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RESEARCH PAPER

Adsorption-Desorption of Ondansetron on Latex Particles

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ABSTRACT

Ondansetron is a carbazol with antiemetic properties. It is used primarily to control nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy, as well as for treatment of postoperative vomiting in gynecological surgery. Ondansetron has a shelf life of about 3 hr; hence, it is a matter of great interest to determine the ideal adsorption-desorption conditions for this drug on latex particles for designs of formulations (oral suspensions) containing polymers with the aim of delivering different drugs in a prolonged and controlled fashion. Time, pH, electrolytes, and concentration of the active principal at which maximal adsorption occurred were determined. Desorption of the drug from latex polymer particles was studied in different media. The results obtained suggest that this polymer is suitable as carrier of drug for obtained formulations of controlled release. The findings suggest that pH is the principal factor influencing the release of the ondansetron from Aquateric®. The greatest release of drug occurs at acid pH, approximately 70% in the first hour; for the basic medium, the release is about 6%.

Key Words: *Cellulose acetophthalate; Ondansetron kinetics of adsorption-desorption.*

INTRODUCTION

Ondansetron is a carbazol with antiemetic properties. It functions as a competitive and selective antagonist for the 5 HT_3 serotonin receptors. It is used primarily to control nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy, as well as for treatment of postoperative vomiting in gynecological surgery (1–3).

Ondansetron is a crystalline white powder soluble in an acid medium. The lower the pH, the greater its chemical stability, reaching its maximum at a pH of 3 or 4 (4).

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Ondansetron has a shelf life (approximately 3 hr); hence, it is a matter of great interest to determine the ideal adsorption-desorption conditions for this drug on latex particles for design of formulations (oral suspensions) containing polymers with the aim of delivering different drugs in a prolonged and controlled fashion.

Latex is an aqueous dispersion of a water-insoluble polymer. Most commercial latexes are prepared by polymerization of a monomer that has been emulsified previously or dissolved in an aqueous phase (5). Another possibility consists of dissolving the polymer in an organic solvent and preparing an oil-in-water (O/W) emulsion. The solvent is then evaporated, giving rise to a stable suspension comprising one-micra spherical particles. Aquateric®, the latex used in this study, is prepared in this way. It is a white, dry powder that is insoluble in water. It mainly is composed of cellulose derivatives, specifically cellulose acetophthalate. It is moderately viscose and is suitable for film formation with the addition of different plasticizers. The disintegration of the polymer and the consequent release of the active principal occur around pH 6.5.

EXPERIMENTAL

Materials

The ondansetron, dihydrated (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazole-1-yl)methyl]-4H-carbazol-4-one] ($C_{18}H_{19}N_3O$), was supplied by Laboratories Vita S.A., Barcelona, 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 (monoglyceride component), and 0.3% Tween 60 (6). 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 it was used to prepare the sediments for study.

Solutions of 0.1 N HCl and NaOH were used for the pH studies. The electrolytes were NaCl, $Cl_2Ca \cdot 4H_2O$, and $Cl_3Al \cdot 6H_2O$ at different concentrations, supplied by Merck (Barcelona, Spain).

Spectrophotometric determinations were performed with a Perkin-Elmer Running Lambda 2 apparatus (Ueberlingen, Germany).

Methods

Latex Characterization

Dilute samples were dried and studied by scanning electron microscopy (SEM) to determine particle shape and size. The electrokinetic properties of the polymer dispersion, and therefore of its electric layer, were determined by measuring electrophoretic mobility (μe) with a Malver Zetasizer 2c apparatus (Malvern Instruments, England). At least 10 determinations were made for each sample at a temperature of 25.0°C ± 0.5°C. The zeta potential ζ was calculated based on the theory of O'Brien and White (7,8).

Adsorption of Ondansetron on Latex

The adsorption kinetics were studied with respect to time, the concentration of the active principle, the pH, and the concentrations of the different electrolytes. The ondansetron was mixed with the Aquateric at a constant temperature of 25°C and stirring at 60 rpm, followed by centrifugation at 14,000 rpm for 30 min to separate the sediment from the supernatant. The free active principle remained in the supernatant and was determined by spectrophotometry at λ 310 nm (maximum wavelength at which the ondansetron shows absorption). The concentration of ondansetron was calculated from calibration curves obtained with standard solutions.

In Vitro Desorption

The sediments for the desorption were prepared using a solution of 30% ondansetron, 60% Aquateric, and 10% NaCl 0.1 M. The suspension was kept in a water bath at 25°C with shaking at 60 rpm for 24 hr. It was then centrifuged for 30 min at 14,000 rpm to separate the sediment from the supernatant.

The desorption of ondansetron was obtained by placing the sediment in an acid medium, an acid-basic medium, and a neutral medium and shaking at 60 rpm at 37°C in a thermostated bath. Determination of the active principle released was performed over a period of 24 hr by measuring absorption of the supernatant. Concentrations of ondansetron were calculated from calibration curves with standard solutions. Before absorption determinations, samples were filtered through 0.22-μm Millipore membranes to eliminate any latex particles present. Blanks containing no drug were prepared in the same way as samples and were tested to compensate for possible interferences. At least three determinations were done for each data point (results presented as their mean value).

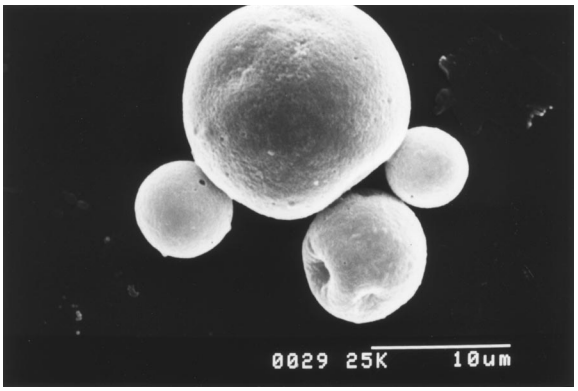

Figure 1. Scanning electron micrographs of Aquateric particles after latex cleaning at a pH about 5.

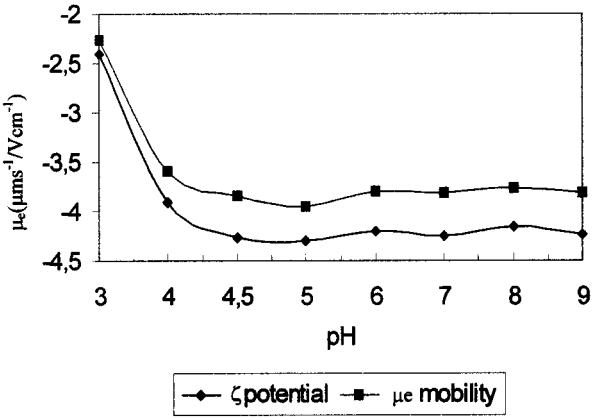

Figure 2. Electrophoretic mobility and zeta potential of Aquateric as a function of pH in the presence of 10^{-3} M NaCl.

RESULTS AND DISCUSSION

Latex Characterization

Aquateric samples were examined by SEM. Figure 1 shows a typical photograph of this latex in which two perfectly distinct populations of particles can be seen. One group is made of larger particles, about 16 μm, while the other has smaller ones, about 3–6 μm; both have a spongy surface. The microphotograph was taken under original latex conditions (pH 5) without modifying any of the medium parameters (9).

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 can be used to obtain the best attraction between the latex particles and the drug.

The electrophoretic mobility was measured as a function of the pH. Figure 2 shows the electrophoretic mobility μe and the zeta potential ζ 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 isoelectric point (or pH zero zeta potential) is observed.

Furthermore, both values (μe and ζ) increase in absolute value on increasing the pH of the medium from pH 3 to pH 5. If the pH is further increased, no changes in either factor, with the plateau values of about -3.9 ms^{-1}/Vcm^{-1}. These results can be explained if we assume that the surface charge is generated by acetate groups. Their dissociation will leave negative charges on the particles, accounting for the negative ζ values observed.

Accordingly, the plateau values must arise due to the circumstance that all of the available groups are disassociated when pH 5 is reached. This explanation is compatible with the pK_a values (4.75) of the acetic acid groups (10).

Mobility data above pH 9 could not be obtained due to the disintegration of the particles. The electron micrographs of the Aquateric particles at basic pH values (Fig. 3) clearly show the decomposition of the colloid in an alkaline environment (11).

Adsorption Study

The adsorption of ondansetron on latex particles was studied to evaluate the potential usefulness of a given suspension as a system for the release of the drug. Several factors were taken into account in this study on the adsorption kinetics of ondansetron, such as time, pH, and concentration, with a constant temperature of the medium and stir-

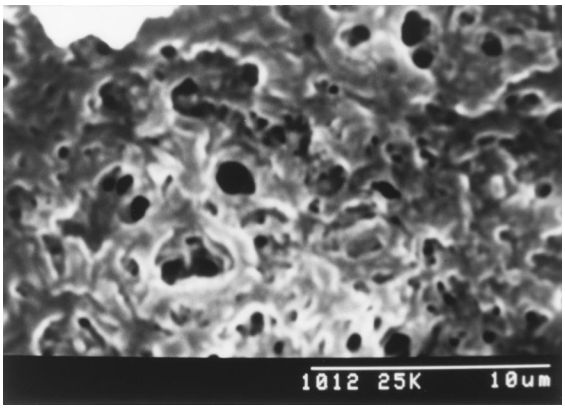

Figure 3. Scanning electron micrographs of Aquateric particles dispersed in basic solutions.

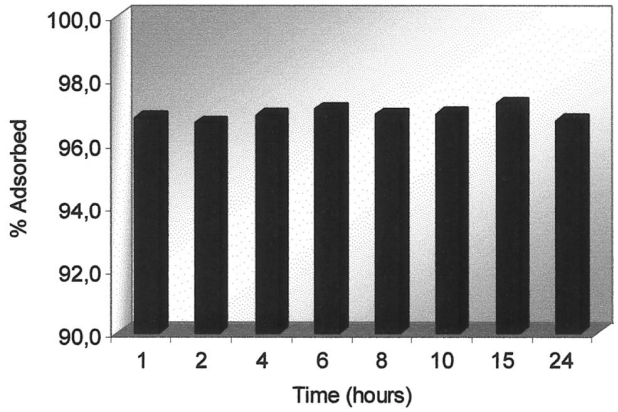

Figure 4. Adsorption kinetics of ondansetron on latex particles at an initial drug concentration of 0.3 mg/ml.

ring. Figure 4 presents the time with respect to the concentration of ondansetron adsorbed. Note that the adsorption undergoes no changes during the 24 hr of the study, which is why this period was used for the subsequent tests.

The effect of variations in the pH on the adsorption of ondansetron on Aquateric is shown in Fig. 5. Adsorption is evidently greatest (98%) at an acid pH (pH 2–4), with a reduction at pH 5, falling to 80% adsorption at pH 7. This effect is logical given the characteristics of the polymer, which can remain stable in acid medium, but decomposes in alkaline medium, as was seen in the mobility and microscopy studies. Furthermore, we must also take into account the charge of the drug, which has a chemical structure that contains groups more capable of joining the polymer charges.

Adsorption as a function of the concentration of ondansetron is shown in Fig. 6. It can be observed that, on

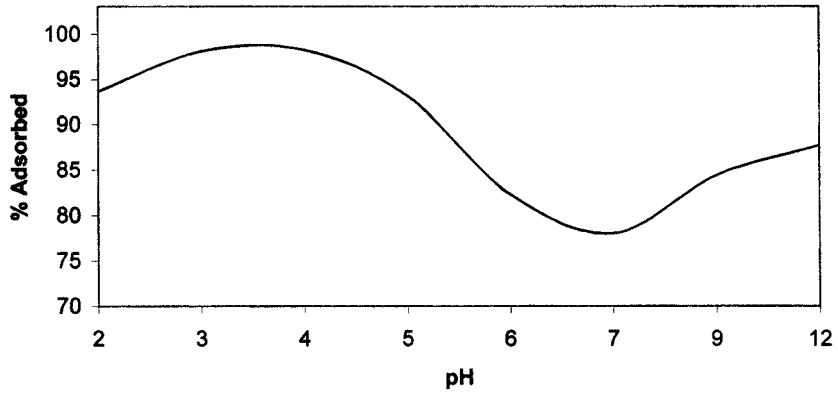

Figure 5. Effect of pH on the amount of ondansetron adsorbed.

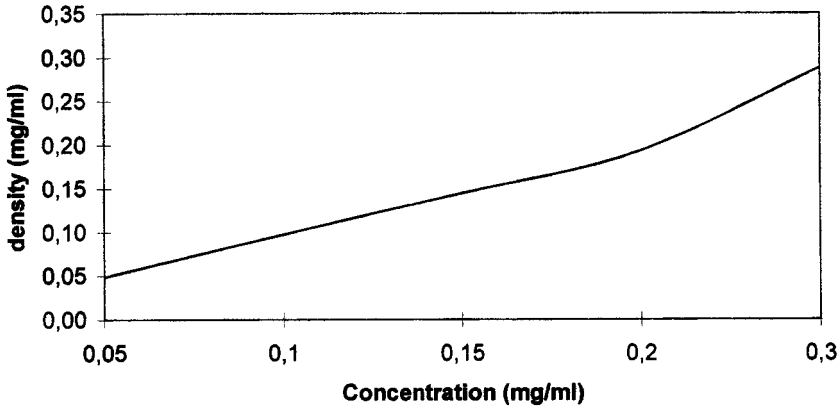

Figure 6. Adsorption density of ondansetron at different initial concentrations of the drug.

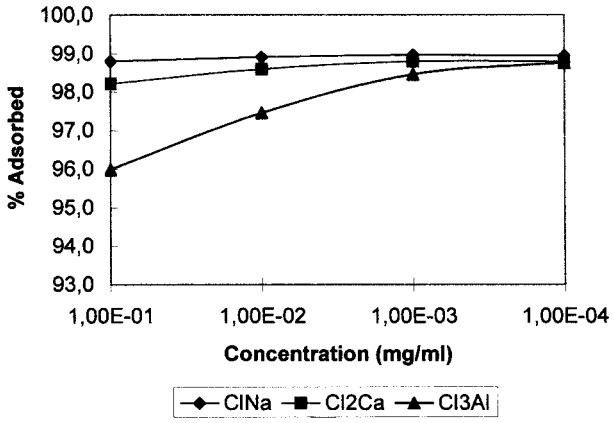

Figure 7. Adsorption density of ondansetron at different concentrations of electrolytes.

increasing the concentration of ondansetron, the adsorption of Aquateric latex particles also increases. The adsorption is a type S isotherm that has been presented in other works (12), which explains the adsorption of the drug in progressive layers on the polymer particles.

Electrolytes have also been studied since they are necessary as flocculating agents in suspensions because they can modify the electrical charge of the particle surface and therefore the adsorption of the drug on the particles. Figure 7 shows the effect of different electrolytes at different concentrations on the adsorption of the drug. Note how the behavior of the NaCl electrolytes (monovalent) and the $Cl_2Ca \cdot 4H_2O$ electrolytes (bivalent) are nearly identical at the same concentrations, although NaCl always gives a slightly higher absorption. Nonetheless, $Cl_3Al \cdot 6H_2O$ (trivalent) at high concentrations produces a decrease in the drug adsorption, probably since the higher positive charge of this electrolyte has a greater attraction for the polymer particles and displaces the ondansetron. This is an expected sequence of events if we examine what happens with the other two, $C1_2Ca \cdot 4H_2O$ and NaCl.

In Vitro Desorption

To evaluate the suitability of the ondansetron-latex complex as an in vivo vehicle for pharmaceutical release, we determined the in vitro desorption at different times and distinct pH: stomach pH 1.5, intestinal pH 7, and acid-basic medium. By acid-basic medium, we refer to the sediment being kept for the first 2 hr at the stomach pH 1.5 and subsequently increasing the pH to approximately 7 (13). The desorption tests were performed at a temperature of 37°C with shaking at 80 rpm.

Figure 8 shows the percentage of drug released over time in the different pH media. Note that the greatest release of active principle (80%) occurs at acid pH and at acid-basic pH.

At an acid pH, 65% of the drug is released in the first hour, reaching 98% at 24 hr. At an acid-basic pH, the trend is similar, as 75% of the drug is released in the first hour, 80% at 2 hr, which is when the pH was changed, and then no further change over the 24 hr of the test. This is interesting as it indicates that somehow a percentage of the pharmaceutical remains joined to the latex and is released progressively. When the ondansetron is placed in an acid medium, 100% is dissolved within a few minutes.

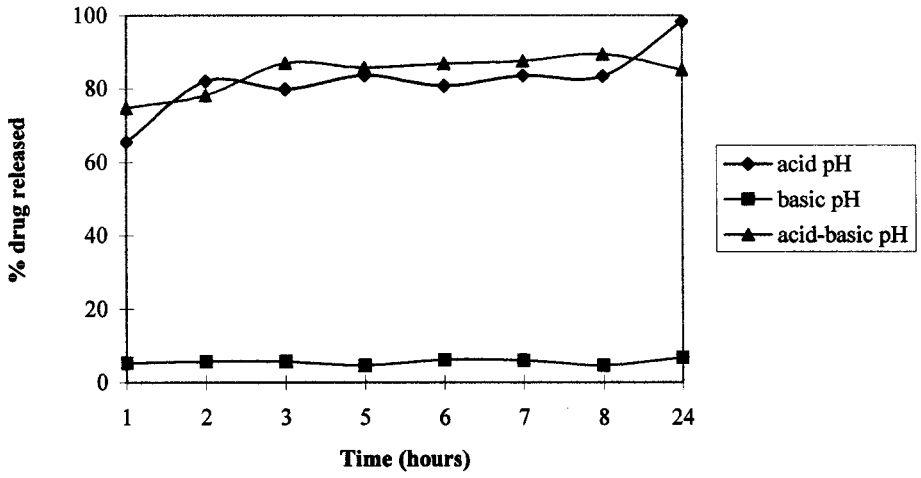

Figure 8. Percentage ondansetron released in different media.

In contrast, when the pH is basic at approximately pH 7, there is a very low release of the active principle, barely reaching 6%. This is obviously due to the fact that, as mentioned above, ondansetron is not soluble in an alkaline medium, thus accounting for its poor release with a basic medium.

All of these results are confirmed by the Aquateric mobility and microscopy studies, discussed above, showing greater electrophoretic mobility at acid pH and the destruction of the latex particles at basic medium; therefore, when the pH is acid, the percentage of ondansetron released is greater.

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