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Short Communication

Adsorption of Omeprazole on latex particles and characterization of the complex

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Abstract

Omeprazole is an antisecretory drug used against gastric ulcers. It quickly decomposes in an acid medium, however, therefore making it a matter of great interest to protect it in these conditions and determine the ideal adsorption conditions for this drug on latex particles for formulation designs — oral suspensions — containing polymers with the aim of delivering different drugs in a sustained and controlled action. Time, pH, and concentration of the active ingredient for which maximum adsorption occurs, were determined. The findings suggest that adsorption is evidently greatest at an acid pH 4–5, that the adsorption of Omeprazole rises concomitantly with the increase in latex particles, and the time is the least influential factor.

Keywords: Cellulose acetophthalate; Omeprazole kinetics of adsorption; Differential scanning calorimetry

1. Introduction

Omeprazole is a substituted benzimidazole ((5-methoxy-2-[methoxy-3,5-dymethyl-2-pyridinyl)methyl]-sulfinyl-1*H*-benzimidazole). This new antisecretory compound acts differently from anticholinergic or H2 histamine antagonists: it is a gastric-acid inhibitor that suppresses gastric-acid secretion by specifically inhibiting the H + /K + ATPase system at the secretory surface of the gastric parietal cell [1–3]. Although its therapeutic effects have been well characterized, few publications have centered on pharmaceutical oral suspensions [4,5].

Omeprazole is a white powder soluble in a basic medium, degrading very rapidly in aqueous solutions at low pH values [6]. The higher the pH, the greater its chemical stability, reaching its maximum at pH 11.

The latex used in this study is Aquateric® (cellulose acetophthalate latex), which plays a fundamental role as a protector in an acid medium. It is a white, dry powder insoluble in water. It is moderately viscose and is suitable for film formation with the addition of different plasticizers. Disintegration of the polymer occurs around pH 6.5.

The aim of this work was to study the adsorption process of Omeprazole on a cellulose polymer. We measured the time, pH and concentration of the drug necessary to produce the best adsorption and obtained drug–polymer complexes that protected the drug from an acid medium.

2. Materials and methods

2.1. Materials

Omeprazole was supplied by Schering-Plough S.A., Madrid, Spain.

The dispersive polymer used was Aquateric® (FMC Corp., USA), supplied by Foret S.A., Spain. It has a composition of 69.7% cellulose acetophthalate, 20% Pluronic F-68 (cationic surfactant), 10% Myvacet 940

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(monoglyceride component), and 0.3% Tween 60. To get rid of the highest possible amount of these surfactants, the original latex was repeatedly centrifuged and redispersed in water until a constant conductivity in the supernatant was obtained. This 'clean' material had a 3% volume fraction of solids, and was used to prepare the sediments to be studied.

Solutions of 0.1 N HCl and NaOH were used for the pH studies, supplied by E. Merck (Barcelona, Spain).

2.2. Methods

2.2.1. Latex characterization

Dilute samples were dried and studied by electron microscopy (SEM and TEM). The determination of particle shape and size in the pharmaceutical–polymer system was carried out by both transmissions (TEM) and scanning (SEM) electron microscopy. The samples were examined under a Hitachi S-510 electron microscope.

The electrokinetic properties of the polymer dispersion, and therefore of its electric layer, were ascertained by measuring electrophoretic mobility (μe) with a Malver Zetasizer 2c apparatus (Malvern Instruments, England). The pH of the suspensions was adjusted from 3 to 9 by adding HCl or NaOH. The suspensions were than allowed to equilibrate for 24 h before electroforetic mobility was determined. At least ten determinations were made for each sample at a temperature of 25.0 ± 0.5°C. The relative error of the measurements was estimated at about 0.5%.

2.2.2. Adsorption of Omeprazole on latex

The adsorption kinetics were studied with respect to time, the concentration of the active ingredient and pH. Omeprazole was mixed with Aquateric® at a constant temperature of 25°C and stirring at 60 rpm, followed by centrifugation at 15 500 rpm for 60 min to separate the sediment from the supernatant. The free active principle remains in the supernatant and was determined by spectrophotometry at λ 300 nm (maximum wavelength where the Omeprazol shows absorption). Spectrophotometric determinations were performed with a Perkin–Elmer running lambda 2 apparatus (Ueberlingen, Germany). The concentration of Omeprazole was calculated from calibration curves obtained with standard solutions.

2.2.3. Characterization of the complexes

Differential calorimetric scanning was performed with a Mettler FP89 apparatus for the range of temperatures from 30 to 300°C, at a heaving rate of 5 min^{-1}. Samples weighed 5–6 mg. Differential calorimetric scanning was used to study the different polymer–drug complexes, which provided information on the possible interaction of Omeprazole–latex. Finally, the scanning electron microscope was used for particle observation.

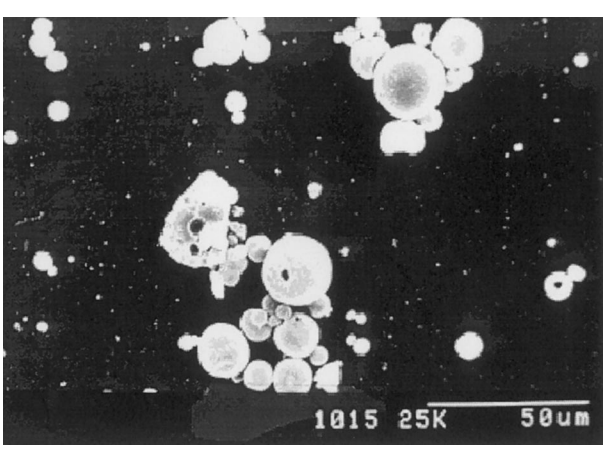


Fig. 1. Scanning electron microphotographs of Aquateric® particles, after latex washing at pH 4.5.

3. Results and discussion

3.1. Latex characterization

Aquateric® samples were examined by scanning electron microscopy. Fig. 1 shows a typical photograph of this latex, where two perfectly distinct populations of particles can be seen. One group comprises larger particles (4 μm) while the other has smaller ones (25–30 nm), both with a spongy surface. The microphotograph was taken under original latex conditions (pH 4.5) without modifying any of the medium parameters [7].

Electrokinetic analysis of the particles is extremely important when characterizing a latex, as it provides information on the type of charge (positive or negative) and therefore what kind of drugs they can be used with to obtain the best attraction between the latex particles and the drug.

The electrophoretic mobility has been measured as a function of the pH. Fig. 2 shows the electrophoretic mobility (μe) of Aquateric® at constant ionic strength (10^{-3} M NaCl). It can be seen that the surface charge of this polymer remains negative for the whole pH range studied, hence, no isolectric point (or pH zero zeta potential) is observed.

Furthermore, there is an increase in the absolute value of the mobility upon increasing the pH of the medium from pH 3 to 5. If the pH is further increased, no changes in either factor occur, with the plateau values of -3.9 ms^{-1}/V cm^{-1}. These results can be explained if we assume that the surface charge is generated by acetate groups. Their dissociation would leave negative charges on the particles, accounting for the negative μe values observed.

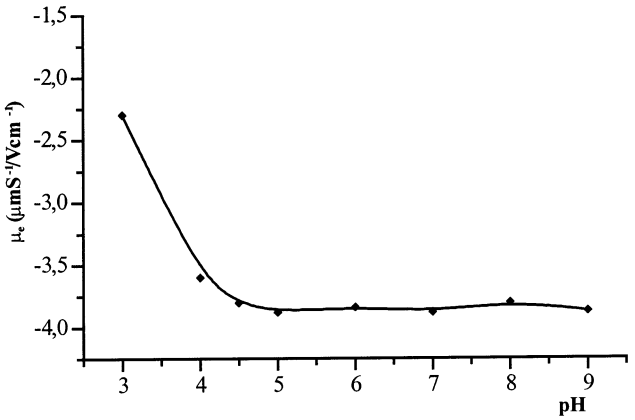


Fig. 2. Electrophoretic mobility of Aquateric® as a function of pH in the presence of 10^{-3} M NaCl.

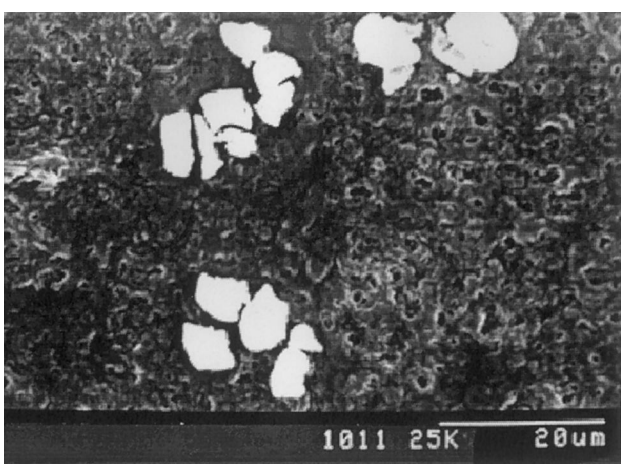


Fig. 3. Scanning electron microphotographs of Aquateric® particles dispersed in basic solutions.

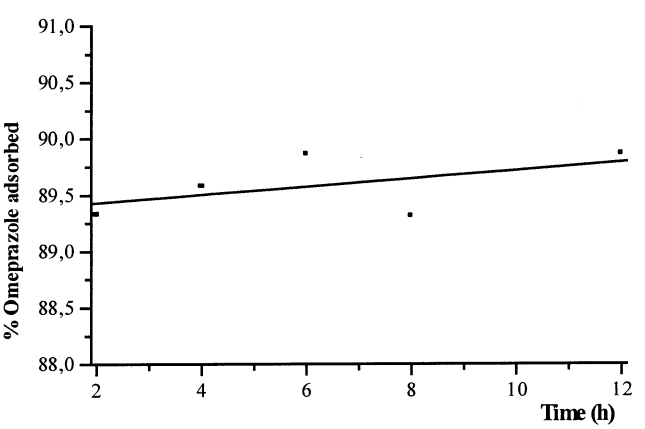


Fig. 4. Adsorption kinetics of Omeprazole on latex particles at an initial drug concentration of 0.04 mg ml^{-1}.

Accordingly, the plateau values must arise due to the circumstance that all of the available groups are disassociated when a pH of 5 is reached. This explanation is compatible with the pK_a values (4.75) of the acetic acid groups [8].

Mobility data above a pH of 9 could not be obtained due to the disintegration of the particles. The electron microphotographs of the Aquateric® particles at basic pH values (Fig. 3) clearly shows the decomposition of the colloid in an alkaline environment [9].

3.2. Adsorption study

The adsorption of Omeprazole on latex particles is studied to evaluate the potential usefulness of a given suspension as a system for the release of the drug, and to protect it.

Several factors have been taken into account in this study on the adsorption kinetics of Omeprazole, such as time, pH and concentration, with constant stirring and temperature. Fig. 4 presents the time with respect to the concentration of Omeprazole adsorbed. Note that the adsorption is nearly complete in all cases and undergoes no changes during the 12 h. These admittedly high data may be due to the circumstance that, at the working pH, Omeprazol and Aquateric® have opposing charges, thus favoring electrostatic adsorption.

The effect of variations in the pH on the adsorption of Omeprazole on Aquateric® is shown in Fig. 5. Adsorption is evidently greatest (90%) at an acid pH (4–5), as the proton concentration increases. Moreover, there is less Omeprazole on latex, probably because the drug is more unstable in acid pH. In an alkaline medium, the same occurs, although to a lesser extent, since the surface charges of the latex and the drug are the same and the electrostatic adsorption is lower.

Adsorption as a function of the concentration of Omeprazole is shown in Fig. 6. It can be observed that upon increasing the concentration of Omeprazole, the adsorption of Aquateric® latex particles also increases. The adsorption is a type C isotherm [10], indicating that the greatest adsorption has occurred in the latex micropores, where the smallest particles of drug predominate.

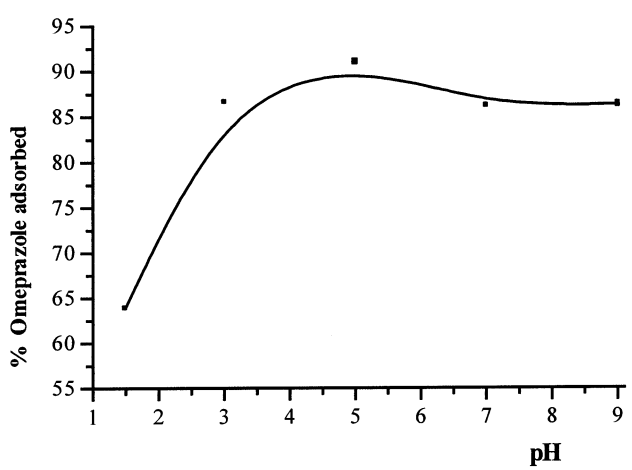


Fig. 5. Effect of pH on the amount of Omeprazole adsorbed.

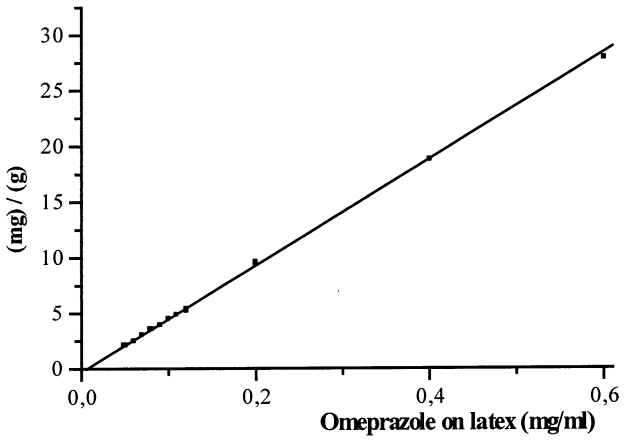


Fig. 6. Adsorption density of Omeprazole at different initial concentrations of the drug.

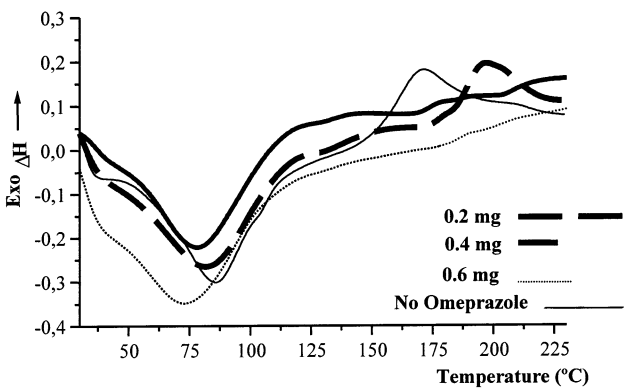


Fig. 7. Calorimetric behavior of latex–drug complexes.

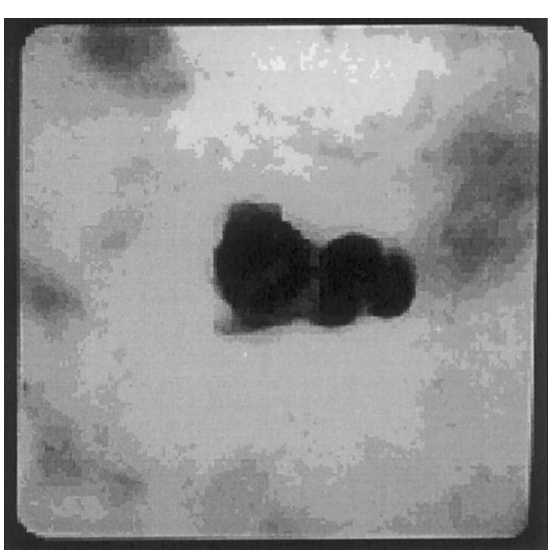


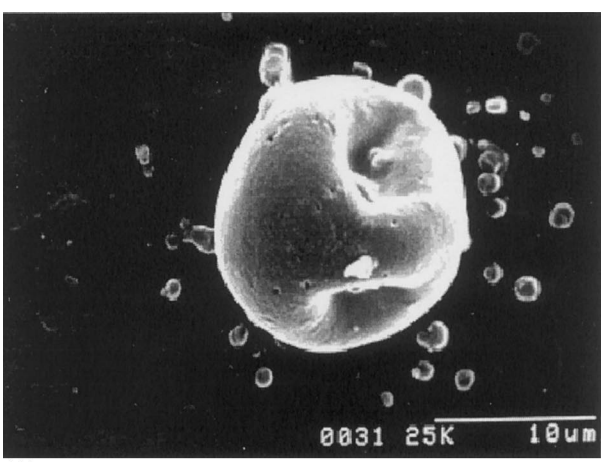
Fig. 8. Microphotograph of latex–drug complexes obtained by TEM.

3.3. Characterization of the complexes

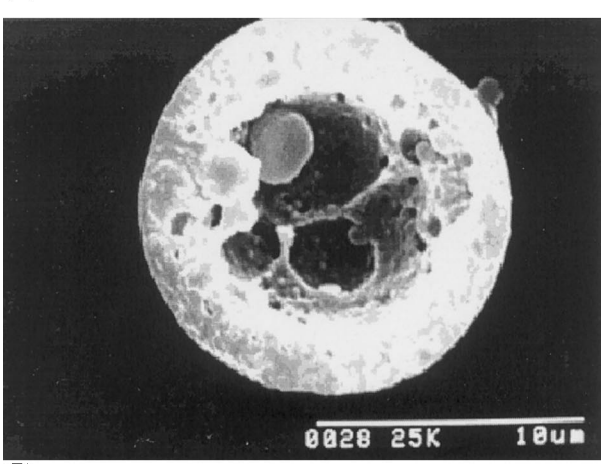
Fig. 7 shows the DSC curves for various drug–polymer complexes, each with different concentrations of the active principle. Their thermograms indicate that, as the amount of Omeprazole in the samples increases, the exothermic peak decreases, or even disappears, for complexes with a greater amount of active ingredient. At the same time, the endothermic minimum is also displaced towards lower temperatures as the amount of Omeprazol increases.

The surface of both substances was analyzed by TEM after the adsorption to determine how the drug adheres to the latex particles, revealing how the Omeprazol particles surround the latex (Fig. 8). However, the SEM microphotographs clearly show how the active ingredient is adsorbed in the polymer, in some cases on the other surface (Fig. 9(A)) and in others inside (Fig. 9(B)).

The results show that the latex is stable at acid pH values and unstable at alkaline ones as observed in the values for the electrophoretic mobility and microphotographs. In the study of adsorption we conclude that time is not an influential factor and that acid pH values produce the greatest adsorption and an increase in concentration increases the adsorption.



(A)



(B)

Fig. 9. (A) Microphotograph of latex–drug complexes obtained by SEM. (B) Microphotograph of latex–drug complexes obtained by SEM.

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