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CROSS-LINKED HYDROPHILIC GELS FROM ABA BLOCK COPOLYMERIC SURFACTANTS

A.A. AL-SADEN, A.T. FLORENCE ** and T.L. WHATELEY *

*Department of Pharmaceutics and * Department of Pharmaceutical Chemistry, University of Strathclyde, Glasgow, G1 1XW (Scotland)*

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SUMMARY

Gelation of aqueous solutions of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block co-polymeric non-ionic surfactants (Pluronics or poloxamers) by the action of γ-rays is reported. Poloxamers with ethylene oxide content below 70% do not gel under the conditions studied, but appear to undergo chain scission, as there is a decrease in cloud point and an increase in hydrodynamic radius which is most likely to be due to increased association of the more hydrophobic polymer. The gels obtained from poloxamers with ethylene oxide content over 70% have a high water uptake capacity. The possibility of using these gels as sustained release drug delivery systems is discussed.

INTRODUCTION

This paper reports on some work carried out as part of a study of novel types of gel systems formed by the polymerization of non-ionic surfactants. Ideally, cross-linked polymerized micellar systems, while theoretically capable of solubilizing poorly soluble drugs would not be subject, as micellar solutions are, to disruption on dilution by body fluids or other solvents, as the micellar units would be held together by inter-micellar or intra-micellar cross-links or both.

Hydrophilic gels prepared from polymerizable monomers, such as hydroxy-alkyl-methacrylates, acrylic acid derivatives, and others have been widely used in drug delivery systems (Ratner and Hoffman, 1976). Drug can be sorbed from solution into the gel and on administration the drug leaches out over a relatively short period. The use of a solubilizing system where the micelles are held together in a polymer matrix should result in higher capacities if the drug is taken up by hydrophobic domains. This should lead to

** To whom correspondence should be addressed.

release times more prolonged than from normal hydrophilic gels where the drug is wholly resident in the hydrophilic regions of the polymer. Non-ionic surfactants, such as poly-oxyethylated long-chain alcohols have sufficiently large hydrated micelles to cause their aqueous solutions to gel at concentrations in the region of 5–10% but these gelled solutions redisperse on dilution. In the absence of oxygen, aqueous solutions of poly(ethylene) glycols cross-link to form gels after γ-irradiation, provided that the concentration of the polymer is above a certain critical value (Stafford 1970). We had hoped that cross-linking could be induced in the same manner between the poly(oxyethylene) chains in micelles or on adjacent micelles of poly(oxyethylated) alkyl ether, but so far, attempts to induce cross-linking of the hydrophilic chains of aqueous non-ionic surfactant solutions (of Triton X-100, Cetomacrogol 1000 and Brij 96) have shown that these non-ionics undergo chain scission under the influence of irradiation leading to the formation of mixed micelles of the starting surfactant monomer and the modified shortened and therefore more hydrophobic surfactant molecules (Al-Saden et al., 1980). In this paper, however, we report the successful gelation by γ-irradiation of block co-polymers of the ABA poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) type or poloxamers, sold under the trade name Pluronics. The poloxamers are non-ionic surfactants (Prasad et al., 1979) which are relatively non-toxic, being used, for example, as emulsifiers in intravenous fat emulsions (Lunsted and Schmolka, 1976). Gelation is not induced by irradiation in all poloxamer solutions as there is a specific hydrophilic chain length requirement, below which the scission noted above occurs.

MATERIALS AND METHODS

Acetanilide was supplied by B.D.H. Poloxamer samples were Pluronics, used as received from Union Carbide (Union Carbide, Rickmansworth, U.K.). The molecular weight and ethylene oxide content of the A-chain of the poloxamers are listed below.

Poloxamer type	Ethylene-oxide content	Average ethylene-oxide units/2 *	Molecular weight
L64	40%	13.5	2917
P75	50%	24	4150
F68	80%	80	8750
F87	70%	60	7500
F88	80%	102	11,250

* Average length in A-chain, from manufacturer's literature.

Preparation of aqueous solutions of the surfactants for γ-irradiation

N_2O, a cross-linking enhancer (Geymer, 1973), was bubbled through the required quantity of distilled water for 2 h and used to prepare the required surfactant solution. The ampoules (25 ml) were three-quarters filled with the surfactant solution and sealed under nitrogen. 2%, 4% and 10% concentrations of the poloxamers were irradiated for 12, 18, 24 and 36 h at a dose rate of 0.33 Mrad h^{-1}. The γ-irradiation was carried in a cobalt-60 source at the Scottish Universities Research Centre, East Kilbride, Glasgow.

Photon correlation spectroscopy

A Malvern model 4300 photon correlation spectrometer with 48 channels was used with a Liconix He/Cd laser operating at 441.6 nm with a power of about 10 mW. Temperature was controlled at 25 ± 0.1°C and the data were analyzed using the method of cumulants (Koppel, 1972). Ln $(g^2(t) - 1)$ was routinely fitted to linear and quadratic functions of the time and the initial slope used to determine the diffusion coefficient, D. In the case of the non-linear fits, the Z-average diffusion coefficient is obtained. Determinations were made at angles 45°, 90° and 135° and were not significantly different. From D the equivalent spherical hydrodynamic radius, R_h, is calculated from the Stokes–Einstein equation,

$$R_h = \frac{kT}{6\pi\eta D}$$

where k is Boltzmann's constant, T is the absolute temperature and η is the solvent viscosity.

Viscosity measurements

These were made using a suspended level dilution viscometer with a flow time of 193 sec for water. Temperature was controlled at 25 ± 0.01°C. The intrinsic viscosity (η) of samples were obtained from plots of the reduced specific viscosity ($\eta_{sp/c}$) vs concentrations of polymer, c at $c \to 0$.

Solubilization of drugs

Acetanilide was solubilized in the poloxamer solutions by shaking at room temperature for 24 h prior to gelation of the samples.

Preparation of samples for scanning electron microscopy (SEM)

To preserve the three-dimensional morphology of the gels, specimens were prepared for microscopy by freeze-drying, a method which reduces problems such as shrinkage and surface tension deformation associated with air-drying. The gel block was placed for about 27 h in a freeze-drier (Edward High Vacuum, Model P.2/764). Small cubes of the freeze-dried material were taken and fixed to electron microscope stubs using double-sided Sellotape, immediately followed by vacuum deposition of a thin gold film to render the specimen conductive. The samples were examined on a Phillips 500 model scanning electron microscope.

Swelling studies

Portions of the gels were dried in a vacuum oven at 25°C over P_2O_5. Small samples of the dried material were taken and placed in the solution and the increase in the weight determined by simply weighing the gel at time intervals up to 6 h, after carefully removing excess surface water.

Drug sorbtion studies

Portions of the dry gels of Pluronic F68 and F88 were each placed in 50 ml of a 0.01% aqueous acetanilide solution for a period of 7 days. The amount of drug sorbed into the swollen gels was determined spectrophotometrically.

Drug release rates

Gel blocks containing the drug were placed in a flask containing 100 ml buffer (pH 7.4) and fixed over a submersible magnetic stirrer (to provide continuous steady stirring) which was then placed in a water bath controlled at 25°C. The absorbance of the supernatant was measured at time intervals at 240 nm. Release rates of the drug from poloxamer gel and solution were obtained by placing the poloxamer gel or solution containing the drug in a dialysis bag.

RESULTS AND DISCUSSION

The poloxamers were chosen for γ-irradiation studies because our previous work had indicated that for successful cross-linking long ethylene-oxide chains were required, (Al-Saden et al., 1980). The Pluronics offer a wide range of ethylene-oxide chain-lengths and high molecular weights. Pluronic L64 (mol. wt. 2917) irradiated at a concentration of 2% for periods of 6, 12, 18 and 24 h did not gel. P.C.S. studies of these irradiated solutions showed (Table 1) that there is an increase in the hydrodynamic radius of the molecules with increasing irradiation time. In addition, the cloud point of the sample irradiated for 24 h was reduced from 64°C to 47°C. The same effect was produced in Pluronic P75 (mol. wt. 4150) (Table 1) where the cloud point was reduced from 95°C to 83°C for the 24 h-irradiated sample. Both of these results suggest that degradation of the ethylene-oxide chain has occurred (Table 1). P.C.S. measurements made on 5% solutions of Triton X-100 irradiated under the same conditions, show the same trend of an increase in R_h with time of irradiation. The cloud point of the sample irradiated for 24 h was lowered to 56°C from 65°C and this was explained previously on the basis of the chain scission (Al-

TABLE 1

PHOTON CORRELATION SPECTROSCOPY RESULTS FOR SOLUTIONS OF POLOXAMERS EXPOSED TO γ-IRRADIATION AT A DOSE RATE OF 0.33 Mrad h^{-1}

Time of irradiation (h)	R_h (nm)	D ($cm^2\ s^{-1} \times 10^{-7}$)
(a) 2% w/v solution of Pluronic L64		
6	6.04	4.05
12	7.32	3.35
18	8.40	2.92
24	9.61	2.55
(b) 4% w/v solution of Pluronic P75		
0	3.84	6.37
3	4.24	5.77
16	4.87	5.03
24	5.24	4.60
(c) 5% w/v solution of Triton X-100		
6	5.3	4.62
12	5.7	4.30
24	6.0	4.10

Saden et al., 1980) leading to the formation of mixed micelles containing the more hydrophobic shorter ethylene-oxide chain molecules. Aggregation thus increases and the cloud point is decreased. It appeared that chain scission is occurring in Pluronic L64 and P75 solutions under the conditions studied. Pluronic L64 has 13.5 ethylene-oxide units and Pluronic P75 24 units in each A-chain. Triton X-100 has a total of 10 ethylene-oxide units.

Poloxamers with longer oxyethylene chains were thought to offer a better chance of cross-linking and Pluronic F68 (mol. wt. 8750) was therefore irradiated at concentrations of 10% for long periods. None of these solutions gelled, but the solutions became very viscous. Viscosity measurements on these irradiated samples are shown in Fig. 1. The large increase in viscosity is characteristic of cross-linking behaviour. Reducing the concentration of the poloxamer in solution to 2% and 4% was successful in producing the gelled state, following irradiation for 12, 18, 24 and 36 h. Pluronic F88 (mol. wt. 11,250) and Pluronic F87 (mol. wt. 7500) also gelled when 2% and 4% solutions were irradiated for 12, 18 and 24 h.

These results suggest that there is a minimum ethylene-oxide chain-length for gel formation; co-polymer molecules containing less than 50 ethylene-oxide units per hydrophilic chain (L64, P75) undergo chain scission. This may be because the length of the ethylene oxide chain is not sufficient to allow the chain entanglement needed for network formation.

The presence of some solutes can inhibit gelation in the long chain polymer systems, however. We have found, for example, that benzoic acid prevents gel formation in Pluro-

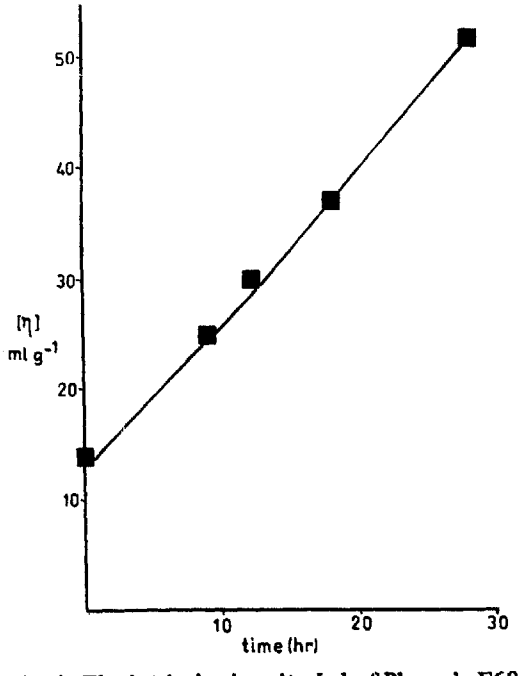
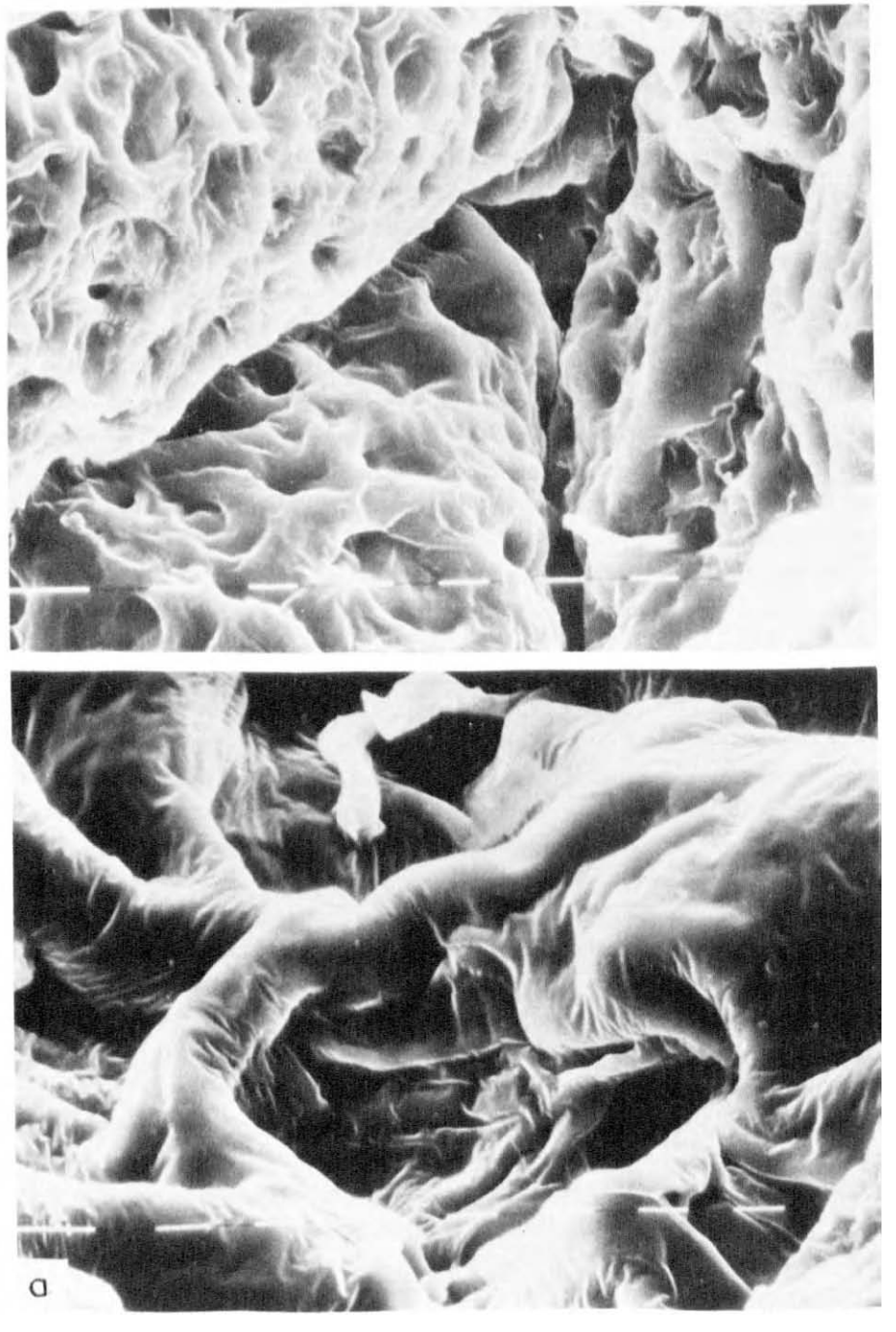


Fig. 1. The intrinsic viscosity $[\eta]$ of Pluronic F68 samples following γ-irradiation as a function of time of irradiation at a dose rate of 0.33 Mrad h^{-1}.

nic F68. This may be due to the conversion of the solvated electron to the hydrogen atom which is a less reactive species. Thus the poloxamers will not gel readily in acidic conditions.

SEM photographs of the freeze-dried gel formed by irradiation of 2% Pluronic F68 for



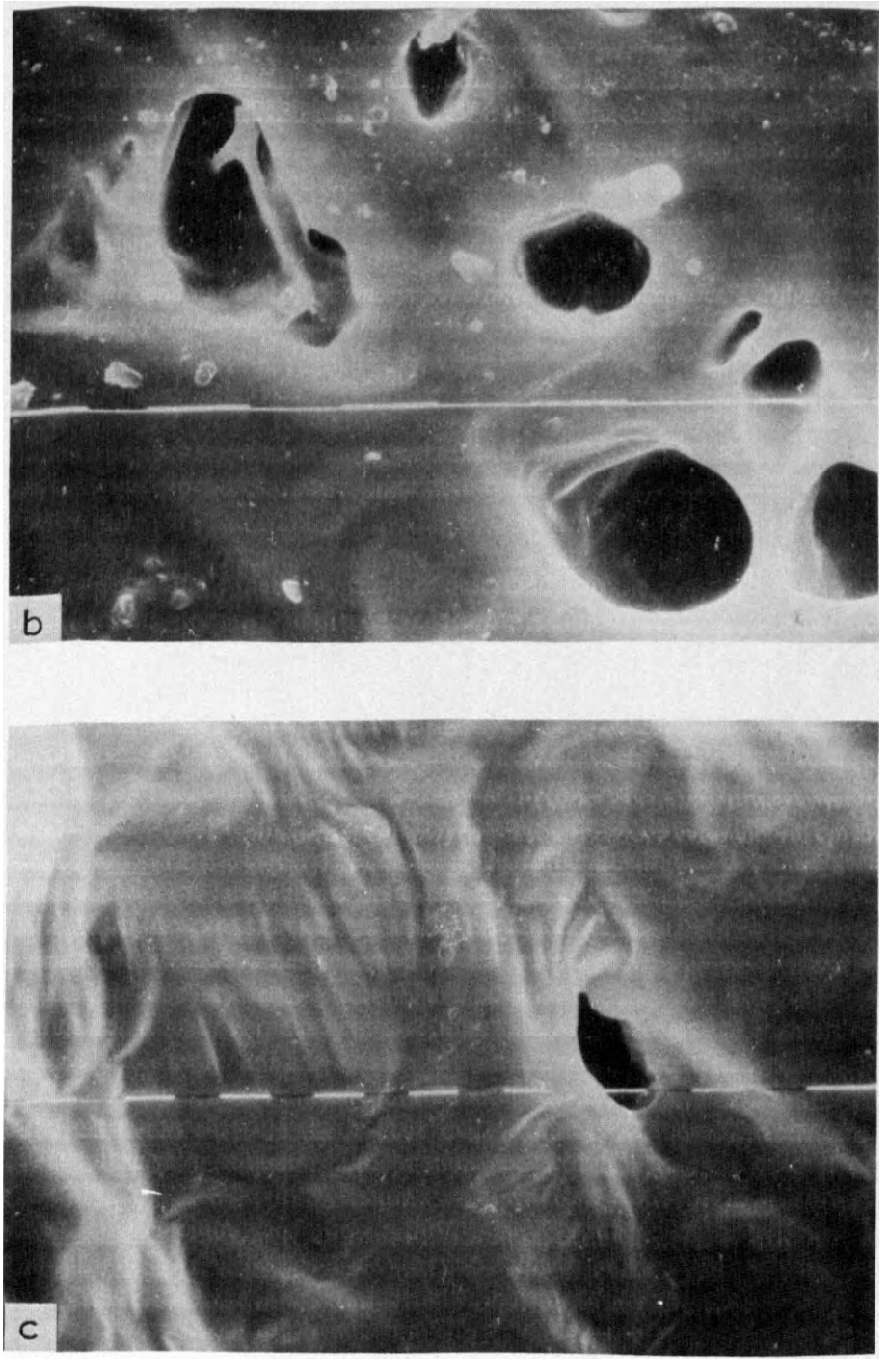


Fig. 2. Scanning electron microscope photographs of freeze-dried gels of: (a) 2% Pluronic F68, scale marker (–) 10 μm; (b) 2% Pluronic F88, scale marker (–) 10 μm; (c) 4% Pluronic F87, scale marker (–) 10 μm.

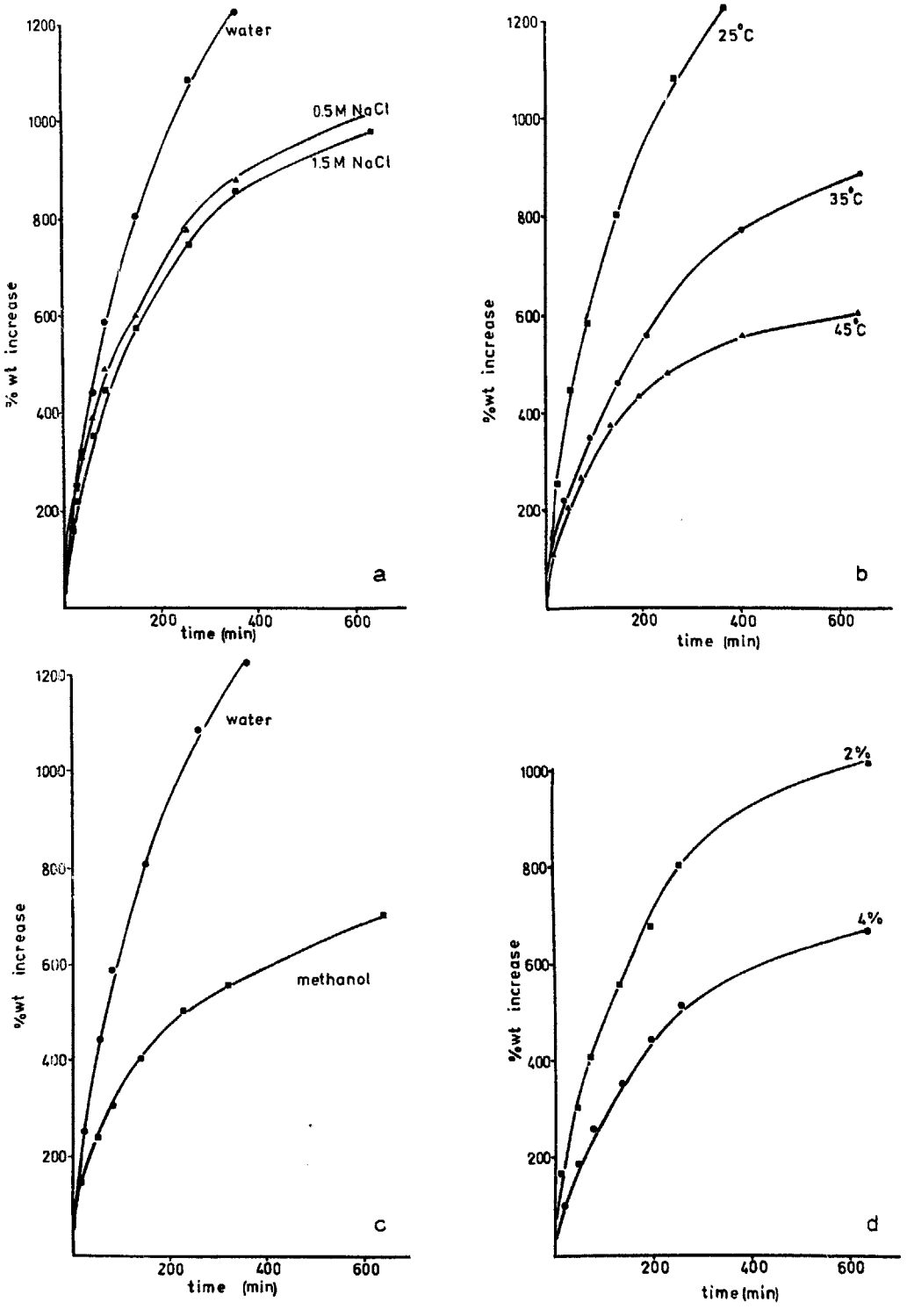


Fig. 3. Swelling capacity of the gels expressed as % weight increase vs time under different conditions. a: gel of 2% Pluronic F68 in different salt solutions. t . gel of 2% Pluronic F68 at different temperatures. c: gel of 2% Pluronic F68 in different solvents. d: gel of 2% and 4% Pluronic F88.

16 h is shown in Fig. 2a. The structure appears to possess a continuous solid phase with the individual pores separated by relatively thin walls. Gels of 2% Pluronic F88 irradiated for the same time have fewer pores and the pore walls appear much thicker relative to the pore diameter (see Fig. 2b). Increasing the poloxamer concentration in solution results in a gel of higher density with fewer pores (see Fig. 2c). Gel consistency can be controlled by adjusting the poloxamer concentration and the radiation dose with low poloxamer concentrations and low doses a liquified gel can be obtained; Pluronic F87 at 2% concentration irradiated for 12, 16 and 18 h gave more viscous semi-gels.

Swelling experiments were performed on gels dried in vacuo; some results are shown in Fig. 3. The gels of 2% Pluronic F68 irradiated for 16 h showed a high hydration capacity of up to 1300% of its dry weight after 400 min in water, indicating its hydrophilic nature. The swelling capacity is affected by additives and temperature (Fig. 3a, b and c). An increase in monomer concentration produces gels of lower swelling ability (Fig. 3d). The presence of sodium chloride and an increase in temperature both dehydrate the oxyethylene chains, and would thus be expected to decrease the extent and rate of water uptake. Although water uptake might be of importance in consideration of the use of these gels as wound dressings, our present interest is in their use as drug release matrices.

Many water insoluble medicinal and pharmaceutical substances can be incorporated into these gels by solubilization in the poloxamer solution before irradiation, although a disadvantage of this procedure is the possibility of radiation-induced degradation. Fletcher and Davies (1974) have shown that micellar solubilization of a drug has some protective action against drug degradation by γ-rays. In aqueous solution approximately 50% and 60% of acetanilide was degraded by 6 and 12 h irradiation respectively, whilst in the poloxamer solution (1% L64), 5% and 20% of the drug was degraded after the same exposure time. This indicates the protection afforded by micellar solubilization.

Pluronics have previously been used to solubilize acetanilide (Collett and Tobin, 1979). In this work, 0.01% acetanilide was solubilized in 2% poloxamer F68 and irradiated for 16 h to form a gel. The release rate of acetanilide from this gel is shown in Fig. 4; for comparison the release rate of the drug from a solution of 2% poloxamer F68 contain-

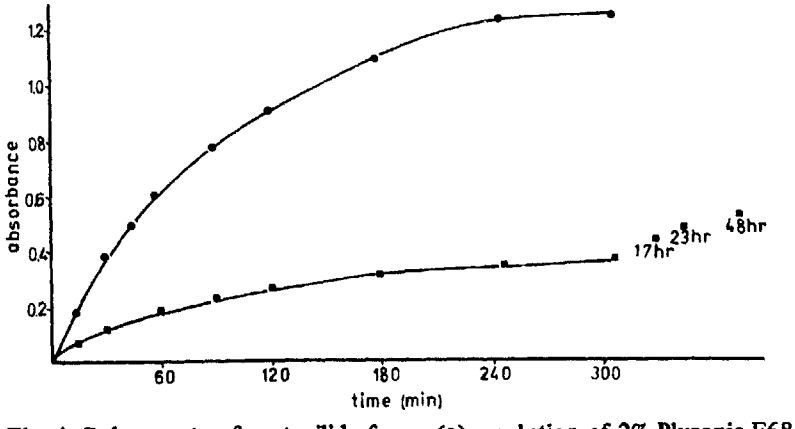


Fig. 4. Release rate of acetanilide from: (•) a solution of 2% Pluronic F68 containing 0.01% acetanilide; and (▪) a gel of 2% Pluronic F68 containing 0.01% acetanilide.

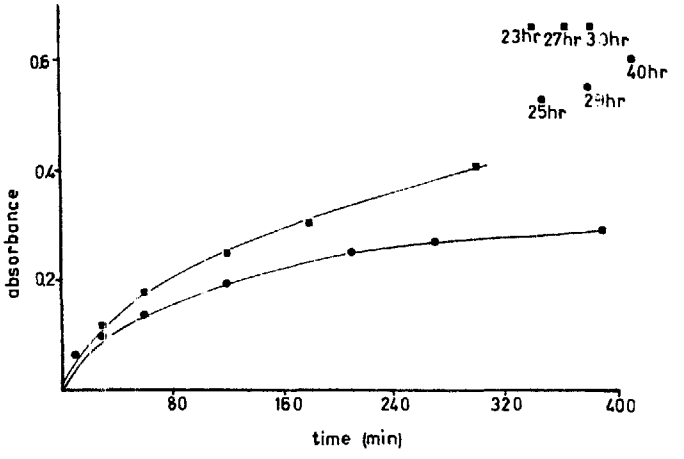


Fig. 5. The release of sorbed acetanilide from a gel of Pluronic F68 formed from a 4% solution and containing 7.9×10^{-4} g drug in 0.39 g gel in its dry state and from a gel of Pluronic F88 formed from a 4% solution and containing 1.0×10^{-3} g acetanilide in 0.39 g dry gel.

ing 0.01% acetanilide is also shown. There is a considerable reduction in the release of the drug from the gel compared to the micellar solutions and the drug was continuously released over a period of 24 h. Although we know from studies in poloxamer L64 solution that some degradation (20% in that case) takes place on γ-irradiation of the solubilized acetanilide, the reduction in rate of release cannot be accounted for on this basis. Release rates from swollen gels of poloxamer F68 and poloxamer F88 which have sorbed acetanilide is shown in Fig. 5. The gel of poloxamer F88 releases acetanilide at a slower rate than the gel of poloxamer F68. This may be due to the lower porosity of the former as indicated by the SEM photograph.

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