Polymer Bulletin 26, 529–534 (1991)

Polymer Bulletin

Sulfonamide release from cellulose acetate membranes

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SUMMARY

Cellulose acetate membranes were chemically modified by esterification with oxalyl chloride which was used as a hydrolytically labile spacer. Then five sulfonamides were attached to the acyl chloride present on the half-esterified membranes to give drug-polymer conjugates. The rate of the hydrolytic cleavage of the spacer-drug linkage was measured in simulated gastric fluids at 37º ± 0.5ºC by determining the amount of drug released by spectrophotometric analysis. The results showed that in all cases the process followed a zero-order kinetics.

INTRODUCTION

Several examples have been reported about release of drugs covalently bonded to polymeric systems (1-7), where two physicochemical processes control the release rate: cleavage of the covalent bond by hydrolysis and diffusion of the free drug through the polymer matrix.

Modification of membrane surfaces, on the other hand is of great importance to produce delivery systems for controlled release of bioactive agents (8).

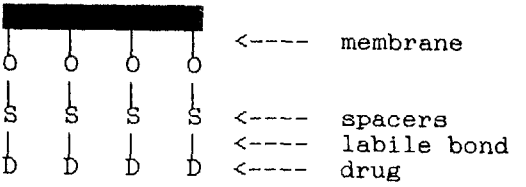

Figure 1. Covalently Attached Membrane-Drug System.

Although there have been studies about surface modification of cellulose fibers and membranes (9a-b), there exists to our knowledge very little information about the modifications of cellulose acetate membranes by chemical reactions. These membranes were modified by reaction between the surface hydroxyl groups and oxalyl chloride. The reactive acyl chloride

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thus originated was then coupled to five sulfonamides (Figure 1) (10). In this work these reactions were confirmed by hydrolysis of the membrane-drug linkage which releases the corresponding sulfonamide. This was identified and determined by spectrophotometry.

EXPERIMENTAL

Chemicals and Reagents: Sulfanilamide, sulfadiazine, sulfamerazine, sulfapyridine sodium and sulfamethazine of analytical grade were used without further purification. The simulated gastric fluids were prepared by a procedure similar to that of the literature (11).

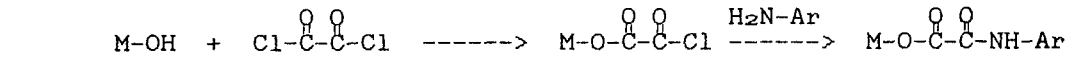
Apparatus: The spectrophotometric studies were carried out on a Shimadzu UV 260 spectrophotometer. The surface of the membranes was examined with a Phillips 501 B scanning electron microscope. A constant-temperature bath which was regulated by a thermostat (Haake E2) with ± 0.5ºC precision was used.

Measurement of Release Rates: A piece of the desired membrane was placed into a tube containing 5 ml of simulated gastric fluids and then stored at 37º ± 0.5ºC with continuos stirring during the experiment. Samples were withdrawn at suitable time intervals (every 24 hs). The drug concentration was determined with a spectrophotometer at the analytical wavelength according to the corresponding sulfonamide. The release medium was completely removed after every measurement. All experiments were in duplicate and the average values were plotted.

RESULTS AND DISCUSSION

The surface hydroxyl groups of the cellulose acetate membranes were transformed, at reduced pressure, into the reactive acyl chloride which was then coupled with amine type drug and suspended in carbon tetrachloride, in order to form an amide linkage through the 4-amino group of the sulfonamides (Scheme 1).

Scheme 1

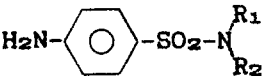


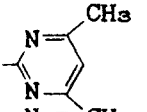
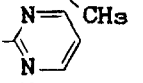
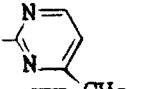
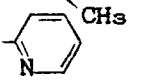
M-OH: Cellulose Acetate Membrane
Ar: $-C_6H_4-SO_2-NR_1R_2$
$(ClCO)_2$: Oxalyl Chloride

The release of the corresponding sulfonamide was carried out in simulated gastric fluids at 37ºC by hydrolysis of the amide group (-CONH-). Spectroscopic studies and chemical assays with sodium nitrite and N-(1-naphtyl)-ethylenediamine dihydrochloride showed that the free drug was present in the reaction medium.

The model drugs, the analytical wavelength and the molar absorptivity coefficients in simulated gastric fluids are shown in Table 1.

Table 1. Structure, Analytical Wavelength and Molar Absorptivity Coefficients of the Sulfonamides.[a]



Sulfonamide	R_1	R_1	λ max	ϵ(l mol^{-1}cm^{-1})
Sulfanilamide	H	H	273	992 (r=0.99)
Sulfamethazine	H		273	3103 (r=1.00)
Sulfadiazine	H		264	4462 (r=0.98)
Sulfamerazine	H		304	1294 (r=1.00)
Sulfapyridine Sodium	Na.H_2O		310	5172 (r=0.99)

a) 37ºC, synthetic gastric fluid

The hydrolytic reactions followed zero-order kinetics, and their calculated rate constants and the correlation coefficients are listed in Table 2. As it can be seen, the rates of release decrease in the order of sulfanilamide > sulfamethazine > sulfadiazine > sulfamerazine > sulfapyridine sodium.

Table 2: Release Rate of Sulfonamides

Sulfonamides	Release Rates (mg.h^{-1})	r
Sulfanilamide	3.10^{-3}	0.97
Sulfamethazine	1.10^{-3}	0.99
Sulfadiazine	8.10^{-4}	0.96
Sulfamerazine	4.10^{-4}	0.97
Sulfapyridine Sodium	3.10^{-4}	0.99

By plotting total amount (mg) of sulfonamide released versus time (Figure 2), a linear relationship was observed (r > 0.96) following an initial burst effect, possibly due to the

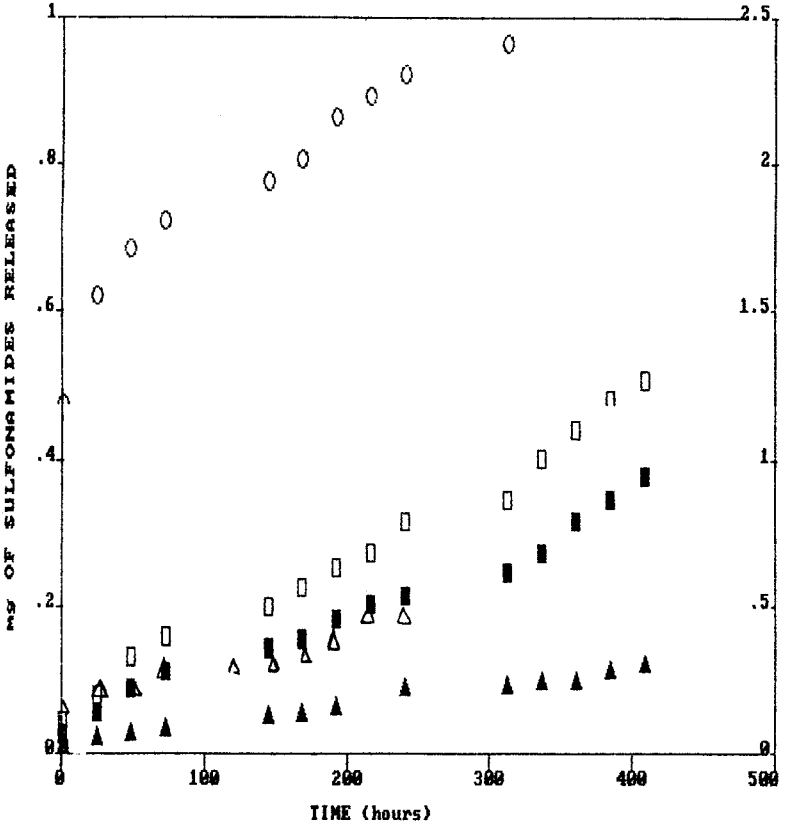


Figure 2: In vitro release of sulfonamides from cellulose acetate membranes: (Δ) sulfamerazine, (▲) sulfapyridine sodium, (□) sulfamethazine, (■) sulfadiazine, (scale on the left); (○) sulfanilamide (scale on the right).

drug physically adsorbed. The parameters for the linear ratio were calculated by means of a standard technique of linear regression, obtaining a good fitting degree.

Direct evidence of the sulfonamides released from the membranes was obtained by scanning electron micrographs (SEM) (Figure 3), which showed variation on the surfaces of the membranes before and after the release occurred.

Figure 3a shows a heterogeneous dispersion structure which would correspond to sulfonamides covalently bonded to the membrane through the spacer, while in Figure 3b is observed the depression zone after the model drugs released when the hydrolysis took place. During all experimental work no membranes alteration was observed.

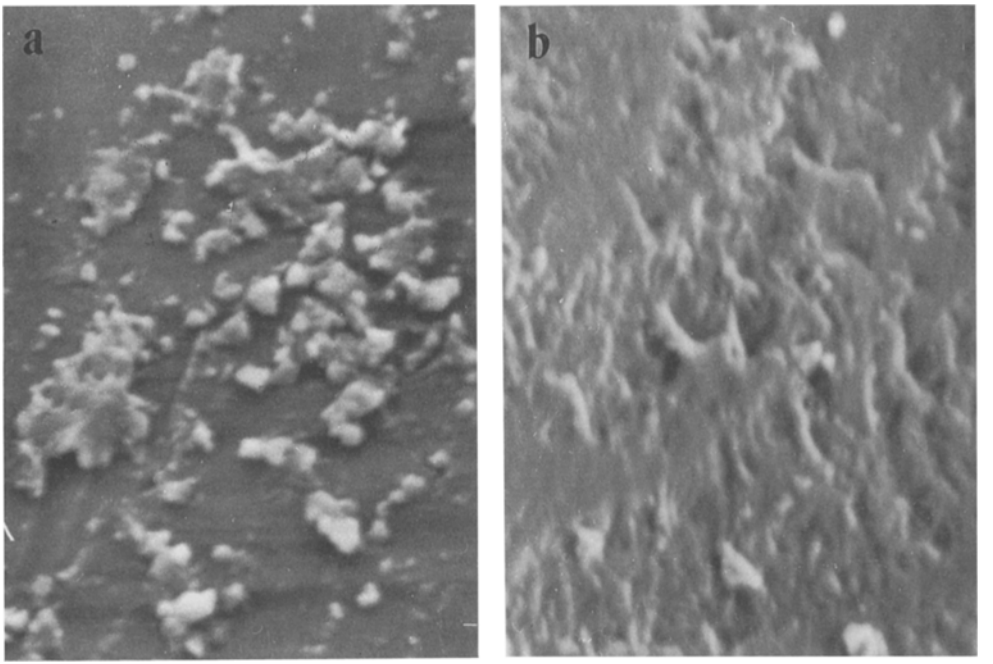


Figure 3: Scanning electron micrographs of the membrane surfaces: a) Before and b) after the release occurs.

CONCLUSIONS

Our present studies show that chemical modification of membrane surfaces is an important way to produce delivery systems for controlled release of bioactive substances, since they follow a zero-order kinetics maintaining a constant amount of drug for extended periods of time.

ACKNOWLEDGMENTS

The authors thank the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the Consejo de Investigaciones de la Provincia de Córdoba (CONICOR), and the Secretaría de Ciencia y Técnica (SECyT) of Argentina for financial support.

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Accepted April 22, 1991 K