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A possible pH-controlled drug delivery system based on a derivative of the polysaccharide scleroglucan

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Four carboxylated derivatives of scleroglucan have been obtained by oxidation, to different extents, of the glucopyranose side chains of the natural polysaccharide. The diffusion of model molecules through aqueous solutions of these new products was measured at various pH values. The reversible pH induced sol–gel transition of some of the polyelectrolyte solutions tested effects a remarkable variation in the diffusion rate of the permeating species; in this sense the most interesting polysaccharide appears to be the product with 70% oxidized glucopyranose moieties. The behaviour of scleroglucan and its derivatives has been compared with that of carboxymethylcellulose and the mechanism involved in drug permeation and release discussed. The possible application of one of the new products in controlled release formulations for oral use is also reported.

A variety of different materials has been used to obtain the sustained release of pharmacologically active compounds. In most instances synthetic or natural polymers have been used (Kim et al 1980; Lyman 1983), the device behaving as a drug reservoir delivering the agent, by different mechanisms, at a constant and predetermined rate. In this respect polysaccharides and their derivatives represent a group of polymers, commonly present in pharmaceutical formulations, whose use for a sustained release has been emphasized recently (Allan et al 1984; Schacht et al 1984).

The unusual behaviour in aqueous solution of some new polyelectrolytes (Crescenzi et al 1983) obtained by oxidation of glucopyranose side chains of the polysaccharide scleroglucan (Rodgers 1973) (see Fig. 1), and, in particular, their reversible pH-induced gelation, prompted us to investigate their possible application as a pH-controlled drug delivery system, capable of responding to the environmental stimuli in the various segments of the gastrointestinal tract.

As reported herein, results obtained in-vitro with model molecules showed that one of the scleroglucan derivatives tested appears to be particularly suitable for a self-regulating drug delivery system (Alhaique et al 1981). The mechanism involved in drug release is discussed and a comparison of the new polysaccharides with carboxymethylcellulose (CMC) is also reported.

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MATERIALS AND METHODS

Materials

Purified scleroglucan, used as starting material for the oxidation reaction, was supplied by CECA A.S. France. Low viscosity sodium carboxymethylcellulose (CMC), with an average molecular weight similar to that of scleroglucan, was purchased from Sigma Chemical Company. Salicylic acid (USP) and Orange II (for microscopy) were Merck-Schuchardt products. All other reagents were of analytical grade. Solutions at different pH values were obtained with diluted HCl and phosphate buffer (ionic strength 0·1 M). Scleroglucan derivatives were prepared according to the procedure proposed by Crescenzi et al (1983) and the scheme of the reaction process is described in Fig. 1.

In the previously reported preparation (Crescenzi et al 1983), a complete oxidation of glucopyranose side chains was effected, thus an excess of oxidizing agent was used for each step (periodate and chlorite). For the present investigation, various products, oxidized to different extents, have been obtained. For this purpose the stoichiometric ratio between oxidizing agent and scleroglucan was changed according to the average number of carboxyl groups required for the final product. The following scleroglucan derivatives were used for this study: S-1·0 (complete oxidation—100%); S-0·7 (70% oxidation); S-0·5 (50% oxidation); S-0·2 (20% oxidation). The degree of oxidation of the compounds was verified both by potentiometric titration and atomic absorption spectroscopic determinations

of Na^+ ions. No variation of the average number of glucopyranose units of the linear chain was detected after oxidation.

Diffusion studies

According to the type of experiment to be made, permeation studies were performed with a two or three compartment diffusion cell described by Alhaique et al (1972, 1977). The area available for diffusion was 5·30 cm^2 and each of the outer compartments occupied a volume of about 8·5 ml, while the central one, when present, contained 2·2 ml and behaved as a barrier to the permeating species. Each compartment was separated from the others by a cellophane membrane that acted as an inert barrier to diffusion. The temperature was kept at 25 ± 1 °C by means of a thermostatic bath, and, when necessary, stirring was maintained throughout the experiments. Samples were taken from the receptor compartment for spectrophotometric measurements (10 mm quartz cells) of absorbance, at the appropriate wavelength. These were used for quantitative determinations of permeating substance. Reference calibration curves were constructed from values obtained in buffer solutions at pH values corresponding to those of the permeation experiments.

Equilibrium dialysis

18/32 type dialysis sacs (The Scientific Instrument Centre) were used. 2 ml of polysaccharide buffer solution containing the permeating species was equilibrated against 5 ml of an aqueous solution buffered at the same pH value. Operating conditions were the same as for the diffusion experiments. Appropriate blanks without permeating substance were set up for each experiment. Quantitative determinations of diffusate were performed by uv analysis. Equilibrium was reached within 24 h and the volume variations of equilibrating solutions were considered for quantitative calculations.

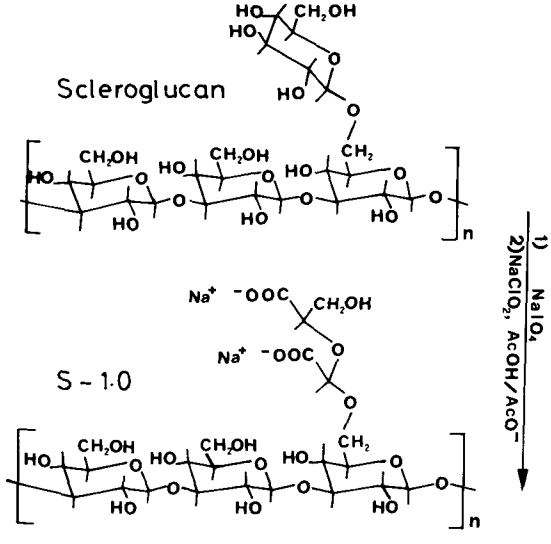

FIG. 1.

Release studies

Release experiments were carried out using a solubility simulator according to Stricker (1969, 1971) (Sartorius Membrane filter). The area available for diffusion was the same in each experiment. Release was determined at different pH values that simulated the stomach and the intestine environmental conditions.

RESULTS AND DISCUSSION

While the viscosity of scleroglucan is not changed by variations of pH over a range from 1–11 (Cottrell 1980), the rheological properties of 'scleroglucan carboxylated derivatives' are, quite naturally, remarkably affected by the pH value of the solution. The main differences have been observed with S-0·7. In fact a 2% (w/v) solution of S-0·7 (Na^+ salt) in pure water or at pH above 6·0 is a viscous but easily flowing fluid, while in acidic medium (below pH 3·5) it is a very compact gel (stable also above 80 °C). Such sol-gel transition brings about a significant variation in the diffusion rate of a permeating species. Diffusion of a dye (10^{-4} M Orange II) from water solutions buffered at different pH values into 2% (w/v) solutions/gels of the scleroglucan derivatives was studied by means of a two compartments model system (see experimental section), no stirring was used during these experiments, and the differences in permeation rate on going from sols to gels could be directly visualized due to the sharp boundary of the coloured zone. Times required to reach equilibrium (i.e. constant concentration in the donor compartment) are reported in Table 1.

No effect of pH on the cellophane barrier between the two compartments was detected. For an increase in scleroglucan derivative concentration, there was a non-linear increase in equilibration time (Sarisuta & Parrott 1982, 1983). As may be seen from Table 1, the main variation in equilibrium time with pH was obtained when S-0·7 was used.

Table 1. Time required to reach equilibrium in a two compartments diffusion cell (permeating solution: 10^{-4} M orange II).

Polysaccharide in the receptor compartment (2% w/v)	Time for equilibrium (h) pH 3	pH 8
Scleroglucan	21	21
S-0·2	24	23
S-0·5	30	23
S-0·7	36	23
S-1·0	22	22
—	16	16

The effect of pH on the diffusion rate of salicylic acid/salicylate (5×10^{-4} M) through a 2% S-0·7 solution is illustrated in Fig. 2. A three compartment cell was used. The diffusion cell was equilibrated to the same pH value and the central compartment (containing S-0·7) was the barrier to the permeating species. In no instance was the diffusion through the Cellophane membrane, separating the cells the rate limiting step of the overall diffusion process, furthermore no effect of pH on Cellophane permeability could be detected (Fig. 2, plot A).

As is possible to observe from the trends of plots B and C of Fig. 2, the permeation rate of salicylic acid determined at pH 2–3 is much lower than that of salicylate at pH 7–8 (no differences between pH = 2 and 3 or between 7 and 8 were detected). The effect of environmental pH on the permeation rate was reversible. As shown in plot D of Fig. 2, for pH variations obtained by alternate additions of 4 M NaOH or HCl to the solution, a corresponding change in diffusion rate can be observed; only a few minutes lag time was detected.

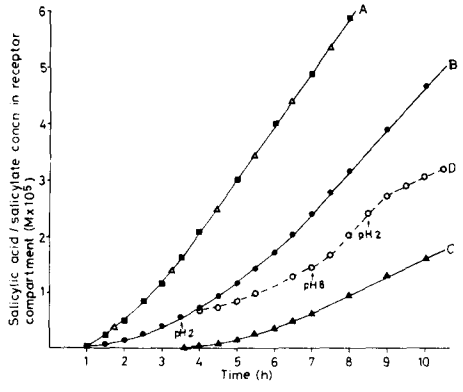

FIG. 2. Effect of pH on the diffusion rate of salicylic acid/salicylate through a S-0·7 solution. The concentration of diffusing species in the receptor compartment is reported as a function of time. Plot A is the reference curve obtained at pH 2 (■) and 8 (△), when no scleroglucan derivative was present in the central compartment of the diffusion cell. Curve B (●) and curve C (▲) represent the diffusion through S-0·7 (2% w/v) at pH 8 and 2 respectively. Results obtained when the pH was changed during the experiment (starting from pH 8) are indicated by plot D (○); the arrow indicates the conditions at which pH has been brought to the indicated value. Initial concentration of salicylic acid/salicylate in the donor compartment was 5×10^{-4} M. Stirring and constant temperature were maintained throughout the experiment.

An increase of S-0·7 concentration in the central compartment of the cell (i.e. the barrier) leads to non-linear decreases in the permeation rate of the diffusate (Sarisuta & Parrott 1982, 1983), both in neutral and acidic medium; but we found the differences between the slopes of the curves determined at the two pH values, not to be appreciably affected by S-0·7 concentration.

The effect of pH on the permeation of salicylic acid/salicylate through 2% solutions of the different scleroglucan derivatives is illustrated in Fig. 3 where the apparent diffusion constant (Lueck et al 1957; Nogami et al 1970) is reported for the various polymer samples used. A comparison with the starting material (scleroglucan) and with CMC is also reported.

As may be seen, the diffusion through S-0·7, S-0·5 and S-0·2 is slower in acidic medium than in a neutral or alkaline solution, while for scleroglucan, S-1·0 and CMC the opposite appertains and the permeation determined at pH 7–8 is lower than at pH 2–3 (a possible explanation is given later). S-0·7 as expected, showed a higher difference of apparent diffusion constant according to pH value.

That the observed variations in permeation rate are to be ascribed to changes in the rheology of S-0·7 solutions and not to substantial variations of the binding of the permeating species onto the polysaccharide macromolecules (Voigt & Thomas 1983), was verified by means of equilibrium dialysis measurements. In Table 2 the results of binding

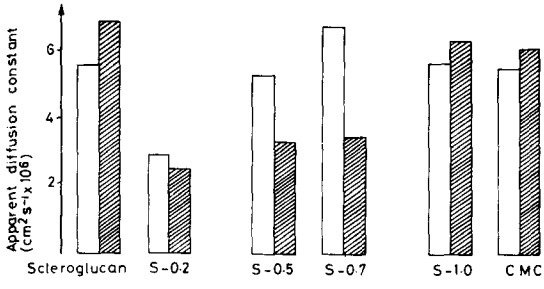

FIG. 3. Apparent diffusion constants of salicylic acid/salicylate as a function of pH and of type of polysaccharide present in the central compartment of the diffusion cell (2% w/v). Open columns pH 8, hatched columns pH 2. Initial concentration of the permeating species in the donor compartment = 5×10^{-4} M.

Table 2. Binding of salicylic acid/salicylate to tested polysaccharides (2% w/v) at different pH values. Results are given as percentage of diffusing species bound to the macromolecules.

pH	Sclero-glucan	S-0·2	S-0·5	S-0·7	S-1·0	CMC
3	3·1	4·0	4·4	5·2	7·0	6·8
8	2·3	2·7	3·0	4·1	5·3	6·2

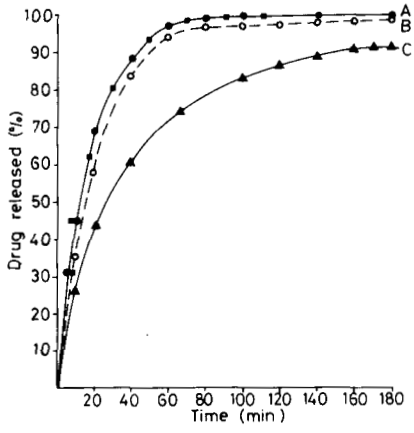

FIG. 4. Effect of pH on the release rate of salicylic acid/salicylate. The percentage of released species is reported as a function of time. (○) pH 6·8; (▲) pH 2·0 from 2% (w/v) S-0·7; (●) and (■) reference obtained without polyelectrolyte at ph 6·8 and 2·0 respectively.

studies performed in the same experimental conditions as the diffusion studies are reported.

At a pH of 8, the binding of salicylate to the macromolecule increases from 2–5% as degree of oxidation is increased from scleroglucan to S-1·0, while the increase of binding of salicylic acid is from 3–7% for an environmental pH of 3. The observed binding variations do not correspond with the trend of the diffusion constants reported in Fig. 2, thus they cannot account for the differences in permeation rates detected in the diffusion experiments. Furthermore, dialysis experiments have shown that in alkaline solution the osmotic pressure induces a significant increase of the volume inside the dialysis sac. This effect may be the cause of the lower apparent diffusion constant values observed at pH 7–8 with S-1·0 and CMC, since more water in the central compartment causes an increase of barrier thickness.

In an attempt to simulate the behaviour of the polysaccharides in controlling the release of salicylic acid from a reservoir device, according to the environmental conditions of the gastrointestinal tract, 2·0 ml of a 2×10^{-2} M solution of salicylic acid in a 2% scleroglucan derivative solution were sealed in a Cellophane tubing, immersed in a buffer at the appropriate pH value, and the release of the diffusing species was determined by means of a dissolution test apparatus according to Stricker (1969, 1971). The results obtained with S-0·7 are reported in Fig. 4.

As could be predicted, the release rate is much lower at pH 2·0 (stomach environment, curve C) than at pH 6·8 (intestinal environment, curve B). Plot A is the reference curve obtained without the polyelectrolyte. Different concentrations of the diffusing species gave plots that showed the same trend. Variations with pH in the release rates were less evident when S-0·5 and S-0·2 were used in the same experimental conditions.

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