fuentes, 1994a,b), 39% of neutralization being the valuer which provided the highest complex weight.

3.7. Comparative study of carteolol and morphine complexes

As previously indicated, morphine is incorporated into the polymer structure as a free base interacting with the resin by means of hydrogen bonds. In contrast, carteolol is present in the complex as an ammonium salt. The most important difference between the structure of both drugs is shown in Fig. 6: the secondary amine group present in the carteolol molecule makes possible the formation of a saline bond. On the other hand, the greater stability of the tertiary amine group of morphine and its considerable volume prevent the establishment of a saline bond. Hence, this molecule can only interact by means of hydrogen bonds.

The differences in strength between both types of bonds are consistent with the results previously obtained in the DSC assays. The observed increase in the T_g value of Eudragit L-carteolol complex would suggest the formation of a strong interaction that has been demonstrated with the NMR spectroscopy data obtained.

In summary, it can be concluded that the proposed complexation process allows the obtaining of Eudragit L-carteolol complexes. The nature of the interaction between the raw materials, based on saline bonds, has been precisely established using spectroscopic techniques. On the other hand, differences in carteolol and morphine complexation behaviours have been found due to the different chemical structure in relation to the amine group of both drugs. Thus, the possible

biopharmaceutical repercussions of both types of interactions as well as the use of these systems as a potential mechanism to extend carteolol and morphine release can be evaluated. These studies will be carried out in later investigations.

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