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Effect of the preservatives antipyrin, benzoic acid and sodium metabisulfite on properties of the nitrofurantoin/solution interface

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Summary

The possible usefulness of a group of pharmaceutical preservatives in aqueous suspensions of nitrofurantoin was analyzed in a previous study (Ruiz Martinez et al., 1987). The analysis of UV spectra and melting point data led to the conclusion that antipyrin (ANT), benzoic acid (BA) and sodium metabisulfite (NaMB) were among the best choices as photoprotector, antibacterial and antioxidant agents, respectively. Given the influence of the electrical properties of the interface on the physical stability of suspensions, we considered it worthwhile to study the effects of the three preservatives on these properties. Using photon correlation spectroscopy, we measured the electrophoretic mobility (μ) in nitrofurantoin suspensions containing different concentrations of ANT, BA and NaMB. Small changes in mobility were observed with concentrations of ANT ranging from 10^{-5} to 10^{-2} M, although μ tended to decrease slightly with concentration. The behaviour appeared to be different with BA and NaMB: mobility (consistently negative) increased initially up to a concentration of $\approx 10^{-4}$ M, then decreased with rising concentration. These results are interpreted on the basis of the variations in conductivity and pH of the suspensions for the different concentrations of the three preservatives studied.

Introduction

A multitude of agents are known to cause deterioration of many types of pharmaceutical preparations. For example, chemical transformations are caused by variations in pH or temperature, the presence of light, oxygen or moisture, or by bacterial or fungal contamination. Several of these factors may occur simultaneously.

These agents frequently necessitate the use of preservatives to eliminate or minimize possible sources of deterioration in the preparation (Martindale, 1989). Such preservatives include antimicrobial agents to eliminate or inhibit the growth of microorganisms which may be present in the ingredients, or which may be added during manufacture or (more commonly) during use. Another significant source of alteration is oxidation of one or more of the ingredients upon ex-

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posure to atmospheric oxygen. Many of the oxidation reactions in pharmaceutical preparations are considered as 'auto-oxidation', i.e., chain reactions initiated by ultraviolet radiation in the presence of traces of oxygen. These cases may require the addition of small amounts of antioxidants or photoprotectors.

In a previous study (Ruiz Martinez et al., 1987) we analyzed some preservatives for suspensions of nitrofurantoin, as this compound is altered with relative ease. We found that antipyrin (ANT), of all the substances tested, was the best photoprotector, while benzoic acid (BA) was a suitable antimicrobial agent and sodium metabisulfite (NaMB) was a good choice as an antioxidant. In the present study, our objective was to determine the possible effects of these preservatives on the nitrofurantoin interface in aqueous solution. The findings are of interest not only because they tell us something of the mode of interaction between the preservative and the active principle, but also because they permit qualitative predictions of the possible effects of the preservative on the physical stability of the suspensions.

Our analysis is based on experimental data of the electrophoretic mobility of nitrofurantoin suspensions with different concentrations of preservative. These findings were complemented with data for electrical conductivity and pH of the medium, to explain, as far as possible, the observed behaviour.

Materials and Methods

All compounds were of 'pro analysis' grade. The water used in the suspensions was twice distilled and filtered through Nuclepore membranes (0.2 μm pore diameter). The stock suspensions were prepared by suspending 10 g nitrofurantoin in 1 l of water, and allowing the mixture to settle for 4 h in order to obtain a suspension of the smallest particle size fraction. To these suspensions were added appropriate volumes of preservative solutions to obtain the desired concentrations. Electrophoretic mobility was determined with a Malvern Zeta-Sizer IIc, based on photon correlation spectroscopy (Barth and Sun, 1985).

Results and Discussion

The effect of pH on the electrophoretic mobility (μ) of nitrofurantoin alone was considered in an earlier paper (Delgado et al., 1990). Mobility rose significantly with pH, and both mobility and consequently surface charge density remained negative throughout the range of pH values studied. This behaviour can be explained by the characteristics of nitrofurantoin and its interaction with the aqueous medium. The acid nature of the hydrogen atom in the imide group of nitrofurantoin favours deprotonation of the molecule, and consequently the formation of a net negative charge on the particle surface. The increase of pH would displace the reaction in the direction of higher deprotonation, thus leaving a more negative charged particle, as in fact observed.

The variation of the electrophoretic mobility of nitrofurantoin particles with ANT concentration is displayed in Fig. 1. The mobility decreases in absolute value up to [ANT] $\approx 10^{-3}$ M, and for higher concentrations the negative surface charge increases. The value of μ corresponding to the lowest concentration of ANT is of the same order as that reported by Delgado et al. (1990) at pH 3.5

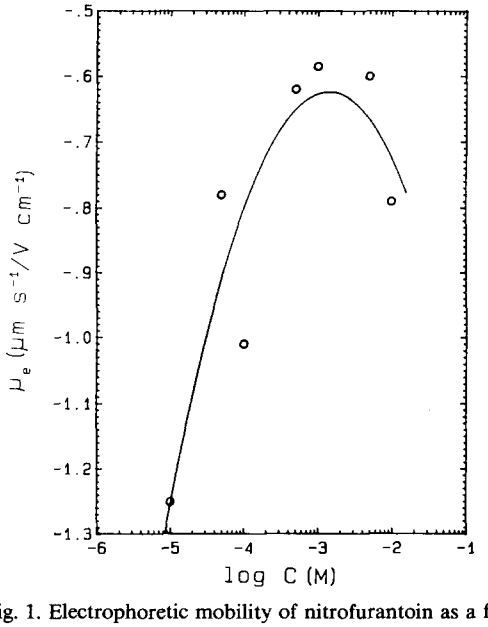

Fig. 1. Electrophoretic mobility of nitrofurantoin as a function of antipyrin concentration.

in the absence of any preservatives. Fig. 2 shows the electrical conductivity and pH of the suspensions for the whole range of ANT concentration studied. As observed in this figure, the pH was approx. 6.5 for the lowest concentration of antipyrin, and our results thus suggest that this preservative is adsorbed to some extent on the drug particles and inhibits deprotonation of the imide group. Fig. 2 also shows that the suspension pH increased for $[ANT] \geq 10^{-3}$ M. Since previous results showed that the negative charge on the particles increased with pH, the change of trend observed in μ (Fig. 1) could thus be explained. It should also be noted that the electrical conductivity (maximum when μ is minimum) is only very slightly altered by concentrations of ANT between 10^{-5} and 10^{-2} M (note the scale of the left axis in Fig. 2), indicating that antipyrin is a very weak electrolyte and appears to adsorb essentially in neutral form onto nitrofurantoin particles.

The effects of changes in BA concentration on the electrophoretic mobility of nitrofurantoin are shown in Fig. 3. The corresponding variations in conductivity and pH of the suspensions displayed in Fig. 4 indicate a considerable dissociation of BA at concentrations above 10^{-4} M. As observed

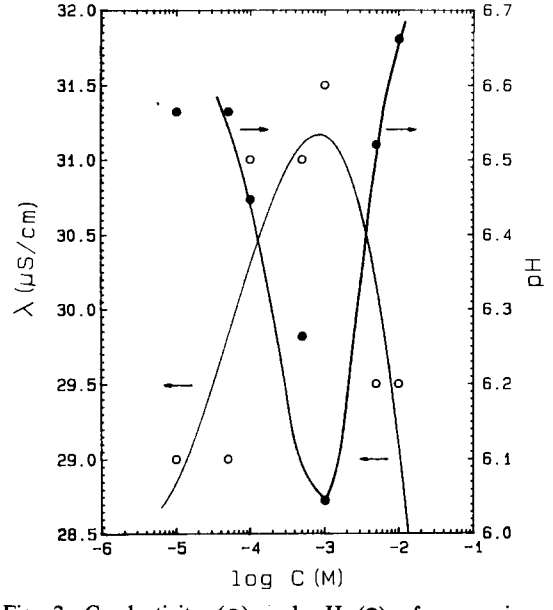

Fig. 2. Conductivity (○) and pH (●) of suspensions of nitrofurantoin as a function of antipyrin concentration.

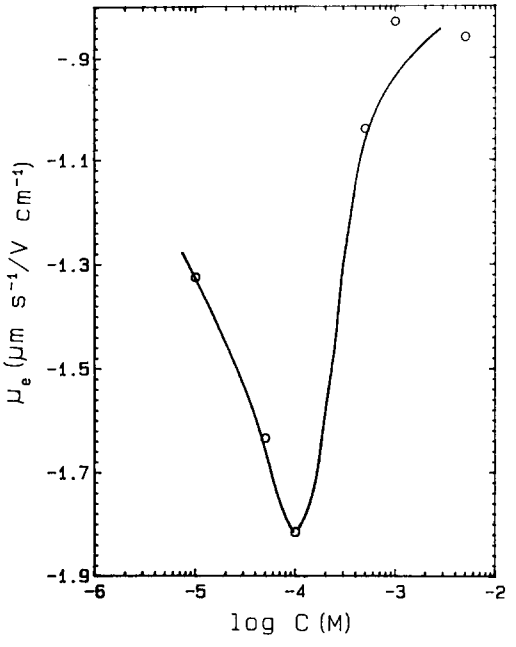

Fig. 3. Electrophoretic mobility of nitrofurantoin as a function of benzoic acid concentration.

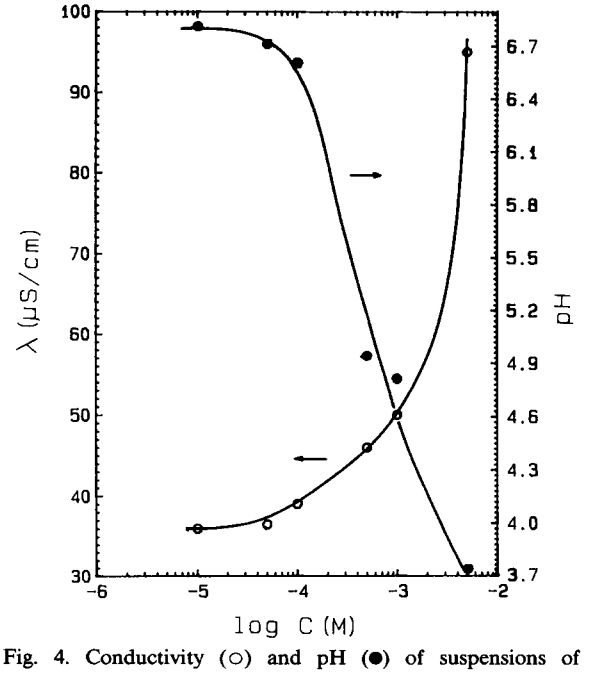

Fig. 4. Conductivity (○) and pH (●) of suspensions of nitrofurantoin as a function of benzoic acid concentration.

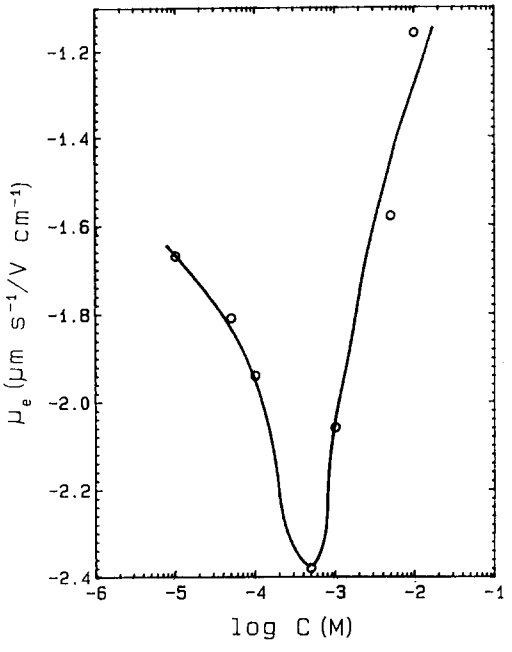

Fig. 5. Electrophoretic mobility of nitrofurantoin as a function of sodium metabisulfite concentration.

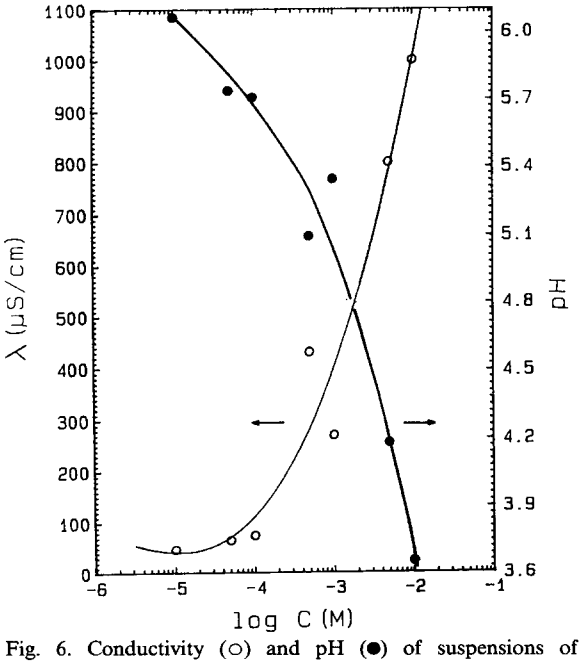

Fig. 6. Conductivity (○) and pH (●) of suspensions of nitrofurantoin as a function of sodium metabisulfite concentration.

in Fig. 3, μ becomes more negative as [BA] increases up to the latter value. Higher concentrations, on the other hand, give rise to a monotonic decrease in $|\mu|$. Adsorption of the negative benzoate ion on the surface of the drug may explain the rise in μ toward more negative values, whereas competition between this ion and H^+ ions (note in Fig. 4 that pH reaches ≈ 3.5 when $[BA] = 10^{-2}$ M) may account for the maximum and subsequent decrease in μ.

Fig. 5 illustrates the changes in μ with increasing concentrations of NaMB. The trend shown by the mobility of nitrofurantoin is very similar to that seen with BA (Fig. 3), although more negative values of μ are found with sodium metabisulphite. These differences must probably arise from the considerable degree of dissociation of NaMB, as shown by the conductivity and pH data in Fig. 6: the larger number of negative ions must lead, in all likelihood, to a higher negative charge on nitrofurantoin, hence the larger $|\mu|$ values.

Conclusions

Our study leads to the conclusion that ANT has little effect on the surface charge of nitrofurantoin, although it may contribute to the destabilization of suspensions by lowering μ. By contrast, the ions supplied by BA and, to a greater extent, by NaMB may have considerable effects on the surface charge of the drug in aqueous suspension. This effect is especially significant at intermediate (high μ values) and high concentrations (low to moderate surface charge).

Acknowledgement

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